Timothy Wilt

Jan 08, 2021 15:07:28 EST
American College of Physicians

Disclosure Purpose: ACP COI Disclosure

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Other	Self	-
Category: Other *Compensation Type:* Other *Annual Compensation:*		*Start Date:* 01/01/2018 *End Date:* *Other Compensation:* 100000 *Additional Information:* Support for our research group to conduct reviews	
American Urological Association Foundation	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*		*Start Date:* 01/01/2018 *End Date:* 07/01/2020 *Other Compensation:* *Additional Information:* I receive support (approximately $150,000) for our research group to conduct reviews. I receive no personal financial support	
American Urological Association Foundation	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*		*Start Date:* 11/11/2020 *End Date:* 04/11/2021 *Other Compensation:* *Additional Information:* Research contract to our evidence review team to conduct evidence review on pharmacologic treatments for BPH for AUA clinical practice guideline	
Merck	Grant / Contract	Other - Subcontract to UM	$263,892.00
Recipient Name: Kristine Ensrud *Grant / Contract Description:* Subcontract to UM from Pacific Medical University *Grant / Contract Amount:* $263,892.00 *Contract Start Date:* 09/07/2017 *Contract End Date:* 02/29/2020		*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Valuation Date:* 01/08/2021 *Additional Information:* Funding for research team. No salary support to Dr. Ensrud	
Midwest CEPAC-ICER	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*		*Start Date:* 01/01/2018 *End Date:* *Other Compensation:* *Additional Information:*	
Midwest CEPAC-ICER	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*		*Start Date:* 01/01/2020 *End Date:* *Other Compensation:* *Additional Information:*	
NHLBI	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*		*Start Date:* 01/01/2019 *End Date:* 01/01/2021 *Other Compensation:* *Additional Information:*	
U.S. Department of Veterans Affairs	Employment	Self	-
Title: Professor *Start Date:* 06/15/2018 *End Date:*		*Position Description:* Staff Physician *Additional Information:*	
VA Preventive Medical Advisory Committee	Consultant	Self	-
Category: Consultant *Compensation Type:* Unpaid *Annual Compensation:*		*Start Date:* 01/01/2018 *End Date:* *Other Compensation:* *Additional Information:*	

Intellectual Property

Type	Is Licensed	Interest Held By	Value
Other Intellectual Property - Research grants/contracts from VA, AHRQ, and ACP ...	-	Self	$210,000.00

Description: Research grants/contracts from VA, AHRQ, and ACP to conduct evidence synthesis reports.
Yearly Income:

Amount	Type	Year	Payment Receipt

Income Source: Funds paid to my institution to support work of our evidence review team. AHRQ contracts can support my salary. Others do not.
Additional Information: The funds of payment through home institution are research support for programs NOT personal salary. I receive approximately 5-10000 annually as additional salary beyond my VA salary for grant support through AHRQ.

$10,000.00	Estimated	2020	Direct Payment
$200,000.00	Estimated	2019	Payment through home institution

Other Intellectual Property - Evidence reports and manuscripts written on oste ...	-	Self	-

Description: Evidence reports and manuscripts written on osteoporosis based on AHRQ-funded research
Yearly Income:

Income Source: AHRQ-EPC program

Additional Information: Director of AHRQ-EPC site that was awarded contract. Wife was a collaborating investigator on this project and received salary support from AHRQ. I was not the PI of this project but rather overall EPC director and project collaborator

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   None

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

   Yes.

   i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

      Yes

   ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

      Yes

   iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

      Yes

   iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

      Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Timothy J. Wilt

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☑ I have interests to report (please list in space below).

☐ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

I have authored AHRQ evidence reviews and manuscripts related to osteoporosis. My wife, Kris Ensrud has authored numerous papers and conducted research on osteoporosis and serves as an ACP-osteopororsis TEP member.

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Timothy J. Wilt

Print Name

TIMOTHY J. WILT 445612 Digitally signed by TIMOTHY J. WILT 445612 Date: 2021.01.08 11:34:45 -06'00' 01/08/21

Signature Date

Devan Kansagara

Dec 16, 2020 17:08:40 EST
American College of Physicians

Disclosure Purpose: clinical guidelines committee conflict

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Grant / Contract	Other - Portland VA Research Foundation	$174,000.00

Recipient Name: Portland VA Research Foundation
Recipient Type: Institution
Grant / Contract Description: Osteoporosis treatment systematic review for ACP Clinical Guideline Committee
Grant / Contract Purpose: Research
Grant / Contract Amount: $174,000.00
Grant / Contract Valuation Date: 12/16/2020
Contract Start Date: 10/01/2020
Contract End Date:
Additional Information: Serving as PI of this project; member of ACP Clinical Guideline Committee

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Devan Kansagara

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☑ I have interests to report (please list in space below).

☐ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Publication re: depression screening in patients with End Stage Renal Disease:
Kondo, K., Antick, J. R., Ayers, C. K., Kansagara, D., & Chopra, P. (2020). Depression screening tools for patients with kidney failure: A systematic review. Clinical Journal of the American Society of Nephrology, 15(12), 1785-1795.

COVID-19 publications:
86. Mackey K, King VJ, Gurley S, Kiefer M, Liederbauer E, Vela K, Sonnen P, and Kansagara D. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor clockers on SARS-CoV-2 infection in adults. A living systematic review Ann Int Med. 2020. PMID: 32422062 [E-pub ahead of print]

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☐ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☐ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Devan Kansagara

Print Name

Devan Kansagara Digitally signed by Devan Kansagara Date: 2020.12.16 14:53:08 -08'00' 12/16/20

Signature Date

Pelin Batur

Mar 23, 2020 16:14:18 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

I do not have any financial interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   none

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

   Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

      Yes

      ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

      Yes

      iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

      Yes

      iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

      Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options,

commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Pelin Batur

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

23. Batur P, Rice S, Barrios P, Sikon A. Osteoporosis management. Journal of Women's Health 2017; 26(8):918-921.

32. Sikka S, Moreno AC, Smith T, Batur P. Clinical updates in women's health 2019: What's new in osteoporosis, breast cancer, contraception and hormonal therapy. Cleveland Clinic Journal of Medicine 2019; 86(6): 400-406.

37. DeSapri KT, Batur P. Osteoporosis update. Journal of Women's Health 2020; 29 (3):287-290.

Facebook q+a for the hospital on osteoporosis - https://www.youtube.com/watch?v=fuMaTOFPu4I

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Pelin Batur

Print Name

Pelin Batur 12/22/2020

Signature Date

Thomas Cooney

Dec 16, 2020 14:48:27 EST
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-21

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Fiduciary Officer	Self	-
Official Title: Chair-elect, Board of Regents *Compensation Type:* Cash *Start Date:* 04/22/2020 *End Date:* 04/19/2021 *Annual Compensation:* *Additional Information:*		*Position Description:* As above *Other Compensation:*	
U.S. Department of Veterans Affairs	Employment	Self	-
Title: Staff Physician *Start Date:* 08/08/1979 *End Date:*		*Position Description:* Attending physician, supervising residents and medical students *Additional Information:*	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   1. I am a current member of ACP Board of Regents 2. I am an Associate Editor of the Journal of Graduate Medical Education

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

      Yes

      ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

      Yes

      iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

      Yes

      iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

      Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Thomas G. Cooney MD MACP

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☒ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☒ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Thomas G. Cooney MD MACP

Print Name

12/16/2020

Signature Date

Carolyn Crandall

Mar 16, 2020 18:36:46 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
American Society for Bone and Mineral Research	Other	Self	-
Category: Other ***Start Date:*** 01/01/2017 ***End Date:*** ***Other Compensation:*** ***Additional Information:*** Professional Practice Committee ***Consultant Description:*** ***Compensation Type:*** Unpaid ***Annual Compensation:***			
California Institute for Regenerative Medicine	Grant / Contract	Spouse/Partner	$100,000.00
Recipient Name: Harley Kornblum ***Grant / Contract Description:*** Spinal cord injury basic science research ***Grant / Contract Amount:*** $100,000.00 ***Contract Start Date:*** 01/01/2017 ***Contract End Date:*** ***Recipient Type:*** Institution ***Grant / Contract Purpose:*** Research ***Grant / Contract Valuation Date:*** 12/23/2019 ***Additional Information:***			
David Geffen School of Medicine, University of California, Los Angeles	Employment	Self	-
Title: Professor of Medicine ***Start Date:*** 07/01/2017 ***End Date:*** ***Position Description:*** Professor in the Dept. Of Internal Medicine ***Additional Information:***			
David Geffen School of Medicine, University of California, Los Angeles	Employment	Spouse/Partner	-
Title: Professor ***Start Date:*** 01/01/2017 ***End Date:*** ***Position Description:*** Professor on Faculty ***Additional Information:***			
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation	Grant / Contract	Spouse/Partner	$100,000.00
Recipient Name: Harley Kornblum ***Grant / Contract Description:*** Neural repair and brain cancer ***Grant / Contract Amount:*** $100,000.00 ***Contract Start Date:*** 01/01/2017 ***Contract End Date:*** ***Recipient Type:*** Institution ***Grant / Contract Purpose:*** Research ***Grant / Contract Valuation Date:*** 12/23/2019 ***Additional Information:***			
International Society for Clinical Densitomnetry	Consultant	Self	-
Category: Consultant ***Start Date:*** 01/01/2019 ***End Date:*** ***Other Compensation:*** ***Additional Information:*** ***Consultant Description:*** ***Compensation Type:*** Unpaid ***Annual Compensation:***			
National Institutes of Health	Grant / Contract	Self	$25,000.00
Recipient Name: Carolyn J. Crandall ***Grant / Contract Description:*** Contract from Western Regional Center for NHLBI-funded Women's Health Initiative Study ***Grant / Contract Valuation Date:*** 12/23/2019 ***Additional Information:*** ***Recipient Type:*** Institution ***Grant / Contract Purpose:*** Research ***Grant / Contract Amount:*** $25,000.00 ***Contract Start Date:*** 01/01/2019 ***Contract End Date:***			
National Institutes of Health	Grant / Contract	Spouse/Partner	$100,000.00
Recipient Name: Harley Kornblum ***Grant / Contract Description:*** Research on brain cancer ***Grant / Contract Amount:*** $100,000.00 ***Contract Start Date:*** 01/01/2017 ***Contract End Date:*** ***Recipient Type:*** Institution ***Grant / Contract Purpose:*** Research ***Grant / Contract Valuation Date:*** 12/23/2019 ***Additional Information:*** Brain cancer research			

North American Menopause Society	Fiduciary Officer	Self	-

Official Title: Secretary
Compensation Type: Unpaid
Start Date: 01/01/2019 ***End Date:***
Annual Compensation:
Additional Information:
Position Description: Secretary of the Board of Trustees, not compensated
Other Compensation:

North American Menopause Society	Consultant	Self	$1,000.00

Category: Consultant
Start Date: 01/01/2017 ***End Date:***
Other Compensation:
Consultant Description:
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2019	$1,000.00	Estimated

Additional Information: Menopause competency exam committee

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Carolyn J. Crandall, MD, MS, FACP

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Carolyn J. Crandall

Print Name

Carolyn J. Crandall

Digitally signed by Carolyn J. Crandall
DN: cn=Carolyn J. Crandall, o=University of California, Los Angeles, ou, email=ccrandall@mednet.ucla.edu, c=US
Date: 2020.12.18 12:12:48 -08'00'

Signature Date

1. Drieling, R.L. LaCroix, A.Z., Beresford, S.A., Boudreau, DM,. Kooperberg, C.L., Gass, M., **Crandall, C.J.,** Chlebowski, R., Heckbert, S.R., Long-term Oral Bisphosphonate Use in Relation to Fracture Risk in Postmenopausal Women with Breast Cancer. *Menopause.* 2016;23(11):1168-1175. PMID: 27433859 PMCID: PMC5079762
2. **Crandall, C.J**., Aragaki, A.K., LeBoff, M.S., Li, W., Wactawski-Wende, J., Cauley, J.A., Margolis, K.L., Manson, J.E. Calcium plus Vitamin D Supplementation and Height Loss: Findings from the Women's Health Initiative Calcium plus Vitamin D Clinical Trial. *Menopause.* 2016; 23(12):1277-1286. PMID: 27483038. PMCID: PMC5118123[1]
3. Watts, N.B., Cauley, J.A., Jackson, R.D., LaCroix, A.Z., Lewis, C.E., Manson, J.E., Neuner, J., Phillips, L.S., Stefanick, M.L., Wactawski-Wende, J., **Crandall, C**. No Increase in Fractures after Stopping Hormone Therapy: Results from the Women's Health Initiative. *J Clin Endocrinol Metab*. 2017;102(1):302–308. PMID: 27820659 PMCID: PMC6287395.
4. Mori, T., **Crandall, C.J**.; Ganz, D.A., Cost-Effectiveness of Combined Oral Bisphosphonate Therapy and Falls Prevention Exercise for Fracture Prevention in the USA. *Osteoporos Int.* 2016;28(2):585-595. PMID: 27726000.
5. Cauley, J.A., Smagula, S.F., Hovey, K.M., Wactawski-Wende, J., Andrews, C.A., **Crandall, C.J.**, LeBoff, M., Li, W., Coday, M., Sattari, M., Tindle, H.A. Optimism, Cynical Hostility, Falls, and Fractures: The Women's Health Initiative Observational Study (WHI-OS). *Journal of Bone and Mineral Research*. 2017;32(2):221–229. PMID: 27566996
6. Ensrud, K.E., Harrison, S.L., Cauley, J.A., Langsetmo, L., Schousboe, J.T., Kado, D.M., Lewis, C.E., Hoffman, A.R., Orwoll, E.S., **Crandall, C.J.**, Stefanick, M.L., Napoli, N., Cawthon, P.M. for the Osteoporotic Fractures in Men (MrOS) Research Group. Impact of competing risk of mortality on association of weight loss with risk of central body fractures in older men. Journal of Bone and Mineral Research. *J Bone Miner Res*. 2017; Mar; 32(3):624-632. PMID: 27739103 PMCID: PMC5425153
7. Wang, Y., Wactawski-Wende, J., Sucheston-Campbell, L., Preus L., Hovey, K.M, Nie, J., Jackson, R.D., Handelman, S., Nassir, R., **Crandall, C.J.,** Ochs-Balcom, H.M. Gene-hormone therapy interaction and fracture risk in postmenopausal women. *Journal of Clinical Endocrinology & Metabolism.* 2017 Jun 1;102(6):1908-1916. PMID: 28324062 PMCID: PMC5470770
8. Gourlay, M.L., Overman, R.A., Fine, J.P., **Crandall, C.J.**, Ensrud, K.E., Gass, M.L., Johnson, K.C., LeBlanc, E.S., Robbins, J., Womack, C.R., Schousboe, J.T., LaCroix, A.Z. Time to clinically relevant fracture risk scores in postmenopausal women. *American Journal of Medicine.* 2017 Jul;130(7):862.e15-862.e23. doi: 10.1016/j.amjmed.2017.02.012. Epub 2017 Mar 9. PubMed PMID: 28285070; PubMed Central PMCID: PMC5474146.
9. Wang, Y., Wactawski-Wende, J., Sucheston-Campbell, LE., Hovey, K.M., Nie, J., Jackson, R.D., Handelman, S.K., Nassir, R., **Crandall, C.J.,** Oches-Balcom. The influence of genetic susceptibility and calcium plus vitamin D supplementation on fracture risk. *Am J Clin* Nutr. 2017; Apr;105(4):970-979. PMID: 28148500 PMCID: PMC5366049

[1] Cited in the European Menopause and Andropause Society clinical guide on Calcium in the prevention of postmenopausal osteoporosis, Maturitas 107 (2018): 7-12

10. Mori, T**., Crandall, C.J**., Ganz, D.A. Cost-Effectiveness of Denosumab versus Oral Alendronate for Elderly Osteoporotic Women in Japan. *Osteoporosis International.* 2017 May;28(5):1733-1744. PMID: 28210776
11. Kling, J.M., Manson, J., Naughton, M.J., Temkit, M., Sullivan, S.D., Gower, E.W., Hale, L., Weitlauf, J.C., Nowakowski, S., **Crandall, C.J.** Association of Sleep Disturbance and Sexual Function in Postmenopausal Women of the Women's Health Initiative Observational Study cohort. *Menopause.* 2017; Jun;24(6):604-612. PMID: 28141665 PMCID: PMC5443696
12. **Crandall, C.J.**, Liu, J., Cauley, Jane, Newcomb, P., Manson, J., Vitolins, M., Jacobsen, L.T., Rykman, K., Stefanick, M. Associations of Parity and Breast-feeding with Bone Mineral Density and Fracture Incidence in the Women's Health Initiative. *Obstetrics and Gynecology*, 2017 Jul;130(1):171-180. PMID 28594759 PMCID: PMC5484587
13. Diem, S.J., Peters, K.W., Gourlay, M.L., Schousboe, J.T., Taylor, B.C., Orwoll, E.S., Cauley, J.A., **Crandall, C.J**., Ensrud, K.E. Screening for Osteoporosis in Older Men: Operating Characteristics of Proposed Strategies for Selecting Men for BMD Testing, *Journal of General Internal Medicine*, 2017 Nov;32(11):1235-1241. PMID: 28815485 PMCID: PMC5653561
14. Harris, R., Chang, Y., Beavers, K., Laddu-Patel, D., Bea, J., Johnson, K., LeBoff, M, Womack, C., Wallace, R., Li, W., **Crandall, C.J.,** Cauley, J. The Risk of Fracture among Women with Sarcopenia, Low Bone Mass or Both. *J Am Geriatr Soc*. 2017 Dec;65(12):2673-2678. PMID: 28960230 PMCID: PMC5729083
15. **Crandall, C.J.**, Vasan, S., LaCroix, A., LeBoff, M.S., Cauley, J.A., Robbins, J.A., Jackson, R.D., Bauer, D.C. Bone Turnover Markers are not Associated with Hip Fracture Risk: A Case-Control Study in the Women's Health Initiative, Journal of Bone and Mineral Research, J Bone Miner Res. 2018 2018 Jul;33(7):1199-1208. PMID: 29923225 PMCID: PMC7060935
16. **Crandall, C.J.,** Larson, J., LaCroix, A., Cauley, J.A., LeBoff, M.S., Li, W., LeBlanc, E.S., Edwards, B.J., Manson, J.E., Ensrud, K. Predicting Fracture Risk in Younger Postmenopausal Women: Comparison of the Garvan and FRAX Risk Calculators in the Women's Health Initiative Study, *J Gen Intern Med.* 2019 Feb;34(2):235-242. PMID: 30334182. PMCID: PMC6374270.
17. Beavers, K.M., Neiberg, R.H., Johnson, K.C., Davis, C.H., Casanova, R., Schwartz, A.V., **Crandall, C.J.**, Lewis, C.E., Pi-Sunyer, X., Kritchevsky, S.B. Impact of body weight dynamics following intentional weight loss on fracture risk: Results from The Action for Health in Diabetes Study, *JBMR Plus. 2018 Oct 25;3(5):e10086.* PMID: 31131339 PMCID: PMC6524677
18. Cauley, J.A., Hovey, K.M., Stone, K.L., Andrews, C.A., Barbour, K.E., Hale, L., Jackson, R.D., Johnson, K.C., LeBlanc, E.S., Li, W., Zaslavsky, O., Ochs-Balcom, H., Wactawski-Wende, J., **Crandall, C.J.** Characteristics of self-reported sleep and the risk of falls and fractures: The Women's Health Initiative (WHI), *J Bone Miner Res.* 2019 Mar;34(3):464-474. PMID: 30461066. PMCID: PMC6563041
19. **Crandall, C.J.**, Larson, J., Manson, J.E., Cauley, J.A., LaCroix, A., Wactawski-Wende, J., Datta, M., Sattari, M., Schousboe, J.T., Leslie, W.D., Ensrud, K.E. A Comparison of U.S. and Canadian Osteoporosis Screening and Treatment Strategies in Postmenopausal Women, *Journal of Bone and Mineral Research*, 2019 Apr;34(4):607-615. PMID: 30536628 PMCID: PMC7354844

20. **Crandall, CJ**, Schousboe, JT, Morin S, Lix, LM, Leslie, W. Performance of FRAX and FRAX-Based Treatment Thresholds in Women Aged 40 and Older: The Manitoba BMD Registry, *Journal of Bone and Mineral Research*, 2019 Aug;34(8):1419-1427. PMID: 30920022
21. Haring, B., **Crandall, C.J.,** Carbone, L., Liu, S., Li, W., Johnson, K., Wactawski-Wende, J., Shadyab, A.H., Gass, M., Kamensky, V., Cauley, J.A., Wassertheil-Smoller, S., Lipoprotein(a) plasma levels, bone mineral density and risk of hip fractures in the Women's Health Initiative, *BMJ Open*, 2019 Apr 24;9(4):e027257. doi: 10.1136/bmjopen-2018-027257. PubMed PMID: 31023762. PMCID: PMC6501983
22. Follis, S., Bea, J., Klimentidis, Y., Hu, C., **Crandall, C.J,** Garcia, D.O., Shadyab, A.H., Nassir, R., Chen, Z. Psychosocial Stress and Bone Loss among Postmenopausal Women: Results from the Women's Health Initiative, *J Epidemiol Community Health.* 2019 Sep;73(9):888-892 PMID: 31289118.
23. Conley, R.B., Adib, G., Adler, R.A., Akesson, K.E., Alexander, I.M., Amenta, K.C., Blank, R.D., Brox, W.T., Carmody, E.E., Chapman-Novakofski, K., Clarke, B.L., Cody, K.M, Cooper, C., **Crandall, C.J.,** Dirschl, D.R., Eagen, T.J., Elderkin. A.L., Fujita, M., Greenspan, S.L., Halbout, P., Hochberg, M.C., Javaid, M., Jeray, K.J., Kearns, A.E., King, T., Koinis, T.F., Koontz, J.S., Kuzma, M., Lindsey, C., Lorentzon, M., Lyritis, G.P., Michaeud, L.B., Miciano, A., Morin, S.N., Mujahid, N., Napoli, N., Olenginski, T.P., Puzas, J.E., Rizou, S., Rosen, C.J., Saag, K., Thompson, E., Tosi, L.L., Tracer, H., Khosla, S., Kiel, D. Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition. *J Bone Miner Res.* 2020 Jan;35(1):36-52, PMID: 31538675
24. Shieh, A., Greendale, G.A., Cauley, J.A., Karvonen-Gutierrez, C., **Crandall, CJ,** Karlamangla, A.S. Estradiol and follicle stimulating hormone as predictors of onset of menopause transition-related bone loss in pre- and perimenopausal women, *J Bone Miner Res*. 2019 Dec;34(12):2246-2253. PMID: 31442329
25. Kremer, P., Laughlin, G., Shadyab, A., **Crandall, C.**, Masaki, K., Orchard, T., Snetselaar, L., LaCroix, A. Association between soft drink consumption and osteoporotic fractures among postmenopausal women: The Women´s Health Initiative, *Menopause*, 2019 26(11): 1234-1241. PMID: 31613830
26. Qaseem, A, Wilt, T., **Crandall, C.,** Hicks, L., Mustafa, R. Screening for Colorectal Cancer in Asymptomatic Average Risk Adults: A Guidance Statement from the American College of Physicians, *Ann Intern Med.* 2019 Nov 5;171(9):643-654. PMID: 31683290
27. Mori, T., **Crandall, C.J.,** Ganz, D.A. Cost-Effectiveness of Sequential Teriparatide/Alendronate versus Alendronate-only Strategies in High-risk Osteoporotic Women in the U.S.: Analyzing the Impact of Generic or Biosimilar Teriparatide, *JBMR Plus* 2019 November 13: 3(11): e10233. PMID: 31768491 PMCID: PMC6874180
28. **Crandall, C.J.**, Larson, J., Cauley, J.A., Schousboe, J.T., LaCroix, A.Z., Robbins, J.A., Watts, N.B., Ensrud, K.E. Do additional clinical risk factors improve the performance of Fracture Risk Assessment Tool (FRAX) Among Postmenopausal Women? Findings from the Women's Health Initiative Observational Study and Clinical Trials, *JBMR Plus*, 2019 Nov 30;3(12):e10239. doi: 10.1002/jbm4.10239. eCollection 2019 Dec. PMID: 31844827. PMCID: PMC6894725

29. **Crandall, C.J.**, Larson, J., Wright, N.C., Laddu, D., Stefanick, M., Kaunitz, A.M., Watts, N.B., Wactawski-Wende, J., Womack, C.R., Johnson, K.C., Carbone, L.D., Jackson, R.D., Ensrud, K.E. Does serial bone density measurement meaningfully improve incident fracture risk prediction in postmenopausal women? Results from the Women's Health Initiative Observational Study and Clinical Trials, JAMA Intern Med. 2020; 180 (9): 1232-1240, PMID: 32730575 PMCID: PMC7385675[2]
30. Conley RB, Adib G, Adler RA, Akesson, KE, Alexander, IM, Amenta, KC, Blank, RD, Brox, WT, Carmody, EE, Chapman-Novakofski, KC, Clarke, BL, Cody, KM, Cooper, C, **Crandall, CJ**, Dirschi, DR, Eagen, TJ, Elderkin, AL, Fujita, M, Greenspan, SL, Halbout, P, Hochberg, MC, Javaid, M., Jeray, KJ, Kearns, AE, King, T, Koinis, TF, Koontz, JS, Kuzma, M, Lindsey, C, Lorentzon, M, Lyritis, GP, Michaud, LB, Miciano, A, Morin, SN, Mujahid, N, Napoli, N, Olenginski, TP, Puzas, JE, Rizou, S, Rosen, CJ, Saag, K, Thompson, E., Tosi, L, Tracer, H, Khosla, S, Kiel, DP. Secondary Fracture Prevention: Consensus Clinical Recommendations From a Multistakeholder Coalition. Orthop Nurs. 2020;39(3):145-161. PMID: 32443087
31. Conley RB, Adib G, Adler RA, Akesson, KE, Alexander, IM, Amenta, KC, Blank, RD, Brox, WT, Carmody, EE, Chapman-Novakofski, KC, Clarke, BL, Cody, KM, Cooper, C, **Crandall, CJ**, Dirschi, DR, Eagen, TJ, Elderkin, AL, Fujita, M, Greenspan, SL, Halbout, P, Hochberg, MC, Javaid, M., Jeray, KJ, Kearns, AE, King, T, Koinis, TF, Koontz, JS, Kuzma, M, Lindsey, C, Lorentzon, M, Lyritis, GP, Michaud, LB, Miciano, A, Morin, SN, Mujahid, N, Napoli, N, Olenginski, TP, Puzas, JE, Rizou, S, Rosen, CJ, Saag, K, Thompson, E., Tosi, L, Tracer, H, Khosla, S, Kiel, DP Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition. J Orthop Trauma. 2020;34(4):e125-e141. PMID: 32195892
32. Northuis CA, Crandall CJ, Margolis KL, Diem SJ, Ensrud KE, Lakshminarayan K. Association between post-stroke disability and 5-year hip-fracture risk: The Women's Health Initiative. *J Stroke Cerebrovasc Dis*. 2020;29(8):104976. PMID: 32689623 PMCID: PMC7394038
33. Carbone, L., Vasan, S., Elam, R., Gupta, S., Tolaymat, O., **Crandall, C.,** Wactawski-Wende, J., Johnson, K.C. The Association of Methotrexate, Sulfasalazine and Hydroxychloroquine Use with Fracture in Postmenopausal Women with Rheumatoid Arthritis: Findings from The Women's Health Initiative, *JBMR Plus*, Vol. 4, No. 10, October 2020, e10393.
34. Karlamangla, A.S., Binkley, N., **Crandall, C.J.** Psychosocial Life Histories and Biological Pathways to Bone Health. Oxford Handbooks Online, Oxford University Press, Eds. C.D. Ryff and R.F. Kreuger. Online Publication Date: Oct 2018 DOI: 10.1093/oxfordhb/9780190676384.013.17. Print Publication Date: Nov 2018
35. **Crandall, C.J.**, Ensrud, K.E. Who should be screened for osteoporosis? Page 1501-1510. Marcus And Feldman's Osteoporosis, 5th Edition, Eds David Dempster, Jane Cauley, Mary Bouxsein, Felicia Cosman, Elsevier Inc., 125 London Wall, London EC2Y 5AS, United Kingdom 2021
36. Ensrud KE, **Crandall CJ.** Osteoporosis. Ann Intern Med. 2017 Aug 1;167(3):ITC17-ITC32. doi: 10.7326/AITC201708010. PubMed PMID: 28761958
37. Karlamangla AS, Burnett-Bowie SM, **Crandall CJ.** Bone Health During the Menopause Transition and Beyond. Obstet Gynecol Clin North Am. 2018 Dec;45(4):695-708. doi:

[2] Selected for New England Journal of Medicine Journal Watch General Medicine Sept. 15, 2020

10.1016/j.ogc.2018.07.012. Epub 2018 Oct 25. Review. PubMed PMID: 30401551; PubMed Central PMCID: PMC6226267.

38. **Crandall, C.J.,** Strong Bones, Strong Body, Women's Preventive Health Care, *Obstet Gynecol Clin N Am* 46 (2019) 541-552. PMID: 31378294
39. Ensrud, K.E., **Crandall, C.J.**, Bisphosphonates for Postmenopausal Osteoporosis, JAMA, 2019 Oct 17. [Epub ahead of print] PubMed PMID: 31621799
40. Leslie, W.D., **Crandall, C.J.**, Population-Based Osteoporosis Primary Prevention and Screening, *Curr Osteoporos, Rep.*, 2019 Dec;17(6):483-490. PubMed PMID: 31673933.
41. **Crandall, C.J.**, Ensrud, Osteoporosis Screening in Younger Postmenopausal Women. *JAMA* 2020;323(4):367-368. PMID 31917384
42. Cauley, J.A., **Crandall, C.J.**, The Women's Health Initiative: A landmark resource for skeletal research since 1992, J Bone Miner Res. 2020 Apr 14. [Epub ahead of print] PMID: 32286708.
43. **Crandall, C.J.** Can We Pave the Pathway to Fracture Prevention?, editorial regarding the NIH Pathways to Prevention Workshop on appropriate use of drug therapies for osteoporotic fracture prevention, published online April 23, 2019, Annals of Internal Medicine, PMID:31009937
44. Ensrud, K.E., **Crandall, C.J.** In older postmenopausal women with osteopenia,zoledronate reduced fragility fractures at 6 years. Invited commentary, Ann Intern Med. 2019 Apr 16;170(8):JC42. doi: 10.7326/ACPJ201904160-042. PubMed PMID: 30986832

Nick Fitterman

Mar 17, 2020 18:29:34 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

I do not have any financial interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations

- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Nick Fitterman

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

nick fitterman

Print Name

nick fitterman Digitally signed by nick fitterman Date: 2020.12.21 11:11:38 -05'00' 12212020

Signature Date

Lauri Hicks

Jan 05, 2021 09:01:39 EST
American College of Physicians

Disclosure Purpose: Clinical Guidelines Committee

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
Centers for Disease Control and Prevention	Employment	Self	-
Title: Director, Office of Antibiotic Stewardship *Start Date:* 07/15/2007 *End Date:*	*Position Description:* I lead CDC's public health efforts related to improving antibiotic use. I am also leading efforts related to the COVID-19 pandemic response. *Additional Information:*		
GI Specialists of Georgia	Employment	Spouse/Partner	-
Title: Physician *Start Date:* 09/01/2010 *End Date:*	*Position Description:* Patient care *Additional Information:*		
Society for Healthcare Epidemiology of America	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2021 *End Date:* *Other Compensation:* *Additional Information:* Board Member, Councilor		

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Lauri Hicks

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Lauri Hicks

Print Name

Lauri Hicks -S7 Digitally signed by Lauri Hicks -S7
Date: 2021.01.05 09:55:57 -05'00' 1/5/2021

Signature Date

Jennifer Lin

Mar 26, 2020 13:41:40 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Kaiser Permanente	Employment	Self	-

Title: research physician, investigator
Start Date: 11/28/2005
End Date:
Position Description: investigator, center for health research, Kaiser Permanente NW
Additional Information: also practicing NW Permanente general internal medicine physician since 2011

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   I am the PI on several AHRQ contracts to support the USPSTF I am a non-voting member on Kaiser Permanente's National Guideline Directors primarily in a consultancy role Please see my CV for publications/presentations and contracts for any DOI in addition to topics on CV: involvement in ongoing topics not yet published include prevention of opioid misuse, healthy lifestyle counseling, screening for colorectal cancer, screening for COPD, COVID-19 forecasting

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

         Yes

      ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

         Yes

      iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

         Yes

      iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

         Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Jennifer S Lin

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☑ I have interests to report (please list in space below).

☐ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Our EPC, for which I am the Director, does reviews on the screening for depression, anxiety and suicide; other than obtaining funding and reviewing deliverables, I am not directly involved in these topics.

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Jennifer S. Lin

Print Name

Signatur 

12/16/2020

Date

Michael Maroto

Aug 12, 2020 08:51:14 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-21

Summary of Financial Interests

I do not have any financial interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   None

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

   Yes.

   i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

   Yes

   ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

   Yes

   iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

   Yes

   iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

   Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Michael Maroto

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Michael Maroto

Print Name

Michael Maroto, Esq. Digitally signed by Michael Maroto, Esq.
Date: 2021.01.25 15:45:54 -05'00'

Signature Date

Reem Mustafa

Jul 28, 2020 17:01:37 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-21.

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Rheumatology	Grant / Contract	Self	-
Recipient Name: *Grant / Contract Description:* *Grant / Contract Amount:* *Contract Start Date:* *Contract End Date:*	*Recipient Type:* *Grant / Contract Purpose:* *Grant / Contract Valuation Date:* 07/28/2020 *Additional Information:*		
American Gastroenterological Association	Grant / Contract	Self	-
Recipient Name: *Grant / Contract Description:* *Grant / Contract Amount:* *Contract Start Date:* *Contract End Date:*	*Recipient Type:* *Grant / Contract Purpose:* *Grant / Contract Valuation Date:* 07/28/2020 *Additional Information:*		
American Society of Hematology	Grant / Contract	Self	-
Recipient Name: Reem Mustafa *Grant / Contract Description:* *Grant / Contract Amount:* *Contract Start Date:* *Contract End Date:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Valuation Date:* *Additional Information:*		
ICER	Grant / Contract	Self	-
Recipient Name: *Grant / Contract Description:* *Grant / Contract Amount:* *Contract Start Date:* *Contract End Date:*	*Recipient Type:* *Grant / Contract Purpose:* *Grant / Contract Valuation Date:* 07/28/2020 *Additional Information:*		
University of Kansas Medical Center	Employment	Self	-
Title: Associate Professor of Internal Medicine *Start Date:* 02/28/2017 *End Date:*	*Position Description:* *Additional Information:*		
World Health Organization	Grant / Contract	Self	-
Recipient Name: *Grant / Contract Description:* *Grant / Contract Amount:* *Contract Start Date:* *Contract End Date:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Valuation Date:* 07/28/2020 *Additional Information:*		

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

Yes

iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Reem Mustafa

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Reem Mustafa

Print Name

Reem Mustafa Digitally signed by Reem Mustafa
Date: 2021.01.11 07:05:09 -06'00'

Signature Date

Jeffrey Tice

Aug 16, 2020 16:41:45 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Division of Cancer Epidemiology and Genetics, National Cancer Institute	Grant / Contract	Self	$4,000,000.00
Recipient Name: UCSF *Grant / Contract Description:* P01: The future of breast cancer screening in community practice: Advanced technologies performance, *Grant / Contract Valuation Date:* 05/22/2019 *Additional Information:* Co-investigator	*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Amount:* $4,000,000.00 *Contract Start Date:* 09/27/2011 *Contract End Date:* 05/31/2022		
institute for clinical and economic review	Grant / Contract	Self	$495,000.00
Recipient Name: UCSF *Grant / Contract Description:* Produce comparative effectiveness reviews in support of ICER *Grant / Contract Amount:* $495,000.00 *Contract Start Date:* 01/01/2018 *Contract End Date:*	*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Valuation Date:* 05/22/2019 *Additional Information:*		
Irving Street Pet Hospital	Other	Dependent Child	-
Category: Other *Start Date:* 08/01/2018 *End Date:* 06/14/2020 *Other Compensation:* *Additional Information:*	*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*		
National MS Society	Other	Self	-
Category: Other *Start Date:* 01/01/2012 *End Date:* *Other Compensation:* *Additional Information:*	*Consultant Description:* *Compensation Type:* Unpaid *Annual Compensation:*		
Patient-Centered Outcomes Research Institute	Grant / Contract	Self	$10,000,000.00
Recipient Name: UCSF *Grant / Contract Description:* Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast *Grant / Contract Valuation Date:* 05/22/2019 *Additional Information:* Co-investigator	*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Amount:* $10,000,000.00 *Contract Start Date:* 09/15/2015 *Contract End Date:*		
Society of General Internal Medicine	Other	Self	-
Category: Other *Start Date:* 01/01/2017 *End Date:* *Other Compensation:* *Additional Information:*	*Consultant Description:* *Compensation Type:* Unpaid *Annual Compensation:*		
University of California San Francisco	Employment	Self	-
Title: Professor of Medicine *Start Date:* 07/01/1999 *End Date:*	*Position Description:* Faculty *Additional Information:* Primary job		
University of California San Francisco	Other	Self	$1,000.00
Category: Other *Start Date:* 07/01/1999 *End Date:* *Other Compensation:* *Additional Information:*	*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*		

Year	Amount	Type
2019	$1,000.00	Estimated

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

        i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

        Yes

        ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

        Yes

        iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

        Yes

        iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

        Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Jeffrey A. Tice, MD

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Jeffrey A. Tice, MD

Print Name

dgim-2r5gtdy-lt.ucsf.edu Digitally signed by dgim-2r5gtdy-lt.ucsf.edu Date: 2020.12.16 16:38:19 -08'00' 12/16/2020

Signature Date

Janice Tufte

Dec 21, 2020 09:50:26 EST
American College of Physicians

Disclosure Purpose: ACP CGC

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
Academy Health	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:
Start Date: 03/30/2020 ***End Date:***
Other Compensation:
Additional Information: Developing Guidance with Learning Health System Stakeholders for Evaluation of COVID19 projects for national Foundations future funding of projects

AcademyHealth	Travel	Self	$5,000.00

Location(s): Seattle to DC
Estimated Value: $5,000.00
Purpose: Meetings & Conferences
Travel Start Date: 02/06/2018 ***Travel End Date:*** 02/24/2020
Valuation Date: 01/23/2020
Additional Information: Attended Health Data Palooza, Annual Research Meeting and Project Paradigm co sponsored and 2xs listed as RWJ conferences and Meetings

Acumen LLC	Travel	Self	$380.00

Location(s): Seattle to DC
Estimated Value: $380.00
Purpose: PCMP CMS Measures
Travel Start Date: 02/05/2020 ***Travel End Date:*** 02/08/2020
Valuation Date: 01/23/2020
Additional Information: Physician Cost Measure Patient Relationship Code TEP Patient Panel member

AHRQ	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:
Start Date: 04/05/2020 ***End Date:***
Other Compensation:
Additional Information: https://digital.ahrq.gov/acts ACTS AHRQ evidence based care transforming supports stakeholder

Boston Medical Center	Other	Self	$500.00

Category: Other
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2018	$500.00	Estimated

Start Date: 09/18/2018 ***End Date:*** 12/19/2019
Other Compensation:
Additional Information: $500 stipend Open Notes BIDMC presenting PFCC conference and $750 total for Patient Advisory Position stipends

Camden Coalition	Other	Self	$2,300.00

Category: Other
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2020	$1,800.00	Estimated
2019	$500.00	Actual

Start Date: 01/01/2018 ***End Date:***
Other Compensation:
Additional Information: Consumer Scholar work and Travel for Putting Care at the Center conference

Cochrane Consumers	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:
Start Date: 04/11/2020 ***End Date:***
Other Compensation:
Additional Information: Reviewing guidance materials for consumer involvement in reviews for crisis management

Hassanah Consulting	Consultant	Self	$17,000.00

Category: Consultant
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2019	$9,000.00	Actual
2018	$8,000.00	Estimated

Start Date: 01/01/2018 ***End Date:***
Other Compensation:
Additional Information: This is total income, and includes compensation such as stipends listed on CVM, Muslim Resource Guides, Islamic Civic Engagement, general consulting 1099s https://janicetufte.com/cvm-patient-partner

Healthcare for the Homeless Seattle King County	Other	Self	$4,700.00

Category: Other
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2020	$2,500.00	Estimated
2019	$2,200.00	Estimated

Start Date: 01/01/2018 ***End Date:***
Other Compensation:
Additional Information: Consumer Representative advisor

Humana Foundation	Travel	Self	$500.00

Location(s): Seattle to DC
Estimated Value: $500.00
Purpose: Food Insecurity Brochure devlopment

Travel Start Date: 08/01/2019 ***Travel End Date:*** 08/03/2019
Valuation Date: 01/23/2020
Additional Information: Patient Partner informing on food insecurity for a brochure to accompany measures

IHI	Travel	Self	$1,050.00

Location(s): Seattle-Florida
Estimated Value: $1,050.00
Purpose: IHI Forum Scholarship as a Patient Advisor

Travel Start Date: 12/05/2019 ***Travel End Date:*** 12/09/2019
Valuation Date: 01/23/2020
Additional Information: IHI Forum Scholarship as a Patient Advisor

Infectious Disease Society of America	Consultant	Self	$0.00

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:

Year	Amount	Type
2020	$0.00	Actual

Start Date: 09/24/2021 ***End Date:***
Other Compensation:
Additional Information: The Guideline TEP had not been initiated when expected to

ITHS University of Washington	Other	Self	-

Category: Other
Compensation Type: Unpaid
Annual Compensation:

Start Date: 03/20/2020 ***End Date:***
Other Compensation:
Additional Information: COVID 19 Research Prioritization Public Reviewer https://www.iths.org/iths-covid-19-research-resources/covid-19-research-portal/

Ludwig Boltzmann Institut für Experimentelle und Klinische Traumatologie	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:

Start Date: 06/01/2020 ***End Date:***
Other Compensation:
Additional Information:

Mathematica	Other	Self	$800.00

Category: Other
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2018	$200.00	Actual
2017	$600.00	Actual

Start Date: 01/01/2016 ***End Date:*** 12/31/2018
Other Compensation:
Additional Information:

McMaster University	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:

Start Date: 10/15/2020 ***End Date:***
Other Compensation:
Additional Information: Public stakeholder on COVID-END Horizon Scan panel looking at Emerging Issues and Long Covid 19 https://www.mcmasterforum.org/networks/covid-end/resources-to-support-decision-makers/horizon-scans-for-emerging-issues

Minnesota Evidence Practice Center	Other	Self	-

Category: Other
Compensation Type: Unpaid
Annual Compensation:

Start Date: 01/01/2019 ***End Date:***
Other Compensation:
Additional Information: CLPC TEP MN-EPC Public perspective Prostrate Cancer Systematic Review/ Protocol

National Institute on Aging	Other	Self	$750.00

Category: Other
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2020	$500.00	Actual

Start Date: 06/01/2019 ***End Date:***
Other Compensation:
Additional Information: Aging Initiative Advisor

2019	$250.00	Actual

National Quality Forum	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:
Start Date: 09/15/2020 *End Date:*
Other Compensation:
Additional Information: Serving on NQF MAP CC Measurement http://www.qualityforum.org/Project_Pages/MAP_Coordinating_Committee.aspx

National Quality Forum	Other	Self	-

Category: Other
Compensation Type: Other
Annual Compensation:
Start Date: 08/30/2020 *End Date:*
Other Compensation: Stipend
Additional Information:

National Quality Forum	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:
Start Date: 11/10/2020 *End Date:*
Other Compensation:
Additional Information: NQF Risk Adjustment Guidance Committee https://www.qualityforum.org/Risk_Adjustment_Guidance.aspx

National Quality Forum	Travel	Self	$1,000.00

Location(s): Seattle to DC to Seattle
Estimated Value: $1,000.00
Purpose: LTSS work group and Core Set MAP
Travel Start Date: 01/01/2017 *Travel End Date:* 12/31/2018
Valuation Date: 01/29/2020
Additional Information: See CVM

Patient CenteredResearch Institute	Travel	Self	$3,000.00

Location(s): Seattle to DC
Estimated Value: $3,000.00
Purpose: Conference Attendance
Travel Start Date: 01/01/2017 *Travel End Date:* 09/20/2019
Valuation Date: 01/23/2020
Additional Information: PCORI paid for multiple conference scholarships and prioritization projcts

Robert Wood Johnson Foundation	Travel	Self	$1,000.00

Location(s): Seattle to DC
Estimated Value: $1,000.00
Purpose: Paradigm Project HSR
Travel Start Date: 06/14/2019 *Travel End Date:* 06/28/2021
Valuation Date: 01/23/2020
Additional Information: Travel only, no stipends, Health Services Research project (also listed under Academy Health)

Society for Participatory Medicine	Travel	Self	$650.00

Location(s): Seattle to Boston
Estimated Value: $650.00
Purpose: Panel Organizer and presenter SDoH
Travel Start Date: 09/07/2019 *Travel End Date:* 09/10/2019
Valuation Date: 01/23/2020
Additional Information: Travel to Boston as a SPM Planning Committee member and panel presenter

University of Washington Instituite for Translational Health Sciences	Consultant	Self	-

Category: Consultant
Compensation Type: Unpaid
Annual Compensation:
Start Date: 03/22/2020 *End Date:*
Other Compensation:
Additional Information: A professional review committee for COVID19 studies for possible work done at University of Washington

University of Washington SORCE	Other	Self	$2,475.00

Category: Other
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2020	$900.00	Estimated
2019	$1,225.00	Actual
2018	$350.00	Actual

Start Date: 01/01/2017 *End Date:*
Other Compensation:
Additional Information: Patient Advisor on the COSMID project started 2019 on going and Patient Advisor on CERTAIN Patient Advisory Group https://www.becertain.org/projects/diverticulitis-care/cosmid-study (2018 and 2019 has general advising $$ included)

Intellectual Property

Type	Is Licensed	Interest Held By	Value
Other Intellectual Property - Peer Reviewer of Cochrane Protocol Musculoskelet ...	-	Self	-

Description: Peer Reviewer of Cochrane Protocol Musculoskeletal Group for Systematic Review
Yearly Income:
Income Source: none
Additional Information:

Other Intellectual Property - Food Insecurity Brochure to accompany NQF measur	-	Self	-

Description: Food Insecurity Brochure to accompany NQF measures
Yearly Income:
Income Source: NQF/ Human travel only
Additional Information: https://store.qualityforum.org/products/food-insecurity-and-health-overcoming-food-insecurity-through-healthcare-based-interventions document I am included in as a co author

Other Intellectual Property - Restoring the Story and Creating a Valuable Clin ...	-	Self	-
Description: Restoring the Story and Creating a Valuable Clinical Note ***Yearly Income:***	***Income Source:*** 0 ***Additional Information:*** https://www.acpjournals.org/doi/10.7326/M20-0934		
Other Intellectual Property - IHI Institute for Health Improvement Developed ...	-	Self	-
Description: IHI Institute for Health Improvement Developed out webinars for Goals Driven Care / Patient Safety ***Yearly Income:***	***Income Source:*** 1000 ***Additional Information:*** Honorarium though MEF Doha, Qatar conference was cancelled		
Other Intellectual Property - Paradigm Project RWJ Academy Health	-	Self	-
Description: Paradigm Project RWJ Academy Health ***Yearly Income:***	***Income Source:*** Academy Health for travel ***Additional Information:*** https://www.academyhealth.org/ParadigmProject I am serving on Design Team 3 B		
Other Intellectual Property - Development of Communication Resource Guide for ...	-	Self	-
Description: Development of Communication Resource Guide for Low income Individuals, Internet and Phone services ***Yearly Income:***	***Income Source:*** none ***Additional Information:*** Development of communication resources available for low income individuals compiled for COVID19 telehealth and more for WA State Health Care Authority and other organizations		
Other Intellectual Property - MuSE Systematic Review Protocol and Reviews	-	Self	-
Description: MuSE Systematic Review Protocol and Reviews ***Yearly Income:***	***Income Source:*** 0 ***Additional Information:*** Under Development		
Other Intellectual Property - https://nam.edu/patient-and-family-engaged-care- ...	-	Self	-
Description: https://nam.edu/patient-and-family-engaged-care-an-essential-element-of-health-equity/ paper ***Yearly Income:***	***Income Source:*** 0 ***Additional Information:*** https://nam.edu/patient-and-family-engaged-care-an-essential-element-of-health-equity/		
Other Intellectual Property - Low Value Research Work Group AA/Latinx Donaghue ...	-	Self	-
Description: Low Value Research Work Group AA/Latinx Donaghue Foundation ***Yearly Income:***	***Income Source:*** Travel for meeting ***Additional Information:*** https://www.academyhealth.org/blog/2019-12/focus-patients-key-reducing-low-value-care Continuation of this work		
Other Intellectual Property - Building out Core Competencies for Complex Care ...	-	Self	-
Description: Building out Core Competencies for Complex Care meetings and build out of documents ***Yearly Income:***	***Income Source:*** Camden Coalition Travel ***Additional Information:*** https://www.nationalcomplex.care/our-work/blueprint-for-complex-care/core-competencies-working-group/ A member		
Other Intellectual Property - Mitre HealthLab	-	Self	-
Description: Mitre HealthLab ***Yearly Income:***	***Income Source:*** ***Additional Information:*** Webinar provided to Mitre HealthLab on COVID19 Response and Vulnerable Populations King County WA https://janicetufte.com/covid19-vulnerable		
Other Intellectual Property - MuSE Systematic Review Paper	-	Self	-
Description: MuSE Systematic Review Paper ***Yearly Income:***	***Income Source:*** ***Additional Information:*** https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-020-1272-5		

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   COSMID multi site pragmatic randomized trial surgical vs medical management for Diverticulitis Patient Advisor and serving in Board roles. https://www.becertain.org/projects/diverticulitis-care/cosmid-study

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

Yes

ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

Yes

iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

Yes

iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Janice Tufte

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☑ I have interests to report (please list in space below).

☐ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

I am a member of the COSMID multi site pragmatic randomized PCORI trial. Co Chair of the Patient Advisory Committee. I also serve on the Executive and Clinical committees. I receive honoraria for my time.
https://www.becertain.org/projects/diverticulitis-care/cosmid-study

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Janice Tufte

Print Name

Signature

12 /20/20

Date

Sandeep Vijan

Dec 30, 2020 15:29:46 EST
American College of Physicians

Disclosure Purpose: Guideilnes committee/Performance measurement committee

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
Endocrine Society	Other	Self	-

Category: Other
Compensation Type: Unpaid
Annual Compensation:
Start Date: 02/01/2019 *End Date:* 12/31/2019
Other Compensation:
Additional Information: Hypoglycemia performance measure development

Medical School, University of Michigan	Employment	Self	-

Title: Professor, Medical Director
Start Date: 06/24/1992 *End Date:*
Position Description: Professor of Internal Medicine, Director of Analytics/Quality
Additional Information:

National Institute of Health	Grant / Contract	Self	$1,820,000.00

Recipient Name: Regents of the University of Michigan
Grant / Contract Description: Implementation of Evidence-Based Practice for Benign Paroxysmal Positional Vertigo
Grant / Contract Valuation Date: 01/28/2020
Additional Information:
Recipient Type: Institution
Grant / Contract Purpose: Research
Grant / Contract Amount: $1,820,000.00
Contract Start Date: 08/01/2013 *Contract End Date:* 07/31/2019

U.S. Department of Veterans Affairs	Employment	Self	-

Title: Physician
Start Date: 07/01/1997 *End Date:*
Position Description: Physician
Additional Information:

U.S. Department of Veterans Affairs	Grant / Contract	Self	$615,000.00

Recipient Name: Sameer Saini
Grant / Contract Description: Promoting Veteran-Centered Colorectal Cancer Screening
Grant / Contract Amount: $615,000.00
Contract Start Date: 04/01/2014 *Contract End Date:* 03/31/2018
Recipient Type: Individual
Grant / Contract Purpose: Research
Grant / Contract Valuation Date: 01/28/2020
Additional Information:

U.S. Department of Veterans Affairs	Grant / Contract	Self	$900,000.00

Recipient Name: Michele Heisler
Grant / Contract Description: Technologically Enhanced Coaching (TEC): A Program for Improving Diabetes Outcomes
Grant / Contract Valuation Date: 02/01/2014
Additional Information:
Recipient Type: Individual
Grant / Contract Purpose: Research
Grant / Contract Amount: $900,000.00
Contract Start Date: 02/01/2014 *Contract End Date:* 01/31/2018

Wolters Klewer Health, Inc.	Consultant	Self	$4,900.00

Category: Consultant
Compensation Type: Cash
Annual Compensation:
Start Date: 11/15/2011 *End Date:*
Other Compensation:
Additional Information:

Year	Amount	Type
2019	$1,800.00	Estimated
2018	$1,600.00	Estimated
2017	$1,500.00	Estimated

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   None

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**

- **National or chapter staff?**
- **Annals of Internal Medicine editorial staff?**
- **Other (meeting guests, contractors, authors, etc.)**

Yes.

i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

   Yes

ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

   Yes

iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

   Yes

iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

   Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Sandeep Vijan

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Ross EL, Vijan S, Miller EM, Valenstein M, Zivin K. The Cost-Effectiveness of Cognitive Behavioral Therapy Versus Second-Generation Antidepressants for Initial Treatment of Major Depressive Disorder in the United States: A Decision Analytic Model. Ann Intern Med. 2019 Dec 3;171(11):785-795. doi: 10.7326/M18-1480

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Sandeep Vijan

Print Name

Sandeep Vijan 12/30/2020

Signature Date

John Williams

Apr 25, 2020 10:15:48 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Agency for Health Care Policy and Research	Grant / Contract	Self	$4,500.00
Recipient Name: Gillian Sanders *Grant / Contract Description:* Evidence Based Practice Center, Associate Editor *Grant / Contract Amount:* $4,500.00 *Contract Start Date:* 10/01/2014 *Contract End Date:* 09/30/2019		*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Valuation Date:* 03/15/2019 *Additional Information:*	
ArcherDx	Other	Spouse/Partner	-
Category: Other *Start Date:* 07/01/2018 *End Date:* 12/31/2018 *Other Compensation:* *Additional Information:*		*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*	
Associate for Molecular Pathology	Other	Spouse/Partner	-
Category: Other *Start Date:* 09/01/1995 *End Date:* *Other Compensation:* *Additional Information:*		*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*	
Debbie's Dream Foundation	Other	Spouse/Partner	$500.00
Category: Other *Start Date:* 05/13/2018 *End Date:* 05/13/2018 *Other Compensation:*		*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*	

Year	Amount	Type
2018	$500.00	Estimated

Additional Information: Honorarium for a scientific presentation

Duke University	Employment	Self	-
Title: Professor of Medicine and Psychiatry *Start Date:* 07/01/2001 *End Date:*		*Position Description:* Faculty *Additional Information:*	
DurhamVeterans Affairs Medical Center	Employment	Self	-
Title: Staff Physician *Start Date:* 07/01/2001 *End Date:*		*Position Description:* Physician and HSR&D Researcher *Additional Information:*	
General Electric	Stock	Self	$0.00
Percentage Ownership: 0 *Valuation Date:* *Additional Information:*		*Estimated Value:* $0.00 *Divestment Date:* 12/26/2018	
Healthwise	Other	Self	-
Category: Other *Start Date:* 05/25/2017 *End Date:* 06/01/2019 *Other Compensation:* *Additional Information:*		*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*	
HSR&D, U.S.Department of Veterans Affairs	Grant / Contract	Self	$825,000.00
Recipient Name: John W. Williams Jr *Grant / Contract Description:* Evidence Synthesis Program *Grant / Contract Amount:* $825,000.00 *Contract Start Date:* 10/01/2017 *Contract End Date:* 09/30/2020		*Recipient Type:* Individual *Grant / Contract Purpose:* Research *Grant / Contract Valuation Date:* 03/15/2019 *Additional Information:*	
HSR&D, U.S.Department of Veterans Affairs	Other	Self	-
Category: Other *Start Date:* 07/08/1995 *End Date:* 05/01/2018 *Other Compensation:* *Additional Information:*		*Consultant Description:* *Compensation Type:* Unpaid *Annual Compensation:*	

JWW Scientific Consulting,LLC	Other Business Ownership	Self	$32,125.00

Form of Business Description: Provide Medical/Scientific editing and research methods education
Percentage Ownership: 99
Investment Amount: $0.00
Annual Compensation:

Year	Amount	Type
2019	$13,625.00	Actual
2018	$18,500.00	Actual

Ownership Category: Sole Proprietor
Partnership Category: LLC
Investment Amount Valuation Date:
Additional Information:

National Institutes of Health	Grant / Contract	Self	$45,000.00

Recipient Name: Duke University
Grant / Contract Description: Clinical Translational Science Award
Grant / Contract Amount: $45,000.00
Contract Start Date: 10/01/2013 *Contract End Date:* 09/30/2018
Recipient Type: Institution
Grant / Contract Purpose: Research
Grant / Contract Valuation Date: 03/15/2019
Additional Information: JWW Salary support only

Oak Ridge Associated Universities	Employment	Self	-

Title: Consultant
Start Date: 03/12/2015 *End Date:*
Position Description: Consultant to CMMI for CPC+ Program: Behavioral health integration
Additional Information:

Patient Centered Outcomes Research Institute	Grant / Contract	Self	$46,899.00

Recipient Name: John W Williams Jr
Grant / Contract Description: Subcontract from Oregon Health Sciences Center; Associate Editor for PCORI
Grant / Contract Valuation Date: 12/26/2019
Additional Information: Total Costs - 2020
Recipient Type: Individual
Grant / Contract Purpose: Research
Grant / Contract Amount: $46,899.00
Contract Start Date: 06/08/2015 *Contract End Date:* 12/31/2020

Promega	Other	Spouse/Partner	-

Category: Other
Start Date: 06/01/2018 *End Date:* 12/31/2018
Other Compensation:
Additional Information:
Consultant Description:
Compensation Type: Cash
Annual Compensation:

Siemens	Stock	Self	$0.00

Percentage Ownership: 0
Valuation Date:
Additional Information:
Estimated Value: $0.00
Divestment Date: 03/15/2019

Tiantan Hospital	Other	Self	$2,500.00

Category: Other
Start Date: 12/12/2019 *End Date:* 12/12/2019
Other Compensation:
Consultant Description:
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2019	$2,500.00	Actual

Additional Information: Honoraria for teaching a research methods workshop

University of Washington	Data And Safety Monitoring	Self	$500.00

Category: Data And Safety Monitoring
Start Date: 06/22/2016 *End Date:*
Other Compensation:
Consultant Description:
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2019	$500.00	Actual

Additional Information:

Intellectual Property

Type	Is Licensed	Interest Held By	Value
Other Intellectual Property - Chapter in UpToDate (Depression Screening)	-	Self	$935.00

Description: Chapter in UpToDate (Depression Screening)
Yearly Income:

Amount	Type	Year	Payment Receipt
$935.00	Actual	2018	Direct Payment

Income Source: Wolters Klewer
Additional Information:

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: John Williams

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Nieuwsma JA, Williams JW Jr, Namdari N, Washam JB, Raitz G, Blumenthal JA, Jian W, Yapa R, McBroom AJ, Lallinger K, Schmidt R, Kosinski AS, Sanders GD. Diagnostic Accuracy of Screening Tests and Treatment for Post-Acute Coronary Syndrome Depression: A Systematic Review. Ann Intern Med 2017 Nov 21;167(10):725-735. doi: 10.7326/M17-1811. Epub 2017 Nov 14. PMID: 29132152 Abstracted in ACP Journal Wise

Basu S, Landon BE, Williams JW Jr, Bitton A, Song Z, Phillips RS. Behavioral health integration into primary care: a microsimulation of financial implications for practices. J Gen Int Med 2017 Dec;32(12):1330-1341. PMID: 28900839

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

John W. Williams Jr.

Print Name

John W Williams Jr Digitally signed by John W Williams Jr
Date: 2020.12.21 05:49:18 -05'00'

Signature Date

Williams – Publication List

Nieuwsma JA, Williams JW Jr, Namdari N, Washam JB, Raitz G, Blumenthal JA, Jian W, Yapa R, McBroom AJ, Lallinger K, Schmidt R, Kosinski AS, Sanders GD. Diagnostic Accuracy of Screening Tests and Treatment for Post-Acute Coronary Syndrome Depression: A Systematic Review. Ann Intern Med 2017 Nov 21;167(10):725-735. doi: 10.7326/M17-1811. Epub 2017 Nov 14. PMID: 29132152 Abstracted in ACP Journal Wise

Basu S, Landon BE, Williams JW Jr, Bitton A, Song Z, Phillips RS. Behavioral health integration into primary care: a microsimulation of financial implications for practices. J Gen Int Med 2017 Dec;32(12):1330-1341. PMID: 28900839

Williams JW Jr, Nieuwsma JA, Namdari N, Washam JB, Raitz G, Blumenthal JA, Jiang W, Yapa R, McBroom AJ, Lallinger K, Schmidt R, Kosinski AS, Sanders GD. Diagnostic Accuracy of Screening Tests and Treatment of Post-Acute Coronary Syndrome Depression: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Nov. PMID: 29697225. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Abstracted in ACP Journal Club

Gierisch JM, Fish LJ, Calhoun PS, Williams JW Jr., Bosworth HB, Olsen, MK, Jeffreys AS, Berkowitz TSZ, Chapman JG, Bastian LA. Impact of Adjunctive Mood Management on Telephone-Based Smoking Cessation Among Veterans with Depression: Results of a Comparative Effectiveness Trial. VA HSR&D National Research Meeting, October 2019; Washington, D.C

Fish LJ, Chapman JG, Feffreys AS, Bastian LA, Bosworth HB, Williams JW Jr, Calhoun PS, Olsen MK, Falkovic MB, Howard TA, Juntilla KA, Berkowitz TSZ, Gierish JM. What Factors Influence Engagement in a Telephone-delivered Smoking Cessation Intervention Among Smokers with Depression? Society for Behavioral Medicine. Washington, DC; March 2019

Williams JW Jr, Nieuwsma JA. Screening for Depression, In Fletcher RH (Section Editor), Sokok HN (Senior Deputy Editor) UpToDate, 2013, UpToDate Inc. I receive royalties annually for this chapter as disclosed on COI statement

Jacqueline Fincher

Aug 14, 2020 14:25:51 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021, 2020 ACP Georgia Chapter Meeting Faculty and Planning Committee

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Cadence	Stock	Spouse/Partner	$1,200,000.00
Percentage Ownership: *Valuation Date:* 04/08/2019 *Additional Information:* self and spouse		*Estimated Value:* $1,200,000.00 *Divestment Date:*	
Center for Primary Care	Employment	Spouse/Partner	-
Title: Partner, Staff Physician *Start Date:* 06/01/2015 *End Date:*		*Position Description:* Fiduciary, Clinical Care of patients *Additional Information:*	
Center for Primary Care	Employment	Self	-
Title: Partner, Staff Physician *Start Date:* 06/01/2015 *End Date:*		*Position Description:* Fiduciary responsibility as Partner, Full time clinical work taking care of patients *Additional Information:*	
Johnson and Johnson	Stock	Spouse/Partner	$17,000.00
Percentage Ownership: *Valuation Date:* 04/08/2019 *Additional Information:* spouse and self		*Estimated Value:* $17,000.00 *Divestment Date:*	
Procter and Gamble	Stock	Self	$33,000.00
Percentage Ownership: *Valuation Date:* 04/08/2019 *Additional Information:* held by spouse and me		*Estimated Value:* $33,000.00 *Divestment Date:*	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

        i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

        Yes

        ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

        Yes

        iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

        Yes

        iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

        Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Jacqueline W. Fincher, MD

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Jacqueline W. Fincher, MD

Print Name

Signature

1/26/21

Date

Heather Gantzer

Apr 29, 2020 17:41:01 EDT
American College of Physicians

Disclosure Purpose: submitting an article to Annals of Internal Medicine

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Abbott	Employment	Other - Daughter Emma Gantzer	-
Title: Biomedical Engineer ***Start Date:*** 04/01/2018 ***End Date:***		***Position Description:*** designs medical devices currently cardiac ablation catheters ***Additional Information:***	
Barr Engineering	Employment	Spouse/Partner	-
Title: Senior environmental scientist ***Start Date:*** 08/08/2004 ***End Date:***		***Position Description:*** engineer ***Additional Information:***	
NelsonSmith LLP	Employment	Other - daughter Edwina Gantzer	-
Title: legal office assistance ***Start Date:*** 08/01/2015 ***End Date:***		***Position Description:*** assists in immigration law firm ***Additional Information:***	
Nordson	Employment	Other - daughter Beatrice Gantzer	-
Title: Quality Systems Specialist ***Start Date:*** 05/01/2015 ***End Date:***		***Position Description:*** documentation and regulatory issues re medical devices ***Additional Information:***	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   I am the Chair of the Board of Regents of the ACP and I receive a stipend for this. I am employed as a primary care internist at Park Nicollet Clinic in St. Louis Park MN, and also a nocturnist on the Methodist Hospital Hospitalist Service in St. Louis Park MN

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

         Yes

      ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board**

of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."

Yes

iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

Yes

iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Heather E. Gantzer

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Heather E Gantzer

Print Name

Heather Gantzer Digitally signed by Heather Gantzer Date: 2021.01.12 07:40:07 -06'00' 1-12-2021

Signature Date

Laura Baldwin

Jan 02, 2020 11:44:34 EST
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2019

Summary of Financial Interests

I do not have any financial interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations

- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Laura Baldwin

Print Name

Signature

1/4/21

Date

Wayne Bylsma

May 03, 2020 10:24:23 EDT
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2020 - 2021, Annual Staff Disclosure 2020

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Employment	Self	-
Title: Chief Operating Officer ***Start Date:*** 10/15/1997 ***End Date:***		***Position Description:*** Oversees operations of the organization ***Additional Information:***	
Ewing Cole	Employment	Spouse/Partner	-
Title: Project Manager ***Start Date:*** 01/01/1998 ***End Date:***		***Position Description:*** Manages building/renovation of health care facilities ***Additional Information:***	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Wayne Bylsma

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Wayne Bylsma

Print Name

Wayne H. Bylsma Digitally signed by Wayne H. Bylsma Date: 2020.12.21 18:58:34 -05'00' 12.21.2020

Signature Date

Kate Carroll

Jan 05, 2021 15:40:31 EST
American College of Physicians

Disclosure Purpose: January 2021 CGC, PMC, SMPC meetings, September 2020 CGC, PMC, SMPC meetings

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Employment	Self	-
Title: Manager, Clinical Policy *Start Date:* 08/26/2014 *End Date:*	*Position Description:* *Additional Information:*		
The Beasley Firm, LLC	Employment	Spouse/Partner	-
Title: Technology Specialist *Start Date:* 09/01/2009 *End Date:*	*Position Description:* *Additional Information:*		

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Kate Carroll

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Kate Carroll

Print Name

Kate Carroll Digitally signed by Kate Carroll Date: 2021.01.05 15:34:50 -05'00' 1/5/2021

Signature Date

Allison Ewing

Jan 23, 2020 13:28:43 EST
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2020

Summary of Financial Interests

I do not have any financial interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations

- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Allison Ewing

Print Name

Allison Ewing Digitally signed by Allison Ewing
Date: 2021.01.05 13:56:44 -05'00'

Signature Date

Andrew Hachadorian

Aug 07, 2020 10:17:31 EDT
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2020 - 2021

Summary of Financial Interests

I do not have any financial interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Andrew Hachadorian

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☒ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☒ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☒ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☒ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations
By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Andrew Hachadorian
Print Name

Andrew Hachadorian 1/4/2021
Signature Date

Shannon Merillat

Jan 05, 2021 10:05:15 EST
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2020 - 2021

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American Academy of Neurology	Employment	Self	-
Title: Senior Guideline Development Program Manager *Start Date:* 11/12/2014 *End Date:* 08/21/2020		*Position Description:* Manage and coordinate development of clinical practice guidelines on topics relevant to neurological disease treatment, diagnosis, prognosis, and screening *Additional Information:*	
Health Dimensions Group	Employment	Spouse/Partner	-
Title: Document Production Coordinator *Start Date:* 08/20/2020 *End Date:*		*Position Description:* Responsible for all aspects of document and presentation preparation and production *Additional Information:* https://healthdimensionsgroup.com/about/	
HealthPartners	Employment	Spouse/Partner	-
Title: Purchasing Agent *Start Date:* 03/13/2018 *End Date:* 08/14/2020		*Position Description:* Procurement of medical equipment and supplies and contract management for orthopedic and laboratory service lines. *Additional Information:* Health Partners is an integrated, nonprofit health care provider and health insurance company https://www.healthpartners.com/about/	
M*Modal	Employment	Spouse/Partner	-
Title: Product Marketing Specialist *Start Date:* 12/15/2017 *End Date:* 03/09/2018		*Position Description:* Developed white papers and marketing materials *Additional Information:* https://www.3m.com/3M/en_US/company-us/about-3m/	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Shannon Merillat

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Shannon Merillat

Print Name

Shannon Merillat Digitally signed by Shannon Merillat Date: 2021.01.05 08:54:51 -06'00' 1/5/2021

Signature Date

Darilyn Moyer

Nov 06, 2020 11:43:18 EST
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021, Faculty - MA ACP Annual Chapter Mtg

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Employment	Self	-
Title: EVP/CEO ***Start Date:*** 01/01/2017 ***End Date:*** ***Position Description:*** EVP/CEO ***Additional Information:***			
American Medical Association	Other	Self	-
Category: Other ***Compensation Type:*** Unpaid ***Annual Compensation:*** ***Start Date:*** 01/01/2017 ***End Date:*** ***Other Compensation:*** ***Additional Information:***			
Council of Medical Subspecialty Societies	Fiduciary Officer	Self	-
Official Title: CMSS Board Member/President ***Compensation Type:*** Unpaid ***Start Date:*** 10/27/2020 ***End Date:*** ***Annual Compensation:*** ***Additional Information:*** ***Position Description:*** CMSS Board member/President ***Other Compensation:***			
Department of Internal Medicine, University of Nebraska Medical Center	Other	Self	-
Category: Other ***Compensation Type:*** Other ***Annual Compensation:*** ***Start Date:*** 03/18/2018 ***End Date:*** 03/19/2018 ***Other Compensation:*** Stipend turned over to ACP ***Additional Information:***			
Inspira Health Woodbury	Employment	Spouse/Partner	-
Title: Physician Staff- Inspira Medical Group ***Start Date:*** 01/01/2017 ***End Date:*** ***Position Description:*** Salaried Pulmonary Critical Care Sleep Physician ***Additional Information:*** Inspira Group Physicians 2950 College Drive Suite 1E Vineland, NJ 08360			
PCPCC	Fiduciary Officer	Self	-
Official Title: PCPCC Board Chair ***Compensation Type:*** Unpaid ***Start Date:*** 01/01/2017 ***End Date:*** ***Annual Compensation:*** ***Additional Information:*** ***Position Description:*** PCPCC Board Chair ***Other Compensation:***			
Temple University	Fiduciary Officer	Self	-
Official Title: Lewis Katz School of Medicine at Temple University Medical Alumni Board ***Compensation Type:*** Unpaid ***Start Date:*** 01/01/2017 ***End Date:*** ***Annual Compensation:*** ***Additional Information:*** ***Position Description:*** Board member ***Other Compensation:***			

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Darilyn Moyer

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☒ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☒ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☒ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☒ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Darilyn V. Moyer

Print Name

Darilyn V. Moyer 1/5/21

Signature Date

Amir Qaseem

Jan 11, 2021 19:06:11 EST
American College of Physicians

Disclosure Purpose: staff

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Employment	Self	-
Title: Vice President *Start Date:* 12/07/2003 *End Date:*	*Position Description:* Clinical Policy *Additional Information:*		
Centers for Disease Control and Prevention	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2016 *End Date:* *Other Compensation:* *Additional Information:* don't have the exact dates		
Cochrane	Other	Self	-
Category: Other *Compensation Type:* *Annual Compensation:*	*Start Date:* 06/01/2019 *End Date:* *Other Compensation:* *Additional Information:*		
Cochrane	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2020 *End Date:* *Other Compensation:* *Additional Information:* dont have exact start date		
COVID-19 Evidence Network to support Decision-making	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 05/01/2020 *End Date:* *Other Compensation:* *Additional Information:* Dont have exact start date		
Dynamed	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2013 *End Date:* *Other Compensation:* *Additional Information:* I do not know the exact start date.		
Dynamed	Other	Self	-
Category: Other *Compensation Type:* Other *Annual Compensation:*	*Start Date:* 07/01/2014 *End Date:* *Other Compensation:* honorarium *Additional Information:*		
European Commission	Other	Self	-
Category: Other *Compensation Type:* *Annual Compensation:*	*Start Date:* 01/01/2021 *End Date:* *Other Compensation:* *Additional Information:*		
GRADE Working Group	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2003 *End Date:* *Other Compensation:* *Additional Information:* I do not have the exact start date		
Guidelines International Network	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 08/01/2010 *End Date:* *Other Compensation:* *Additional Information:* dont have exact start date		
Measures Application Partnership	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2014 *End Date:* *Other Compensation:* *Additional Information:* I do not remember the exact start date.		
MedBiquitous	Other	Self	-
Category: Other	*Start Date:* 01/01/2013 *End Date:* 01/01/2019		

Compensation Type: *Annual Compensation:*	*Other Compensation:* *Additional Information:* Do not have exact start or end dates		
National Academies of Sciences, Engineering, and Medicine	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2019 *End Date:* *Other Compensation:* *Additional Information:* don't have the exact dates		
National Quality Forum	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2015 *End Date:* *Other Compensation:* *Additional Information:* Don't have the exact start date		
National Quality Forum	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2019 *End Date:* 07/01/2020 *Other Compensation:* *Additional Information:* don't have the exact dates		
National Quality Forum	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2018 *End Date:* *Other Compensation:* *Additional Information:* don't have the exact dates		
PCPI	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2017 *End Date:* 07/31/2020 *Other Compensation:* *Additional Information:* don't have the exact start date		
PCPI	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2015 *End Date:* 07/31/2020 *Other Compensation:* *Additional Information:* Do not have exact start date		
RIGHT Working Group	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 01/01/2014 *End Date:* *Other Compensation:* *Additional Information:* I do not have the exact start date		
Thomas Jefferson University	Other	Self	-
Category: Other *Compensation Type:* *Annual Compensation:*	*Start Date:* 01/01/2017 *End Date:* *Other Compensation:* *Additional Information:*		
Women's Preventive Services Initiative	Other	Self	-
Category: Other *Compensation Type:* Unpaid *Annual Compensation:*	*Start Date:* 05/01/2016 *End Date:* *Other Compensation:* *Additional Information:* don't have the exact dates		

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

Yes

iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Amir Qaseem

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

N/A

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

N/A

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

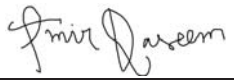
Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Amir Qaseem

Print Name



Digitally signed by Amir Qaseem
Date: 2021.01.12 11:05:11 -05'00'

Signature Date

Patricia Siemion

Jan 05, 2021 10:03:50 EST
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2019, Annual Staff Disclosure 2020 - 2021

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Employment	Self	-
Title: Coordinator, Clinical Policy ***Start Date:*** 04/14/2014 ***End Date:***	***Position Description:*** Provides administrative support to the Clinical Policy Department and CGC, PMC and SMPC meetings and webinars. ***Additional Information:***		
International Association of Bridge, Structural, Ornamental and Reinforcing Ironworkers	Employment	Spouse/Partner	-
Title: ***Start Date:*** 06/01/1989 ***End Date:***	***Position Description:*** ***Additional Information:***		

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Patricia Siemion

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Patricia Siemion

Print Name

Patricia Siemion Digitally signed by Patricia Siemion Date: 2021.01.05 10:12:07 -05'00' January 5, 2021

Signature Date

Samantha Tierney

Jul 28, 2020 13:03:32 EDT
American College of Physicians

Disclosure Purpose: Annual Staff Disclosure 2020 - 2021

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Employment	Self	-
Title: Senior Scientist, Clinical Policy ***Start Date:*** 06/15/2020 ***End Date:*** ***Position Description:*** Leading the performance measurement strategy ***Additional Information:***			
Boehringer Ingelheim	Other	Self	-
Category: Other ***Start Date:*** 01/01/2018 ***End Date:*** 12/31/2018 ***Other Compensation:*** ***Additional Information:*** As a result of my participation at the following stakeholder meeting, my former employer received honoraria: Boehringer Ingelheim, Stakeholder, Advancing Quality for Patients with Type 2 Diabetes and Established Cardiovascular Disease, 2018 ***Consultant Description:*** ***Compensation Type:*** Cash ***Annual Compensation:***			
Discern Health	Other	Self	-
Category: Other ***Start Date:*** 01/01/2018 ***End Date:*** 03/01/2020 ***Other Compensation:*** ***Additional Information:*** As a result of my participation on the following roundtables/stakeholder meetings/work groups, my former employer has received honoraria: Discern Health, interviewee, Understanding Quality Measurement Priorities for Breast Cancer, 2020 Discern Health, Expert Panel Member, Cancer Immunotherapy Quality Measurement, 2019 Discern, Advisor, Telehealth Measurement Gaps, 2018 ***Consultant Description:*** ***Compensation Type:*** Cash ***Annual Compensation:***			
PCPI Foundation	Employment	Self	-
Title: Senior Director, Measurement Science ***Start Date:*** 01/01/2017 ***End Date:*** 06/12/2020 ***Position Description:*** Orchestrate daily activities of the Measurement Science Program, developing and implementing key performance measures, and monitoring performance to uphold market competitiveness. ***Additional Information:*** My salary at the PCPI was supported by services provided as a contractor and subcontractor to CMS and non-profit organizations for measure development, specification, testing and endorsement.			
Pharmacy Quality Alliance (PQA)	Other	Self	-
Category: Other ***Start Date:*** 01/01/2019 ***End Date:*** 12/31/2019 ***Other Compensation:*** ***Additional Information:*** As a result of my participation on the following roundtable, my former employer has received honoraria: PQA, roundtable member, Patient Engagement Rubric, 2019 ***Consultant Description:*** ***Compensation Type:*** Cash ***Annual Compensation:***			

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   None

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

         Yes

ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

Yes

iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

Yes

iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Samantha Tierney

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☑ I have interests to report (please list in space below).

☐ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

I have developed measures related to depression around 2010 and maintained a CMS stewarded measure related to screening and follow up for depression.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Samantha Tierney

Print Name

Samantha Tierney Digitally signed by Samantha Tierney Date: 2021.01.09 13:04:30 -05'00' 1/9/2020

Signature Date

Itziar Etxeandia Ikobaltzeta

Mar 17, 2020 14:11:28 EDT
American College of Physicians

Disclosure Purpose: Annual Governance Disclosure 2020-2021

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
American College of Physicians	Consultant	Self	-
Category: Consultant *Start Date:* 09/01/2018 *Other Compensation:* *Additional Information:*	*End Date:*	*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*	
Cochrane Response	Consultant	Self	-
Category: Consultant *Start Date:* 07/01/2018 *Other Compensation:* *Additional Information:*	*End Date:* 02/15/2019	*Consultant Description:* *Compensation Type:* Cash *Annual Compensation:*	
INSTIT.SALUD PUBLICAY LABORAL NAVARRA	Consultant	Self	-
Category: Consultant *Start Date:* 01/01/2018 *Other Compensation:* *Additional Information:*	*End Date:* 12/31/2019	*Consultant Description:* *Compensation Type:* Cash, Unpaid *Annual Compensation:*	
McMaster University MacGRADE Centre	Consultant	Self	-
Category: Consultant *Start Date:* 01/01/2018 *Other Compensation:* *Additional Information:*	*End Date:* 07/31/2019	*Consultant Description:* *Compensation Type:* Cash, Unpaid *Annual Compensation:*	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Itziar Etxeandia Ikobaltzeta

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☐ I have publications to report (please list in space below).

☑ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

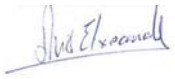
Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Itziar Etxeandia Ikobaltzeta

Print Name



2021.01.05 16:16:49 +01'00'

Signature Date

Jennifer Yost

Aug 21, 2020 13:53:05 EDT
American College of Physicians

Disclosure Purpose: CGC/PMC/SMPC Meetings

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Canadian Institutes of Health Research	Grant / Contract	Self	$22,600.00

Recipient Name: Dr. Sandra Carroll
Grant / Contract Description: Following the C-SPIN Roadmap: Realizing Meaningful Patient Engagement
Grant / Contract Valuation Date: 03/01/2016
Additional Information:
Recipient Type: Individual
Grant / Contract Purpose: Research
Grant / Contract Amount: $22,600.00
Contract Start Date: 03/01/2016
Contract End Date: 02/28/2018

Canadian Institutes of Health Research	Grant / Contract	Self	$226,000.00

Recipient Name: Dr. Michael McGillion
Grant / Contract Description: THE SMArT VIEW, CoVeRed
Grant / Contract Amount: $226,000.00
Contract Start Date: 03/01/2016
Contract End Date: 02/28/2018
Recipient Type: Individual
Grant / Contract Purpose: Research
Grant / Contract Valuation Date: 03/01/2016
Additional Information:

Canadian Institutes of Health Research	Grant / Contract	Self	$9,310,000.00

Recipient Name: Dr. Michael McGillion
Grant / Contract Description: The SMArT VIEW, CoVeRed
Grant / Contract Amount: $9,310,000.00
Contract Start Date: 10/15/2015
Contract End Date: 09/30/2019
Recipient Type: Individual
Grant / Contract Purpose: Research
Grant / Contract Valuation Date: 10/15/2015
Additional Information:

COVID-END	Other	Self	-

Category: Other
Start Date: 05/01/2020
End Date:
Other Compensation:
Additional Information:
Consultant Description:
Compensation Type: Unpaid
Annual Compensation:

Evidence Based Research Network	Fiduciary Officer	Self	-

Official Title: Steering Committee Member
Compensation Type: Unpaid
Start Date: 10/01/2016
End Date:
Annual Compensation:
Additional Information:
Position Description:
Other Compensation:

Evidence Synthesis International	Fiduciary Officer	Self	-

Official Title: Secretariat
Compensation Type: Unpaid
Start Date: 03/01/2018
End Date:
Annual Compensation:
Additional Information:
Position Description: Organize and support activities of the organisation
Other Compensation:

McMaster University	Employment	Self	-

Title: Assistant Professor
Start Date: 06/01/2010
End Date: 06/30/2017
Position Description:
Additional Information:

Sigma Theta Tau International	Fiduciary Officer	Self	-

Official Title: President - Alpha Nu Chapter
Compensation Type: Unpaid
Start Date: 09/01/2019
End Date: 08/31/2021
Annual Compensation:
Additional Information:
Position Description: President - Alpha Nu Chapter
Other Compensation:

University of Bologna	Other	Self	$5,213.19

Category: Other
Start Date: 11/16/2019
End Date: 11/22/2019
Other Compensation:
Consultant Description:
Compensation Type: Cash
Annual Compensation:

Year	Amount	Type
2019	$5,213.19	Actual

Additional Information: Guest Lecturer			
Villanova University	Employment	Self	-
Title: Associate Professor ***Start Date:*** 08/22/2017	***End Date:***	***Position Description:*** ***Additional Information:***	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   N/A

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

         Yes

      ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

         Yes

      iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

         Yes

      iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

         Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the last page)

Name: Jennifer Yost

Disclosures of Interests: Supplemental Questions for Clinical Guidelines Committee and Scientific Medical Policy Committee

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: COVID-19; Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the above topic areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Qaseem, A., Yost, J., Etxeandia-Ikobaltzeta, I., Miller, M., Abraham, G. M., Obley, A. J., Forciea, M. A., Jokela, J. A., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. Should remdesivir be used for the treatment of patients with COVID-19? Rapid, living practice points from the American College of Physicians (Version 2). Submitted to Annals of Internal Medicine December 18, 2020.

Qaseem, A., Yost, J., Forciea, M., Jokela, J., Miller, M., Obley, A. J., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. The Development of Rapid, Living Practice Points: Summary of Methods from the Scientific

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Disclosures of Interests: Supplemental Questions for Performance Measurement Committee

Please review the following measures or topic areas and report any intellectual interests held by you or any household members that may be relevant to the measures or topic areas under discussion.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas:

Please review the list of measures in the attached Word/Excel document and other topic areas listed above. The PMC will review these measures and other topics during the upcoming meeting.

Within the last 3 years, have you or any household members contributed towards the development, testing and/or maintenance of one of these measures or a competing measure (measure on the same topic)?

☐ Yes (please provide additional details below).

☑ No

Within the last 3 years, have you or any household members published on any of the clinical topic areas covered by these measures or other topics areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog)

☐ Yes (please provide additional details below).

☑ No

If you answered yes to either question above, please list any relevant measures publications in space below (or send list of relevant measures/publications as attachment). Otherwise, you may leave blank.

American College of Physicians
Department of Clinical Policy
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Jennifer Yost

Print Name

Jennifer Yost Digitally signed by Jennifer Yost Date: 2021.01.11 09:27:23 -05'00' Jan 11, 2021

Signature Date

Qaseem, A., Yost, J., Etxeandia-Ikobaltzeta, I., Miller, M., Abraham, G. M., Obley, A. J., Forciea, M. A., Jokela, J. A., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. Should remdesivir be used for the treatment of patients with COVID-19? Rapid, living practice points from the American College of Physicians (Version 2). Submitted to Annals of Internal Medicine December 18, 2020.

Qaseem, A., Yost, J., Forciea, M., Jokela, J., Miller, M., Obley, A. J., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. The Development of Rapid, Living Practice Points: Summary of Methods from the Scientific Medical Policy Committee of the American College of Physicians. Submitted to Annals of Internal Medicine November 23, 2020.

Qaseem, A., Etxeandia-Ikobaltzeta, I., Yost, J., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. (2020). Update alert: What is the effectiveness of N95 respirators, surgical masks, and cloth masks in community and healthcare settings for prevention of COVID-19? What is the effectiveness for re-use or extended use of N95 respirators for prevention of COVID-19? Living Practice Points from the American College of Physicians. Submitted to Annals of Internal Medicine. doi: 10.7326/L20-1268.

Qaseem, A., Yost, J., Etxeandia-Ikobaltzeta, I., Miller, M., Abraham, G. M., Obley, A. J., Forciea, M. A., Jokela, J. A., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. Should remdesivir be used for the treatment of patients with COVID-19? Rapid, living practice points from the American College of Physicians (Version 1). (2020). Annals of Internal Medicine. doi: 10.7326/M20-5831

Qaseem, A., Yost, J., Etxeandia-Ikobaltzeta, I., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. (2020). Update alert 2: Should clinicians use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of COVID-19? Living practice points from the American College of Physicians. Annals of Internal Medicine, 173(5), W88-W89. doi: 10.7326/L20-1007

Qaseem, A., Etxeandia-Ikobaltzeta, I., Yost, J., Miller, M., Abraham, G. M., Obley, A. J., Forciea, M. A., Jokela, J. A., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. (2020). What is the effectiveness of N95 respirators, surgical masks, and cloth masks in community and healthcare settings for prevention of COVID-19? What is the effectiveness for re-use or extended use of N95 respirators for prevention of COVID-19? Living Practice Points from the American College of Physicians (Version 1). Annals of Internal Medicine. doi: 10.7326/M20-3234

Qaseem, A., Yost, J., Etxeandia-Ikobaltzeta, I., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. (2020). Update alert: Should clinicians use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of COVID-19? Living practice points from the American College of Physicians. Annals of Internal Medicine, 173(2), W48-W51. doi: 10.7326/M20-3862

Qaseem, A., Yost, J., Etxeandia-Ikobaltzeta, I., Miller, M., Abraham, G. M., Obley, A. J., Forciea, M. A., Jokela, J. A., Humphrey, L. L., for the Scientific Medical Policy Committee of the American College of Physicians. (2020). Should clinicians use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of COVID-19? (Version 1) Annals of Internal Medicine. doi: 10.7326/M20-1998

Chelsea Ayers

Dec 22, 2020 14:50:47 EST
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Interests

I do not have any interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
    - **ACP board, committee, council, task force, and/or other governance group?**
    - **Chapter Council or other Chapter leadership role?**
    - **National or chapter staff?**
    - **Annals of Internal Medicine editorial staff?**
    - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

    You are not disclosing any interests to this organization.

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Chelsea Ayers

Print Name

Chelsea K Ayers 1566561 Digitally signed by Chelsea K Ayers 1566561 Date: 2020.12.22 11:51:29 -08'00' 12/22/2020

Signature Date

Rochelle Fu

Dec 24, 2020 20:03:28 EST
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Interests

I do not have any interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   No additional information

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

   Yes.

   i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

      Yes

   ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

      Yes

   iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

      Yes

   iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

      Yes

   You are not disclosing any interests to this organization.

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Rongwei (Rochelle) Fu

Print Name

Rongwei (Rochelle) Fu Digitally signed by Rongwei (Rochelle) Fu
Date: 2020.12.24 17:08:15 -08'00' 12/24/2020

Signature Date

Curtis Harrod

Dec 22, 2020 14:21:37 EST
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Interests

Company or Organization

Entity	Type	Interest Held By	Value
Oregon Health & Science University	Employment	Self	-

Title: Research Director
Start Date: 11/17/2014
End Date:
Position Description: I provide oversight on methods and direct supervision to researchers.
Additional Information:

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**
    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Curtis Harrod

Print Name

Curtis Harrod Digitally signed by Curtis Harrod Date: 2020.12.22 11:37:57 -08'00' 12/22/2020

Signature Date

Brittany Lazur

Dec 22, 2020 14:31:09 EST
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Interests

I do not have any interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    No.

    You are not disclosing any interests to this organization.

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Brittany Lazur

Print Name

Brittany Lazur Digitally signed by Brittany Lazur Date: 2020.12.22 11:34:45 -08'00' 12-22-20

Signature Date

Mandi Mizuta

Dec 22, 2020 21:59:47 EST
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Interests

I do not have any interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
    - **ACP board, committee, council, task force, and/or other governance group?**
    - **Chapter Council or other Chapter leadership role?**
    - **National or chapter staff?**
    - **Annals of Internal Medicine editorial staff?**
    - **Other (meeting guests, contractors, authors, etc.)**

    Yes.

    i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

    Yes

    ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

    Yes

    iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

    Yes

    iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

    Yes

    You are not disclosing any interests to this organization.

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Gaelen Adam

Dec 21, 2020 11:17:18 EST
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Interests

I do not have any interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    No.

    You are not disclosing any interests to this organization.

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Gaelen P. Adam

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Balk EM, Adam GP, Cao W, Danko K, Bhuma MR, Mehta S, Saldanha IJ, Beland MD, Shah N. Management of Colonic Diverticulitis. Comparative Effectiveness Review No. 233. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015- 00002-I.) AHRQ Publication No. 20(21)-EHC025. Rockville, MD: Agency for Healthcare Research and Quality; October 2020. DOI: https://doi.org/10.23970/AHRQEPCCER233.

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Gaelen P. Adam

Print Name

Gaelen Adam Digitally signed by Gaelen Adam Date: 2020.12.21 11:13:39 -05'00' 12/21/20

Signature Date

Ethan Balk

Aug 14, 2020 10:34:00 EDT
American College of Physicians

Disclosure Purpose: Contractor/Guest Annual Disclosure 2020 - 21

Summary of Financial Interests

Company or Organization

Entity	Type	Interest Held By	Value
Agency for Healthcare Research and Quality	Grant / Contract	Self	$350,000.00
Recipient Name: Brown Evidence-based Practice Center *Grant / Contract Description:* Multi year contract. Specific contract to conduct systematic review (nominated by ACP) *Grant / Contract Valuation Date:* 03/29/2019 *Additional Information:*		*Recipient Type:* Institution *Grant / Contract Purpose:* Research *Grant / Contract Amount:* $350,000.00 *Contract Start Date:* 03/29/2019 *Contract End Date:*	
Brown University	Employment	Self	-
Title: Associate Professor *Start Date:* 07/01/2014 *End Date:*		*Position Description:* Center Co-Director *Additional Information:*	

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**

   None

2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

   a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
      - **ACP board, committee, council, task force, and/or other governance group?**
      - **Chapter Council or other Chapter leadership role?**
      - **National or chapter staff?**
      - **Annals of Internal Medicine editorial staff?**
      - **Other (meeting guests, contractors, authors, etc.)**

      Yes.

      i. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Disclosure of Interests and Management of Conflicts Policy.**

      Yes

      ii. **I, the undersigned, enter into the Non-Disclosure Agreement between myself and the American College of Physicians, which governs the disclosure and furnishing of ACP's members of the Board of Regents, Board of Governors, Committees, Councils, Governors-elect and Chapter Personnel in any such Work Group of ACP, with information developed for ACP, deemed "Proprietary Information."**

      Yes

      iii. **I, the undersigned, intending to be legally bound, hereby declare and agree to terms of participation in the ACP Group activities of ACP as specified in the ACP Intellectual Property Policy.**

      Yes

      iv. **I, the undersigned, acknowledge I have read and agree to abide by the American College of Physician's Anti-Harassment Policy.**

      Yes

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Please enter your name: (You will need to sign on the second page)

Name: Ethan Balk, MD MPH

Disclosures of Interests: Supplemental Questions

Please review the following topic areas and report any intellectual interests held by you or any household members that may be relevant to the topic areas.

- *Intellectual interests* are defined as academic ideas or activities or specific viewpoints and relate to such issues as academic advancement, clinical revenue streams, or community standing. Examples of types of intellectual interests include publications, unpaid participation on workgroups, panels, or committees, or membership in special interest groups.

Topic Areas: Diverticulitis; Depression; Osteoporosis

Within the past 3 years, have you or any household members published on any of the areas? Please include both peer-reviewed and non-peer-reviewed sources (e.g., newspaper op-ed; blog).

☑ I have publications to report (please list in space below).

☐ I have no publications to report.

Do you or any household members have any other intellectual interests related to any of the areas above?

☐ I have interests to report (please list in space below).

☑ I have no interest to report.

If you answered yes to either of the above questions, please provide additional details on the relevant interests (if not already captured in the Convey System) and list any relevant publications in the space below (or send a list of relevant publications as attachment).

Report for AHRQ:
Balk EM, Adam GP, Cao W, Danko K, Bhuma MR, Mehta S, Saldanha IJ, Beland MD, Shah N. Management of Colonic Diverticulitis. Comparative Effectiveness Review No. 233. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015- 00002-I.) AHRQ Publication No. 20(21)-EHC025. Rockville, MD: Agency for Healthcare Research and Quality; October 2020. DOI: https://doi.org/10.23970/AHRQEPCCER233.

American College of Physicians
Clinical Guidelines Committee
Disclosure of Interests: Supplemental Questions and Attestation

Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Ethan Balk

Print Name

Ethan Balk Digitally signed by Ethan Balk Date: 2020.12.21 12:39:22 -05'00' 12/21/2020

Signature Date

Gerald Gartlehner

Mar 26, 2020 06:34:40 EDT
American College of Physicians

Disclosure Purpose: Disclosure of Interests, Disclosure o finterest

Summary of Interests

I do not have any interests to disclose at this time.

Additional Information:

1. **Please specify any additional information which you consider relevant to this disclosure.**
2. **ACP requires your annual affirmation to abide by its Disclosure of Interests and Management of Conflicts Policy, Non-Disclosure Agreement, Intellectual Property Policy, and Anti-Harassment Policy *if* you're submitting your disclosures to ACP as a member of an ACP governance group or as College staff, as part of ACP's annual disclosure process.**

    a. **Are you submitting your disclosures to ACP as a member of one of the following groups:**
        - **ACP board, committee, council, task force, and/or other governance group?**
        - **Chapter Council or other Chapter leadership role?**
        - **National or chapter staff?**
        - **Annals of Internal Medicine editorial staff?**
        - **Other (meeting guests, contractors, authors, etc.)**

    No.

    You are not disclosing any interests to this organization.

Certification

By submitting this form, I attest that I have disclosed all interests related to healthcare from the last 3 years on behalf of myself and any household members, including consideration of interests in the following areas:

- Research and consulting support (e.g., grants, contracts, sponsorships, honoraria, or any other fees related to role as consultant, speaker's bureau participation, or expert as part of regulatory, legislative, or judicial process)
- Investments and proprietary interests excluding broadly diversified investments such as mutual or pension funds (e.g., stocks, bonds, stock options, commercial business interests, patents, trademarks, copyrights)
- Membership on boards, workgroups, panels, or committees through other medical societies or healthcare organizations
- Participation in advocacy or lobbying activities, including any roles or relationships with disease advocacy organizations

Other aspects of my background or present interests not addressed above that might be perceived as affecting my objectivity or independence

Convey Global Disclosure System | AAMC

American College of Physicians
Clinical Guidelines Committee, Performance Measurement Committee,
& Scientific Medical Policy Committee
Disclosure of Interests: Attestation and Supplemental Questions

Guest Disclosures of Interests: Acknowledgements and Attestations

By signing this form,

- I acknowledge that in order to maintain transparency, all participants' disclosure of interests will be publicly available on ACP's website and a link to the disclosures will be included in each published work.
- I attest that I have reviewed the attached Convey disclosures report and that my disclosures are up to date.
- I attest that I have disclosed all healthcare-related financial and intellectual interests for myself and any household members from the last 3 years and I will promptly disclose any changes. These include but are not limited to: research and consulting roles; investments and proprietary interests, and intellectual interests such as participation in workgroups, panels, or committees through other medical societies or healthcare organizations.

Gerald Gartlehner

Print Name

Gerald Gartlehner Digital unterschrieben von Gerald Gartlehner Datum: 2021.01.05 11:42:38 +01'00' 5th January, 2021

Signature Date

Clinical Guidelines Committee (CGC) Meeting
September 9-10, 2020
Philadelphia, PA
Webinar Minutes

Call to Order: The meeting was called to order at 1:30 PM ET.

Welcome
Timothy J. Wilt, MD, & Amir Qaseem, MD

Dr. Wilt welcomed the committee and called the meeting to order. Ms. Carroll introduced new clinical policy team members, Sam Tierney and Shannon Merillat.

Disclosure of Interests and Management of Conflicts of Interest
Timothy J. Wilt, MD & Clinical Policy Staff

The CGC managed any potential conflicts of interest by discussing all disclosures and excluding individuals from discussion and/or voting for topics where a conflict was determined, as appropriate. Ms. Carroll described the recent change to the way disclosures are reported at in the summary: In the interest of full transparency, the summary now reports the COI assessment for all individuals attending the meeting, and indicates if an individual has a low-level conflict of interest or if no conflict of interest was identified. The conflict management for this meeting is summarized in the Appendix.

Governance Leadership Remarks
Heather E. Gantzer, MD, Chair, ACP Board of Regents
Darilyn V. Moyer, MD, EVP & CEO, ACP

Drs. Gantzer and Moyer each gave brief remarks emphasizing ACP's critical themes and goals for the 2020-21 committee year: innovation; diversity, engagement and inclusion; and valued professional identity.

Approval of Minutes
CGC Members

The CGC approved the April 29, 2020 meeting minutes.

Item: April 29, 2020 meeting minutes

Action:	☒ Approve item **(14)** ☐ Do not approve item ☐ Item needs revision
Approve:	Batur, Cooney, Crandall, Fitterman, Hicks, Kansagara, Lin, Maroto, Mustafa, Tice, Tufte, Vijan, Williams, Wilt
Do not Approve:	n/a
Abstain:	n/a
Absent, approved via email post-meeting:	n/a
Absent:	n/a

Highlights from the Scientific Medical Policy (SMPC)

Devan Kansagara, MD, Vice Chair, SMPC

Dr. Kansagara gave a brief update on the Scientific Medical Policy Committee's (SMPC) work including recent publications and works in process:

Recent Practice Points Publications

- Should Clinicians Use Chloroquine or Hydroxychloroquine Alone or in Combination With Azithromycin for the Prophylaxis or Treatment of COVID-19?
    - Update Alert 2 (July 2020)
    - Update Alert 1 (June 2020)
    - Version 1 (May 2020)
- Use of N95, Surgical, and Cloth Masks to Prevent COVID-19 in Health Care and Community Settings (Version 1, June 2020) (collaboration with the Agency for Healthcare Research and Quality)

Practice Points in progress:

- Remdesivir for the treatment of patients with COVID-19 *Collaboration with VA Evidence Synthesis Program (under review at *Annals*)
- Immunity after COVID-19 (collaboration with the Agency for Healthcare Research and Quality)
- Care and treatment of persons diagnosed with chronic hepatitis C virus infection (under review at *Annals*)
- Duration of antibiotics use
- Diagnostic imaging for hematuria
- Cardiac imaging

Highlights from Performance Measurement Committee (PMC)

Nick Fitterman, MD, Chair, PMC

Dr. Fitterman gave a brief update on the Performance Measurement Committee's (PMC) work which includes numerous engagements with external organization's such as Centers for Medicare & Medicaid Services (CMS), Core Quality Measure Collaborative (CQMC), National Academy of Medicine (NAM), National Quality Forum (NQF) and Physician Consortium for Performance Improvement (PCPI). The PMC is currently developing a paper on "Barriers to Patient Reported Outcome-based Performance Measurement" and will be reviewing MIPS Measures for Telehealth Applicability at the Friday, September 11, 2020 meeting.

Appropriate Use of Point-of-Care Ultrasound (POCUS) in Patients with Acute Dyspnea in Emergency Department or In-patient Settings: Guideline and Evidence Review

Subpanel: Nick Fitterman, MD, Devan Kansagara, MD, & Reem Mustafa, MD, Tim Wilt, MD, & Amir Qaseem, MD

Evidence Review Team: Cochrane Austria

ACP Methods Consultants: Itziar Etxeandia-Ikobaltzeta, PhD & Yuqing "Madison" Zhang, MD

Dr. Mustafa presented an overview of the Appropriate Use of Point-of-Care Ultrasound (POCUS) in Patients with Acute Dyspnea in Emergency Department or In-patient Settings guideline and draft recommendations. Dr. Gartlehner and the Cochrane Austria Evidence Review Team (ERT) joined the conference call to answer questions pertaining to the evidence review.

Key Questions

The key questions included:

Key Question 1) In patients with acute dyspnea, what are the beneficial and harmful health effects of POCUS plus clinical examination compared to clinical examination alone?

Key Question 2) What is the diagnostic test accuracy of POCUS in patients with acute dyspnea to detect congestive heart failure, pneumonia, pulmonary embolism, pleural effusion and pneumothorax as the underlying cause of acute dyspnea?

Outcomes

Dr. Mustafa stated that both the CGC members and the CGC Public Panel members rated the patient important outcomes that resulted in seven top outcomes: mortality, time to initiate therapy, time to accurate diagnosis, unnecessary use of antibiotics, need to use breathing support, hospital length of stay, and quality life. Both the CGC and the public panel also rated the test accuracy outcomes, which highlighted the false negative and false positive for different diagnoses. The rating results showed that the CGC and public panel both rated the false negatives rate higher than the false positives for the conditions, with the exception of pleural effusion. Dr. Mustafa noted that while the group was reviewing the evidence, the subgroup found that there are studies that look at a concept of "correctness of diagnosis." While the idea of correctness of diagnosis as an outcome was not part of the rated patient important

outcomes, “correctness of diagnosis” directly relates to the test accuracy outcomes and the subgroup decided that correctness of diagnosis is actually either critical or important for decision making.

Summary of Evidence

Dr. Mustafa briefly summarized the summary of evidence including the number of studies and participants, the population of the studies, the intervention/POCUS role, and reference standard. Dr. Mustafa noted the role the test in the studies, which included parallel (POCUS plus standard diagnostic pathway), replacement (POCUS or standard diagnostic pathway), triage (using POCUS to decide the pathway) and add-on (using POCUS after completion of standard diagnostic pathway) and stated the since parallel and replacement were not clear terms these would not be used in the guideline.

Dr. Mustafa addressed the evidence for POCUS combined with the standard diagnostic pathway compared to the standard diagnostic pathway alone, the focus of KQ1, and the critical and important health outcomes (In-hospital mortality, time to diagnosis, time to treatment, correctness of diagnosis, and length of hospital stay.)

- In-hospital mortality – low certainty; did not show a mortality benefit, although the direction of the effect points toward a small reduction but it depends on how you consider the confidence interval; considered desirable because we do not think there is harm
- Correctness of diagnosis – moderate certainty; adding POCUS likely results in a large improvement in the proportion of correct diagnosis, from 59% to 91%;
    - Assuming correctness of diagnosis has a close and causal relationship to health outcomes
    - Inappropriate diagnosis of the underlying cause of acute dyspnea was significantly associated with higher mortality in older patients; although the generalizability of this study is limited and more research is needed to confirm a direct linkage between health outcomes and correctness of diagnosis
    - Did consider this a desirable outcome; was the largest effect we have seen based on these studies that looked at outcomes
- Length of hospital stay – moderate certainty; adding POCUS to standard pathway likely does not affect the length of stay
- Time to diagnosis – insufficient certainty; median of 20 minutes or less
- Time to treatment – insufficient certainty; median of 21 minutes or longer

Dr. Mustafa summarized the effects on patient outcomes (for KQ1): there is low certainty of evidence that adding POCUS to standard of care may result in small reduction in hospital mortality, though the confidence interval is very large. However, there is moderate certainty that adding POCUS to standard care has a large effect on increasing the correctness of diagnosis (59% to 91%) and there is moderate certainty that it does not affect the length of hospital stay.

Test Accuracy Data

Dr. Mustafa continued with the focus of KQ2, test accuracy of POCUS plus standard diagnostic pathway, summarizing the evidence for direct comparative test accuracy and indirect single test accuracy.

Direct comparative test accuracy

Dr. Mustafa noted that direct comparative test accuracy referred to POCUS plus standard diagnostic pathway vs. standard diagnostic pathway:

- Based on one study; 315 participants; low risk of bias
- Prevalence is based on the average pretest probably with a patient with dyspnea
- The false positive or false negative teste results for the low, medium, and high-risk for each of these conditions may differ or may mean something different according to the condition
    - An example of a false negative consequence in the acute setting – it may be more serious to miss a diagnosis of pneumonia or pulmonary embolism than to miss a diagnosis of heart failure or pleural fusion
- POCUS plus standard of care, the sensitivity ranged from 79% to 100%, the specificity ranged from 63% to 99%
    - Standard diagnostic pathway alone, the sensitivity ranged from 18% to 83% and the specificity ranged from 72% to 97% depending on different conditions

Dr. Vijan noted that he was uncomfortable about the abstraction of that data in the original study since the same trial gives the insufficient evidence for the time to diagnosis and to treatment. Dr. Vijan could not understand how the trial, treatment happened before diagnosis in the control arm of this study. Dr. Gartlehner stated that the review team did notice this, but since it was insufficient certainty, the team did not obtain an explanation.

Dr. Mustafa summarized that in patients where there is diagnostic uncertainty, the combination of POCUS with standard of care when compared with the use of standard pathway alone may reduce false negative test results across all potential underlying conditions. However, use of POCUS plus standard of care compared to standard diagnostic pathway alone may reduce, have no impact, or increase false positives depending on the specific condition.

Indirect single test accuracy

Indirect single test accuracy referred to POCUS plus standard diagnostic pathway:

- Based on three studies; 544 participants; 2 studies with low risk of bias; 1 study with unclear risk of bias
- Same prevalence as KQ1 used for easier comparison
- In light of potential consequences, false positive and false negative rates are generally acceptable for congestive heart failure and plural diffusion; which are considered as probably of low to moderate severity (depending on size of effusion)
- In light of potential consequences, false positive rates and false negative rates in average patients are of concern for pneumonia, where potential consequences of false

positive results are considered as probably low or moderate and false negative results are moderate to severe
- In light of potential consequences, false positive rates in average patients are of concern for PE and considered as probably severe together with a false negative test results
- Harms of POCUS as a parallel test
    - None of the studies reported on consequences of false positive or false negatives
    - None reported on proportion of inconclusive results
    - None reported on other potential complications of POCUS

Dr. Mustafa summarized that POCUS, as a parallel test (POCUS plus standard diagnostic pathway) is potentially useful for patients with suspected congestive heart failure or plural effusion but that clinicians should consider use of POCUS with caution if suspected pneumonia or pulmonary embolism is very high. Dr. Crandall asked for clarification of whether the prevalence for pulmonary embolism was for emergency department (ED) or in-patient settings. Dr. Mustafa noted that the prevalence is based on the average patient with acute presentation in the ED. Clinicians should consider the pretest probability for any of these underlying conditions in their decision.

In conclusion, Dr. Mustafa stated that adding POCUS to standard of care:
- May result in a small reduction in in-hospital mortality (low strength of evidence)
- Likely results in a large improvement in the proportion of correct diagnoses (moderate strength of evidence)
- Likely does not affect the length of hospital stay (moderate strength of evidence)
- Time to treatment and time to diagnosis have insufficient strength of evidence

Dr. Mustafa presented the recommendation and suggested that the following remarks should always accompany the recommendation:
- This recommendation applies to a scenario in which there is diagnostic uncertainty.
    - It is important to consider the likelihood of underlying diseases in the decision to include POCUS as part of the diagnostic pathway.
    - In patients who are clinically unstable, the use of POCUS should not delay management actions derived from results of other diagnostic tests in the pathway or delay decisions about performing other tests.
    - Focusing POCUS on the anatomic sites that are consistent with the diagnostic and treatment uncertainties is important.
    - It is expected that only clinicians who are trained to use and interpret findings from POCUS will be using it.
    - This recommendation applies to standard mobile devices in emergency departments and an inpatient setting.

Values and Preferences Summary
Dr. Yost presented a brief summary of the CGC Public Panel's values and preferences:

- Trend toward a preference for adding POCUS as a parallel test (POCUS plus standard diagnostic pathway)
- Very few responded with preference for POCUS as a replacement test (POCUS or standard diagnostic pathway)
- More consistency between preference based on desirable and undesirable effects and false positives and false negatives and potential consequences for POCUS as a parallel test
- Preferences are generally consistent with draft recommendation
    - Consideration should be given to mixed preferences ("yes" and "unsure") for parallel use of POCUS in terms of false positives and false negatives
- Additional insights
    - Although unavailable, information pertaining to time to diagnosis and time to treatment might influence response
    - Knowing how long standard practices have been in place would be helpful
    - More information about costs would be considered helpful
    - Questioning the relevance of making recommendations for which there is low certainty evidence

Committee Discussion

Dr. Wilt thanked Dr. Mustafa for her presentation and asked for comments and questions. Dr. Fitterman noted that the enthusiasm for POCUS outpaced the evidence and stated that ACP needs to convey to the reader is that POCUS needs to be contextualized and synthesized with the clinical findings and the individual patient.

General Discussion

- The CGC discussed the evidence rating for the mortality outcome: the evidence team had graded it as low but several committee members suggested it should be insufficient due to the width of the confidence interval and the small effect size. The evidence review team responded that following GRADE guidance, they could only get to low (downgrading twice for imprecision) but that they were in agreement that it is insufficient. Dr. Mustafa clarified that GRADE allows for downgrading 3 times.
    - *Outcome:* There was agreement between CGC and the evidence review team to grade the mortality outcome as insufficient.
- There was debate over the linkage between test accuracy and health outcomes. Some expressed discomfort in making a recommendation without direct evidence on benefit in terms of health outcomes.
    - Though the evidence review identified 1 study that reported correlation between correctness of diagnosis and reduced mortality, not all committee members felt it was sufficient to stand alone as evidence of a direct linkage.
    - Responses to the concern about linkage included that there were no signals of potential harm in the data, it is not associated with high costs, and diagnosis (symptomatic patients) is different clinical context than screening (asymptomatic patients).

- *Outcome:* The committee agreed it was comfortable with a diagnostic recommendation based on test accuracy so long as the rationale is transparent that correctness of diagnosis is the basis, rather than improvement in health outcomes.

Discussion on Draft Recommendation

> *Original Draft Recommendation: ACP suggests that clinicians use point of care ultrasound as part of the diagnostic pathway if it will inform management when there is diagnostic uncertainty in patients with acute dyspnea in emergency department or in-patient settings (conditional recommendation; low-certainty evidence).*

The committee discussed the draft recommendation including the following points:

- Several members expressed concern that the term "parallel" was not intuitive and would confuse readers, and also that the phrase "as part of the diagnostic pathway" in the recommendation was unclear
  - Dr. Mustafa noted that the term "add-on" has a specific meaning in the diagnostic world that is distinct from the parallel role, so its use should be avoided in the context of parallel tests.
  - *Outcome:* The CGC agreed to replace the term "parallel" with the phrase "in addition to" throughout the document.
- Remove "if it will inform management" to reduce redundancy and make the statement more clear
- There was some discussion as to how to word the recommendation so that it was not interpreted as a recommendation for universal adoption of POCUS.
  - *Outcome*: The majority committee agreed to add the word "may" ("clinicians may use point of care ultrasound…") to reflect the conditional grading of the strength of the recommendation. Dr. Mustafa was against the change because it the messaging is redundant - conditional recommendations by definition are not universal, and that the remarks included in the rationale/clinical considerations appropriately convey the qualifiers and caveats.
  - Drs. Lin and Mustafa noted that from a methods perspective and for internal consistency, the committee needed to be consistent on using same terminology for conditional recommendations.

Discussion of Rationale Language

Dr. Qaseem noted that the rationale language would incorporate Dr. Mustafa's suggested remarks. Other points included:

- Dr. Crandall suggested that line 449, "clinicians need to be trained to use and interpret findings from POCUS" needs clarification.
  - *Outcome:* The line was revised to "clinicians who use POCUS should be trained…"
- Dr. Wilt asked if the guideline would link to ACP's own POCUS training initiative.
  - *Outcome:* The Committee agreed that ACP educational content and other educational content that meets ACP standards could be linked on ACP website

after publication, but that the guideline itself would not include any reference to or promotion of ACP educational materials as that would be a conflict of interest.

Recommendation: *ACP suggests that clinicians may use point of care ultrasound in addition to the standard diagnostic pathway when there is diagnostic uncertainty in patients with acute dyspnea in emergency department or in-patient settings (conditional recommendation; low-certainty evidence).*	
Action:	☒ Approve item **(12)** ☐ Do not approve item (**1**) ☐ Item needs revision
Approve:	Batur, Cooney, Crandall, Hicks, Kansagara, Lin, Maroto, Tice, Tufte, Vijan, Williams, Wilt
Do not Approve:	Mustafa
Recused:	None
Absent during vote, approved via email post-meeting:	Fitterman
Absent:	None

Next Steps

1. Ms. Carroll and Dr. Etxeandia-Ikobaltzeta will revise the guideline based on the committee's comments.
2. Ms. Carroll will circulate the finalized manuscript for electronic approval.

Post-Meeting Addendum (via email)

Via email following the meeting, the CGC voted to approve the final manuscript.

Manuscript: **Appropriate Use of Point-of-Care Ultrasound (POCUS) in Patients with Acute Dyspnea in Emergency Department or In-patient Settings: Guideline and Evidence Review**	
Action:	☒ Approve item **(13)** ☐ Do not approve item ☐ Item needs revision
Approve:	Batur, Cooney, Crandall, Hicks, Fitterman, Kansagara, Lin, Maroto, Mustafa, Tice, Tufte, Williams, Wilt
Do not Approve:	None

Recused:	None
Absent: Vijan	

Appropriate Use of High Flow Nasal Oxygen in Hospitalized Adults with Acute Respiratory Failure: Guideline and Evidence Review

Subpanel: Nick Fitterman, MD, John Williams, Jr., MD, Devan Kansagara, MD, & Amir Qaseem, MD

Evidence Review Team: Minneapolis

ACP Methods Consultants: Itziar Etxeandia-Ikobaltzeta, PhD & Yuqing "Madison" Zhang, MD

Dr. Kansagara chaired during this discussion since Dr. Wilt had a moderate-level COI for this topic. The Minneapolis VA Evidence-synthesis and Dissemination Core (MEDIC) Evidence Review Team (ERT) joined the conference call to present updated findings from the evidence review. Dr. Williams presented an over of the evidence and findings of the High-Flow Nasal Oxygen review.

Key Questions
The key questions included:

> Key Questions 1) What is the comparative effectiveness of high flow nasal oxygen (HFNO) versus noninvasive ventilation (NIV) or conventional oxygen therapy (COT) for hospitalized patients with acute respiratory failure?
> Key Question 1a) Does comparative effectives of HFNO vary by patient characteristics, disease/diagnosis characteristics, protocol/devise settings, or location of administration?
>
> Key Question 2) What are the harms of high flow nasal oxygen (HFNO) versus noninvasive ventilation (NIV) or conventional oxygen therapy (COT) for hospitalized patients with acute respiratory failure?
> Key Question 2a) Do harms vary by patient characteristics, disease/diagnosis characteristics, protocol/devise settings, or location of administration?

Dr. Williams noted that there was limited ability to explore patient characteristics due to the overall small number of studies and subgroup analysis resulted in very small groups, none of which showed important differences by any of the characteristics. Dr. Williams also stated that the analysis stratified the comparisons into two scenarios – initial management of acute respiratory failure and post-extubation. The evidence summary for each scenario follows:

Initial Management - HFNO vs NIV

- Low-certainty evidence showing some proven benefits of HFNO vs NIV for initial management: HFNO improves clinically meaningful outcomes with large reductions in

mortality, modest reduction in intubations, and improvement in patient comfort and may reduce hospital-acquired pneumonia by a modest amount.
- Additional factors beyond the evidence – most patients can use HFNO and there is contraindications unless related to issues with fitting the nasal cannula
- Moderate cost - HFNO is reimbursed at a lower rate by Medicare for home health rental use vs noninvasive ventilation
- Recommendation made in favor of HFNO over NIV

Initial Management HFNO vs COT
- Low-certainty evidence showed that HFNO may improve patient comfort, dyspnea and reduce hospital acquired-pneumonia
- For other outcomes, low-certainty evidence showed no difference
- There was insufficient evidence for ICU admission
- HFNO is more expensive than conventional oxygen
- Overall, evidence does not favor either HFNO or COT: No recommendation made

Post-extubation – HFNO vs NIV
- Desirable effect was a large reduction in skin breakdown; the confidence interval included no effect and it was low certainty of evidence
- Undesirable effect included a small increase, clinically may not be important adverse effect, from high flow nasal oxygen on all-cause mortality; small increase on re-intubation with low certainty of evidence
- Overall, effect sizes were inconsistent, small and not statistically significant, hence evidence is inconclusive for or against the use of HFNO over NIV for the management of post-extubation acute respiratory failure
- Overall, evidence does not favor either HFNO or NIV: No recommendation made

Post-extubation – HFNO vs COT
- Hospital length of stay, dyspnea and skin breakdown were rated as insufficient.
- Low overall certainty of evidence that showed HFNO may reduce re-intubations by a small amount compared to COT and low certainty that it probably improves patient comfort
- Low certainty and moderate evidence also shows HFNO did not perform worse than COT with regard to all-cause mortality, hospital-acquired pneumonia and length of ICU stay (moderate
- Although the magnitude of effect did not pass the CGC's predetermined thresholds, the direction of effects consistently points towards potential benefit
- Moderate costs, although likely more expense than COT based on monthly Medicare rental rates
- Recommendation made in favor of HFNO over COT

Evidence Review Team Update

Dr. Melzer of the ERT gave a brief review of the journal comments on the evidence report and the updated literature review:

- 2 new trials found for HFNO vs COT for post-extubation.
- In response to *Annals* editor's request for additional risk of bias assessment for the "incomplete outcome data" and "selective outcome reporting", the ERT provided description of how elements were operationalized to determine the overall risk of bias;
    - This did change 3 trials from low to moderate risk of bias but did not impact the final certainty of evidence grades.
- In response to a reviewer's comment, the ERT removed one bronchoscopy study from the intubation/mortality outcomes, which consisted of hospitalized patients with respiratory failure that were in a very specialized sub-setting of being in a procedural timeframe.
    - Upon reviewing that study more closely the ERT decided to only report dyspnea and physiological outcomes from this study, which is similar to how the ERT included short-duration, cross-over studies
    - Removing the study from the intubation and mortality data did not change certainty of evidence
- The ERT added a box in the introduction section with a comparison of key characteristics of conventional oxygen therapy (COT), noninvasive ventilation (NIV) and high flow nasal oxygen HFNO)
    - This included information on the interface, flow rate, the FiO_2, heat/humidification, positive pressure, and ventilator support.
- The ERT also included a Certainty of Evidence Map, which shows certainty of evidence (high, moderate, low, insufficient) in circles and directionality (benefit, little to not effect, harms, unclear direction) in color
    - Based on the committee's feedback, the ERT agreed to revisit how they were presenting unclear direction and insufficient findings (currently color coded the same in the table).

Dr. Melzer concluded that based on the above changes the ERT changed the conclusion, stating that high flow nasal oxygen as initial management may improve <u>several</u> clinical outcomes (changed from <u>most</u> clinical outcomes) and when used as post-extubation management <u>may reduce intubations and improve patient comfort</u> (changed from improve <u>selected</u> outcomes.)

Values and Preferences Summary

Dr. Yost presented a brief summary of the CGC Public Panel's values and preferences:

- No one indicated a preference against high flow nasal oxygen (HFNO) across all comparisons
- The impact of cost was a consideration as well as the availability of the different types of technology, which can be important in decision making
- In terms of HFNO and NIV, there was consistent favoring of HFNO over NIV for the initial management of acute respiratory failure, which is consistent with the draft recommendation

Committee Discussion:
The committee discussion was concentrated on draft Recommendation 1 and its key points:

> *Draft Recommendation 1: ACP suggests that clinicians use high flow nasal oxygen rather than noninvasive ventilation in hospitalized hypoxemic adults for the initial management of acute respiratory failure (conditional recommendation; low-certainty evidence).*

Key Points

- The CGC debated whether to grade Recommendation 1 as strong or conditional
    - Dr. Tice leaned toward a strong recommendation because the totality of the evidence favored high flow nasal oxygen – all outcomes trend in the direction of benefit and there are substantial reductions in mortality and intubations and the public panel also showed a strong preference.
    - Dr. Lin commented that if grading as strong, the recommendation should only be for hypoxic, nonhypercapnic population
        - Dr. Lin commented that if grading as strong, the recommendation should only be for hypoxic nonhypercapnic population
    - The CGC also discussed concern about the certainty of evidence for the mortality outcome, given that the number of events was <50.
    - The overall certainty of evidence is low, and Dr. Qaseem noted that ACP rarely issues strong unless there is a compelling rationale.
    - Several commented that strong recommendations are considered as appropriate for translation into performance measures, and given the extent of debate within the committee about the strength of the recommendation, it would be appropriate to take the conservative route and keep as conditional.
    - *Outcome*: The CGC agreed to keep Recommendation 1 as conditional
- Several members suggested removing the word "initial" from recommendation 1 since it may not appropriately reflect the patient population. Dr. Lin noted that patients being considered for HFNO, COT, or NIV are not the same as patients who clinicians are considering to put on, for example, a non-rebreather mask.
    - The word "initial" was originally included to distinguish from post-extubation population, and there was some concern that without it the recommendation would be interpreted as applying to post-extubation population. Others were concerned the term would cause confusion and be interpreted as applying to a broader patient population.
    - *Outcome*: The CGC agreed to delete the word "initial" from the recommendation statement and to clarify in the rationale that this recommendation does not apply to post-extubation.
- The CGC considered adding the phrase "who have failed COT" to the recommendation statement based on the understanding that the study supporting the mortality outcome enrolled patients who initially failed COT, but the evidence review team checked the study and verified that was not the case.
    - *Outcome*: The CGC did not add the phrase to the recommendation.

- The CGC requested the addition of more details on the patient population and applicability information to the guideline, under the rationale or clinical considerations.

Draft Recommendation 2: ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy in hospitalized hypoxemic adults with post-extubation acute respiratory failure (conditional recommendation; low-certainty evidence).

The committee was satisfied with draft recommendation 2 and did not discuss further, but did agree to renumber the recommendations as 1a and 1b since they are meant to be considered together.

Cost Data

- Drs. Cooney and Tice flagged concerns related to the cost data, as the Medicare reimbursement rates represent outpatient costs but not inpatient.
- The committee also discussed the complexity in assessing comparative costs and resource use for this topic in terms of facility variations in factors impacting overall upstream and downstream costs/savings, and the evidence review team did not identify any literature describing these cost considerations.
- *Outcome:* The guideline will keep the Medicare cost data but add language describing the limitations/indirectness of the cost information.

Areas of Inconclusive Evidence

The CGC discussed whether to add a recommendation stating the equivalence of HFNO and COT for the initial management.

- Dr. Mustafa pointed to this as a methods concern and that the committee lacks clear, transparent guidance on when it will decide to make a recommendation versus not. She felt it was not clear, process-wise, why the committee was not making a recommendation here since there is evidence on the comparison.
    - Dr. Vijan agreed that to not have a recommendation on the comparison seem arbitrary given that there are evidence tables.
    - Drs. Batur and Hicks countered that one of the roles of a guideline developer is to make judgments based on each clinical scenario, and that too much rigidity could be detrimental.
- Dr. Tice and Kansagara noted that one potential consequence is that readers would likely interpret the combination of Recommendation 1 (use HFNO over NIV) and a 3rd equivalence recommendation (HFNO = COT) as COT is a reasonable treatment for patients with acute respiratory failure and should be used over NIV.
- Dr. Lin suggested that a recommendation on the apparent equivalence of HFNO vs COT would need to specify the patient population (hypoxic).
- *Outcome*: the CGC decided against a third recommendation stating the equivalence of HFNO and COT, but agreed that the section discussing "non-recommendations" should be more clearly identified as "Areas of Inconclusive Evidence" to distinguish that there is evidence available (rather than no evidence or insufficient).

Recommendation 1a: *ACP suggests that clinicians use high flow nasal oxygen rather than noninvasive ventilation in hospitalized hypoxemic adults for the management of acute respiratory failure (conditional recommendation; low-certainty evidence).*	
Action:	☒ Approve item **(13)** ☐ Do not approve item ☐ Item needs revision
Approve:	Batur, Cooney, Crandall, Fitterman, Hicks, Kansagara, Lin, Maroto, Mustafa, Tice, Tufte, Vijan, Williams
Do not Approve:	n/a
Recused:	Wilt
Absent, approved via email post-meeting:	n/a
Absent:	n/a

Recommendation 1b: *ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy in hospitalized hypoxemic adults with post-extubation acute respiratory failure (conditional recommendation; low-certainty evidence).*	
Action:	☒ Approve item **(13)** ☐ Do not approve item ☐ Item needs revision
Approve:	Batur, Cooney, Crandall, Fitterman, Hicks, Kansagara, Lin, Maroto, Mustafa, Tice, Tufte, Vijan, Williams
Do not Approve:	n/a
Recused:	Wilt
Absent, approved via email post-meeting:	n/a
Absent:	n/a

Next Steps

1. The ERT will share the final version of the updated evidence review.
2. Ms. Carroll and Dr. Etxeandia-Ikobaltzeta will update the guideline based on the final evidence report, revise the manuscript based on the committee comments and circulate the final manuscript for electronic approval.

Post-Meeting Addendum (via email)
Via email following the meeting, the CGC voted to approve the final manuscript.

Manuscript: **Appropriate Use of High Flow Nasal Oxygen in Hospitalized Adults with Acute Respiratory Failure: Guideline and Evidence Review**	
Action:	☒ Approve item **(12)** ☐ Do not approve item ☐ Item needs revision
Approve:	Batur, Cooney, Crandall, Hicks, Fitterman, Kansagara, Lin, Maroto, Mustafa, Tice, Tufte, Williams
Do not Approve:	None
Recused:	Wilt
Absent: Vijan	

Management of Colonic Diverticulitis: Draft Evidence Review
Subpanel: Nick Fitterman, MD, Jennifer Lin, MD, Tim Wilt, MD, & Amir Qaseem, MD
Evidence Review Team: Brown (Agency for Healthcare Research and Quality)
ACP Methods Consultant: Itziar Etxeandia-Ikobaltzeta, PhD

The Brown Evidence-based Practice Center (EPC) Evidence Review Team (ERT) joined the call to present the draft evidence review on the management of colonic diverticulitis. The Agency for Healthcare Research and Quality (AHRQ) funded the diverticulitis review following ACP's topic nomination.

Key Questions
The key question topics included:

Key Question 1) Diagnosis of acute diverticulitis specifically with CT
Key Question 2) Non-surgical management of acute diverticulitis
Key Question 3) Issues regarding colonoscopy after an episode of acute diverticulitis
Key Question 4) Prevention of recurrence

Methods
The eligibility criteria included adults with suspected, diagnosed, or with a history of acute diverticulitis, including complicated and uncomplicated diverticulitis. Dr. Balk noted that the ERT excluded diverticulosis including symptomatic uncomplicated diverticular disease, which overlaps with diverticulosis. The interventions and comparators where specific to the key questions and included:

- KQ 1) Computed Tomography (CT) on presentation with symptoms of acute diverticulitis.
- KQ 2a) Outpatient vs inpatient management for acute diverticulitis.
- KQ 2b) Antibiotics vs other for acute diverticulitis.
- KQ 2c) Use of interventional radiology procedures vs. noninvasive procedures for acute diverticulitis.
- KQ 3) Colonoscopy after an episode of acute diverticulitis, looking at both (KQ 4a) nonsurgical interventions and (KQ 4b) elective surgery interventions to prevent reoccurrence.

Next Dr. Balk stated that outcomes also varied by specific key questions and included:

- KQ 1) Test accuracy of CT for both diagnosis and staging; clinical benefits and harms; and incidental findings and sequelae related to getting a CT.
- KQ 2) Clinical diverticulitis outcomes (death, symptom resolution, morbidities, procedures, recurrence); other patient-centered outcomes (quality of life, functional outcomes, missed work); resource use (length of stay); and harms (adverse events) related to interventions.
- KQ 3) Risk of colorectal cancer and colorectal cancer death; high-risk colonic premalignant lesions; also looked for outcomes related to tolerance, feasibility, and complications from the colonoscopy itself.
- KQ 4) Clinical diverticulitis outcomes (death, recurrent diverticulitis); other patient-centered outcomes; surgery-related clinical outcomes, stoma placement as an example; and surgical complications and another harms.

Next Dr. Balk stated that the ERT included studies of various designs based the key questions, including existing systematic reviews (KQ1), randomized controlled trials (RCT) and nonrandomized comparative studies (NRCS) with adjustment for potential cofounders (KQ 2 and 4), single group studies (KQ 2, 4a and b) and RCTs, NRCS and large single group studies (KQ3.) The ERT used standard AHRQ methodology for systematic reviews to assess the risk of bias individual studies and strength of evidence across studies. The ERTs screened 15,000 abstracts from multiple databases including looking through existing systematic reviews and guidelines, which resulted in 77 primary studies across all the questions and two systematic reviews for Key Question 1.

Dr. Balk continued to review the detailed results by key question and summarized the main point as follows:

- KQ1 - Diagnosis of acute diverticulitis specifically with CT
    - Moderate strength of evidence (SoE) that CT accurately diagnoses acute diverticulitis but insufficient evidence regarding CT accuracy to stage acute diverticulitis;
    - Low SoE that CT may increase appropriate management versus clinical diagnosis;

    - Low SoE that misdiagnoses on CT may not increase the risk of poor clinical outcomes; and low SoE that while incidental findings on CT are common, their clinical significance is unclear.
- KQ2 - Non-surgical management of acute diverticulitis
    - Low SoE that for patients with a complicated acute diverticulitis, outpatient management may be as effective as inpatient care, but insufficient evidence regarding important clinical outcomes including treatment failure, mortality or emergency surgery;
    - Low SoE that for patients with uncomplicated diverticulitis, antibiotic treatment may not affect important clinical and patient-centered outcomes; insufficient evidence regarding the choice of antibiotics, if they are used; insufficient evidence regarding effectiveness of percutaneous drainage for patients with complicated acute diverticulitis.
- KQ 3 – Issuing regarding colonoscopy after an episode of acute diverticulitis
    - Low SoE that patients with recent diverticulitis (within 6 to 12 months) have an increased likelihood of having undiagnosed colorectal cancer (CRC) compared with the general population;
    - Patients who undergo colonoscopy soon after an episode of acute diverticulitis (within about two to 12 months) may ultimately have similar rates of CRC diagnosis as patients who did not undergo colonoscopy; but there is insufficient evidence regarding the risk of colorectal cancer death in the comparative studies.
    - Among people with recent acute diverticulitis those who are 50 years or older who have complicated diverticulitis are at increased risk of advanced colonic neoplasia (high SoE), colorectal cancer (moderate SoE), and advanced adenoma (low SoE).
    - There is high SoE that colonoscopies conducted within 1.5 to 12 months after acute diverticulitis rarely have complications or incomplete test.
- KQ4 – Prevention of reoccurrence
    - High SoE that 5-ASA provides no benefit to reduce the risk of recurrence of diverticulitis; insufficient evidence regarding other nonsurgical interventions;
    - No studies that looked at nutrition related interventions.
    - High SoE that for patients with prior complicated or smoldering/frequently recurrent (after uncomplicated) diverticulitis, elective surgery reduces the risk of recurrence disease
        - But no evidence regarding which patients would benefit most.
    - Moderate SoE that surgical adverse events were not uncommon.

Dr. Wilt thanked Dr. Balk for the presentation and the committee briefly gave the ERT a few suggestions for further information:

- Dr. Lin suggested that since the review does not have a comparator group, it would be helpful to understand the underlying prevalence of colorectal cancer, advanced neoplasias or advanced adenomas in a general population or a population without diverticulitis.

    - Dr. Balk responded that his team would be willing to track down that information and provide it.
- Ms. Tufte asked for clarification on whether adverse events were present in both complicated and uncomplicated diverticulitis populations.
    - Due to time constraints, this question was tabled for further discussion between the subgroup and ERT.
- Dr. Hicks noted that even though there is limited or insufficient evidence to make a statement for or against antibiotic therapy, it is a significant finding that antibiotic treatment may not affect important clinical and patient-centered outcomes.

Next Steps

1. Clinical Policy staff will schedule subgroup calls to discuss the diverticulitis evidence review manuscript and begin work on the guideline.

Adjournment: 2:30 PM ET

CGC Members
Timothy J. Wilt, MD, MPH, MACP, *Chair*
Devan L. Kansagara, MD, MCR, FACP, *Vice Chair*
Pelin Batur, MD, NCMP, CCD, FACP
Thomas G. Cooney, MD, MACP
Carolyn J. Crandall, MD, MS, FACP
Nick Fitterman, MD, MACP, SFHM
CAPT Lauri A. Hicks, DO
Jennifer S. Lin, MD, MCR, FACP
Michael Maroto, JD, MBA (Public Member)
Reem A. Mustafa, MD, MPH, PhD, FACP
Jeffrey Tice, MD
Janice Tufte (Public Member)
Sandeep Vijan, MD, MS
John Williams, Jr., MD, MHS, FACP

ACP Governance Leadership
Heather E. Gantzer, MD, FACP, *Chair, Board of Regents*

ACP Staff
Laura Baldwin
Kate Carroll, MPH
Allison Ewing, MJ
Andrew Hachadorian
Shannon A. Merillat, MLIS
Darilyn V. Moyer, MD, FACP, FRCP, FIDSA
Amir Qaseem, MD, PhD, MHA, MRCP (London), FACP
Trish Siemion, MS

Samantha Tierney, MPH

ACP Methods Team
Itziar Etxeandia-Ikobaltzeta, PharmD, PhD
Jennifer Yost, RN, PhD

Consultant
Yuqing "Madison" Zhang, MD, PhD, MSc

Invited Guests
Cochrane Austria *(For the Point-of-Care Ultrasound (POCUS) discussion on Wednesday only)*

Gerald Gartlehner, MD, MPH: Lead Investigator
Lisa Affengruber, MSc
Andrea Chapman, MA, BSc
Andreea Dobrescu, PhD
Gernot Wagner, MD

AHRQ Evidence-based Practice Center (EPC) Program *(for the Management of Colonic Diverticulitis Evidence Review discussion on Thursday only)*

Lionel Bañez, MD, *AHRQ Task Officer*
Ethan Balk, MD, MPH, *Principal Investigator, Associate Professor, Health Services, Policy & Practice, Co-Director, Brown Evidence-based Practice Center*
Gaelen Adam, MPH, *Senior Research Associate, Brown Evidence-based Practice Center for the Effective Healthcare Program of AHRQ*
Ian Saldanha, MBBS, PhD, MPH, *Assistant Professor, Center for Evidence Synthesis in Health, Department of Health Services, Policy, and Practice, Brown University School of Public Health*

Minneapolis VA Evidence-synthesis and Dissemination Core (MEDIC) *(for the High Flow Nasal Oxygen for Acute Respiratory Failure Evidence Review discussion on Thursday only)*

Arianne Baldomero, MD, MS, *Pulmonologist, Critical Care, Contributing Investigator*
Nancy Greer, PhD, MN-MEDIC, Assistant Director
Eric J. Linskens, BS
Roderick MacDonald, MS
Anne Melzer, MD, MS, *Pulmonologist, Critical Care, Project Lead*

Appendix

Disclosure of Interests and Management of Conflicts of Interest

Conflicts of Interest Management
Clinical Guidelines Committee
September 9-10, 2020

Name	COI	Agenda Items Impacted	Management this meeting[1]
Committee Members			
Tim Wilt	**Moderate** Conducting systematic review ACP guideline on high flow nasal oxygen	• High flow nasal oxygen guideline	• Participates in discussion • Recused from authorship and voting
Pelin Batur	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Tom Cooney	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Carolyn Crandall	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Nick Fitterman	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Lauri Hicks	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Devan Kansagara	**No COI identified**	• None	• Participates in discussion, authorship, and voting

[1]When a participant has more than one conflict, only the highest level is reported. Please see full signed reports for complete list of disclosures from all meeting participants.

Jennifer Lin	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Michael Maroto	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Reem Mustafa	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Jeff Tice	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Janice Tufte	**No COI identified**	• None	• Participates in discussion, authorship, and voting
Sandeep Vijan	**No COI identified**	• None	• Participates in discussion, authorship, and voting
John Williams	**Low** (Inactive) Previously owned stock Siemens; (inactive) household member received speaker funds from ArcherDx and Promega	• None	• Participates in discussion, authorship, and voting
Other Attendees – ACP Staff, Leadership, and Guests (do not participate in committee votes)			
Kate Carroll	**Moderate** Household member is employed by The Beasley Firm, LLC (personal injury and medical malpractice firm)	• All guidelines and evidence reviews	• Participates in discussion • Recused from authorship • Voting n/a
Gaelen Adam	**No COI identified**	• Only in attendance for diverticulitis evidence review	• Participates in discussion and authorship • Voting n/a
Lisa Affengruber	**No COI identified**	• Only in attendance for POCUS guideline (partial)	• Participates in discussion and authorship • Voting n/a

Arianne Baldomero	**No COI identified**	• Only in attendance for high flow nasal oxygen guideline (partial)	• Participates in discussion and authorship • Voting n/a
Laura Baldwin	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Ethan Balk	**No COI identified**	• Only in attendance for diverticulitis evidence review	• Participates in discussion and authorship • Voting n/a
Lionel Bañez	**No COI identified**	• Only in attendance for diverticulitis evidence review	• Participates in discussion and authorship • Voting n/a
Wayne Bylsma	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Andrea Chapman	**No COI identified**	• Only in attendance for POCUS guideline (partial)	• Participates in discussion and authorship • Voting n/a
Andreea Dobrescu	**No COI identified**	• Only in attendance for POCUS guideline (partial)	• Participates in discussion and authorship • Voting n/a
Itziar Etxeandia-Ikobaltzeta	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Allison Ewing	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Heather Gantzer	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Gerald Gartlehner	**No COI identified**	• Only in attendance for POCUS guideline (partial)	• Participates in discussion and authorship • Voting n/a
Nancy Greer	**No COI identified**	• Only in attendance for high flow nasal oxygen guideline (partial)	• Participates in discussion and authorship • Voting n/a

Andrew Hachadorian	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Eric Linskens	**No COI identified**	• Only in attendance for high flow nasal oxygen guideline (partial)	• Participates in discussion and authorship • Voting n/a
Roderick MacDonald	**No COI identified**	• Only in attendance for high flow nasal oxygen guideline (partial)	• Participates in discussion and authorship • Voting n/a
Shannon Merillat	**Low** Household member employed by HealthPartners; (inactive) Household member employed by Abbott Laboratories; M*Modal	• None	• Participates in discussion and authorship • Voting n/a
Anne Melzer	**No COI identified**	• Only in attendance for high flow nasal oxygen guideline (partial)	• Participates in discussion and authorship • Voting n/a
Darilyn Moyer	**No COI identified**	• None	• Participates in discussion • Authorship and voting n/a
Amir Qaseem	**No COI identified**	• None	• Participates in discussion and authorship • Voting n/a
Ian Saldanha	**No COI identified**	• Only in attendance for diverticulitis evidence review	• Participates in discussion and authorship • Voting n/a
Trish Siemion	**No COI identified**	• None	• Participates in discussion and authorship • Voting n/a
Sam Tierney	**No COI identified**	• None	• Participates in discussion and authorship • Voting n/a

Gernot Wagner	**No COI identified**	• Only in attendance for POCUS guideline (partial)	• Participates in discussion and authorship • Voting n/a
Jennifer Yost	**No COI identified**	• None	• Participates in all discussion and authorship • Voting n/a
Yuqing Zhang	**No COI identified**	• None	• Participates in discussion and authorship • Voting n/a

Updates from the Performance Measurement Committee (PMC)
January 2021 Report

Chair: Nick Fitterman, MD
Lead ACP Staff: Sam Tierney, MPH

Measure Reviews in Progress:

Modified version of the RAND/UCLA method for internal medicine measures in national programs yet to be reviewed

- Merit-based Incentive Payment System (MIPS) 479 (Adaptation of NQF 1789) - Hospital-Wide, 30-Day, All-Cause Unplanned
- Was NQF 1768 - Plan All-Cause Readmissions (PCR)
- NQF 0576/ Quality ID# 391 - Follow-Up After Hospitalization for Mental Illness (FUH)
- NQF 2483 - Gains in Patient Activation (PAM) Scores at 12 Months
- NQF 3568 - Person-Centered Primary Care Measure PRO-PM
- NQF 3227 - CollaboRATE Shared Decision Making Score

High level review of measures under consideration (MUC) for clinician level national programs
MIPS
Cost Measures

- MUC20-0015: Asthma-Chronic Obstructive Pulmonary Disease (COPD) Episode-Based Cost Measure
- MUC20-0017: Diabetes Episode-Based Cost Measure
- MUC20-0019: Sepsis Episode-Based Cost Measure

Quality Measures

- MUC20-0034: Risk-Standardized Acute Unplanned Cardiovascular-Related Admission Rates for Patients with Heart Failure for the Merit-based Incentive Payment System
- MUC20-0040: Intervention for Prediabetes
- MUC20-0042 Person-Centered Primary Care Measure Patient Reported Outcome Performance Measure
- MUC20-0043: Preventive Care and Wellness (composite)
- MUC20-0045 SARS-CoV-2 Vaccination by Clinicians

Medicare Shared Savings Program (Shared Savings Program)

- MUC20-0033: ACO-Level Days at Home for Patients with Complex, Chronic Conditions

PMC Papers Currently Under Development

- Recommending Caution in Patient Reported Outcome-based Performance Measurement

Updates from the Scientific Medical Policy Committee (SMPC)
January 2021 Report

Chair: Linda Humphrey, MD, MPH, MACP
Lead ACP Staff: Shannon Merillat, MLIS

Rapid, living practice points on COVID-19

Recent publications:

- Use of N95, surgical, and cloth masks to prevent COVID-19 in health care and community settings **Collaboration with the Agency for Healthcare Research and Quality*
  - Update Alert 1 (October 2020)
  - Version 1 (June 2020)
- Remdesivir for the treatment of patients with COVID-19 **Collaboration with VA Evidence Synthesis Program*
  - Version 1 (October 2020)

In progress:

- Remdesivir for the treatment of patients with COVID-19 (Version 2) **Collaboration with VA Evidence Synthesis Program* (under journal review)
- Immunity after COVID-19 **Collaboration with the Agency for Healthcare Research and Quality* (under journal review)

Best practice advice

Recent publications:

- World health organization guidelines on treatment of hepatitis C virus infection (October 2020)

In progress:

- Appropriate use of short-course antibiotics in common infections (under journal review)
- Diagnostic imaging for hematuria
- Cardiac imaging

Other (response letters, editorials, papers, methods)

In progress:

- The development of rapid, living practice points: summary of methods (under journal review)

Clinical Policy Media Coverage	REPORT START: January 1, 2007 REPORT END: December 21, 2020	
Topic	**Publication Date**	**Audience**
Clinical Guidelines		
Acute Pain From Non–Low Back	November 3, 2020	**13,082,143**
Testosterone Treatment in Adult Men	January 7, 2020	**28,766,844**
DOI/COI Paper	September 3, 2019	**262,720**
Methods Paper	June 11, 2019	**7,861,835**
Breast Cancer Screening	April 9, 2019	**79,997,905**
A1C Targets UPDATE	March 6, 2018	**85,231,906**
Osteoporosis to Prevent Fractures UPDATE	May 9, 2017	**74,793,866**
Hypertension	January 17, 2017	**111,064,391**
Low Back Pain UPDATE	February 14, 2017	**444,327,902**
Oral Treatment of Type 2 Diabetes UPDATE	January 3, 2017	**25,522,334**
Gout Management and Diagnosis	November 6, 2016	**9,062,362**
Insomnia Management	May 3, 2016	**259,189,023**
Depression Treatment	February 9, 2016	**23,937,091**
Pressure Ulcers	March 3, 2015	**359,877**
Nephrolithiasis Management and Prevention	November 4, 2014	**36,950,445**
Urinary Incontinence in Women	September 16, 2014	**59,084,649**
Obstructive Sleep Apnea Diagnosis	August 5, 2014	**30,481,155**
Pelvic Exam	July 1, 2014	**314,965,394**
Anemia in Patients with Heart Disease	December 3, 2013	**2,143,381**
Chronic Kidney Disease	October 22, 2013	**9,230,003**
Obstructive Sleep Apnea Management	October 1, 2013	**34,836,628**
Stable Ischemic Heart Disease	November 20, 2012	**3,947,309**
Oral Treatment of Type 2 Diabetes	February 7, 2012	**3,813,927**
Venous Thromboembolism Prophylaxis	November 1, 2011	**1,028,426**
COPD Diagnosis and Management	August 2, 2011	**68,637,963**
Intensive Insulin Therapy	February 15, 2011	**17,320,109**
Erectile Dysfunction	November 3, 2009	**53,191,554**
2nd Generation Antidepressants	November 18, 2008	**29,228,166**
Osteoporosis in Men Screening	May 6, 2008	**95,790,357**
Dementia Pharm Treatment	March 8, 2008	**29,604,372**
Palliative Care	January 15, 2008	**3,682**
Low Back Pain	October 2, 2007	**116,796,450**
Screening Mammography	April 3, 2007	**169,251,489**

Clinical Guidelines App: Summary Stats on Android and iOS Downloads

Downloads	Total Android (all-time count)	Total iOS (all-time count)	Android % increase (count)	iOS % increase (count)	Avg. downloads / month	Total increase downloads % increase (count)	Android Active Installs
Launch-8/20/2015	45,641	109,900	--	--	--	--	--
8/20/2015-1/13/2016	53,995	117,000	--	--	--	--	21,506
1/15/2016 - 5/15/2016	63,360	125,000	17.3% (9,365)	6.9% (8,000)	3,473	10.2% (17, 365)	25,146
5/15/2016-8/9/2016	68,135	130,000	7.5% (4,775)	4.0% (5,000)	3,258	5.2% (9,775)	25,937
8/9/2016-1/3/2017*	81,208	133,421	19.2% (13,073)	2.6% (3,421)	3,299	8.3% (16,494)	20,861
1/13/2017-5/19/2017	87,873	135,912	7.9% (6,665)	1.9% (2,491)	2,289	4.2% (9,156)	20,047
5/19/2017-8/18/2017	91,520	143,438	4.2% (3,647)	5.5% (7, 526)	3,724	5.0%% (11,173)	19,146
8/18/2017-1/3/2018	95,943	145,784	4.8% (4,423)	1.6% (2,346)	1,504	2.8% (6,769)	17,634
1/3/2018-4/3/2018	99,261	147,621	3.5% (3,318)	1.3% (1,837)	1,718	2.1% (5,155)	17,455
4/3/2018-8/15/2018	103,570	163,343	4.3% (4,309)	10.7% (15,722)	6,163	7.5% (20,031)	16,353
8/16/2018-12/31/2018	106,896	178,628	3.2% (3,326)	9.0% (15,285)	4,135	7.0% (18,611)	15,502
1/1/2019-3/31/2019	109,252	180,459	2.2% (2,356)	1.0% (1,831)	1,395	1.5% (4,187)	15,633
4/1/2019-7/31/2019	112,281	181,940	2.7% (3,029)	.81% (1,481)	1,128	1.5% (4,510)	15,306
7/31/2019-12/31/2019	116,363	185,871	3.5% (4,082)	2.1% (3,931)	1,603	1.4% (8,013)	15,697
1/1/2020-7/31/2020	125,560	189,927	7.3% (9,197)	2.1% (4,056)	1,893	4.2% (13,253)	14,561
7/31/2020-12/31/2020	133,747	193,454	6.1% (8,187)	1.7% (3,257)	2,343	3.6% (11,714)	13,661
TOTAL DOWNLOADS	**327,201**						

ACP Guidelines Web Hits: Active Publications

	Publication Date	Page Views Through 12/31/2020
Non-Pharmacological and Pharmacological Management of Acute Pain from Non-Low Back, Musculoskeletal Injuries in Adults: A Clinical Guideline from the American College of Physicians and American Academy of Family Physicians	11/3/2020	26,977

	Publication Date	Total Hits Through 5-11-2020
Testosterone Treatment in Adult Men with Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians		
Guideline	1/7/2020	93,531
Evidence Review	1/7/2020	5,560
Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians	11/5/2019	17,487
Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians	9/3/2019	2,610
The Development of Clinical Guidelines and Guidance Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods	6/18/2019	2,716
Screening for Breast Cancer in Average-Risk Women: A Guidance Statement From the American College of Physicians	4/9/2019	74,838
Hemoglobin A1c Targets for Glycemic Control with Pharmacologic Therapy in Non-Pregnant Adults with Type 2 Diabetes Mellitus (Guidance Statement)	3/8/2018	238,371
Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women		
Guideline	5/9/2017	167,691
Evidence Review	11/18/2014	74,707
Noninvasive Treatments for Acute, Subacute, and Chronic		

Low Back Pain		
Guideline	2/14/2017	432,602
Pharma Evidence Review	2/14/2017	44,870
Non-Pharma Evidence Review	2/14/2017	76,542
Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus		
Guideline	1/3/2017	128,585
Evidence Review	6/7/2016	12,416
Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets		
Guideline	1/17/2017	152,868
Evidence Review	1/17/2017	39,975
Diagnosis of Acute Gout		
Guideline	11/1/2016	35,413
Evidence Review	11/1/2016	15,177
Management of Acute and Recurrent Gout		
Guideline	11/1/2016	179,034
Evidence Review	11/1/2016	22,858
Management of Chronic Insomnia Disorder in Adults		
Guideline	7/19/2016	108,885
Evidence Review	7/19/2016	9,451
Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder		
Guideline	3/1/2016	96,366
Evidence Review	3/1/2016	7,115

Appropriate Use of High Flow Nasal Oxygen in Hospitalized Patients for Initial or Post-Extubation Management of Acute Respiratory Failure: A Clinical Guideline from the American College of Physicians (Manuscript# - M20-7533)

Note: Draft responses will be circulated via separate email ahead of the meeting. Comments are provided here for your reference.

Editorial Comments

Comment	Response
1. About half of the text of this paper is a summary of the evidence in the systematic review. This resulted in a great many comments and confusion by one of the reviewer, who thought that the point of this paper was the report the findings of the systematic review, rather than the focus which is on using the evidence from the systematic review to make guideline recommendations. While this paper did a good job describing the guideline process, it gets lost in the overwhelming description of the evidence from the systematic review, which is more than would be expected for an original manuscript. Instead this paper should make clearer the evidence that is from the systematic review and focus on highlighting the summary and referencing the systematic review appropriately.	
2. In order to make sense, the two papers need to be co-published, or the systematic review needs to be published first so that it may be referenced appropriately. We are glad to discuss further different options to make this work given the comments and revisions needed. The search date for this review was last conducted in June. We would request an updated search prior to publication.	
3. Consider how the comments by reviewers that are applicable to the systematic review may affect the implications or presentation of this guideline. As suggested by reviewers, clarify for readers whether these guidelines apply to only hypoxic respiratory failure or how to consider hypercarbic and hypoxic respiratory failure. Also clarify the settings included in "hospitalized" such as ED etc.	
4. The background should include a better description of reason and goal of guideline . What was impetus for doing guideline? Is there evidence of variation? Is there process to nominate topics for guideline? What is the uncertainty? What were the clinical questions behind this guideline? The KQ listed in the methods are those for the systematic evidence review, not for the guideline; what are the guideline questions? I see them in the titles of Supplemental Tables 1 and 2, but they do not appear anywhere in the text or earlier.	

Appropriate Use of High Flow Nasal Oxygen in Hospitalized Patients for Initial or Post-Extubation Management of Acute Respiratory Failure: A Clinical Guideline from the American College of Physicians (Manuscript# - M20-7533)

Reviewer Comments

Comment	Response
Reviewer 1	
1. This clinical guideline examines the role of high flow nasal oxygen (HFNO) in the management of acute respiratory failure for patients treated in a hospital setting. The manuscript utilizes a rigorous approach including a comprehensive literature review, a priori thresholds to categorize magnitude of effect for outcomes and GRADE methodology. This guideline has already undergone a peer review process. An additional strength is the inclusion of perspectives of members of the public. While the evidence supporting the recommendations is not compelling (especially for recommendation 1b), the specific recommendations appear to be carefully considered and reasonable. The topic is timely given the growing use of HFNO and the increasing cases of acute hypoxemic respiratory failure secondary to COVID-19. I have only two comments.	
2. Recommendation 1a addresses “hypoxemic adults with acute respiratory failure”. As stated, this comprises a broad category of patients and would include those with both hypoxemic respiratory failure as well as those with hypercapnic respiratory failure (who almost always have some degree of hypoxemia). As it stands, this recommendation would indicate that COPD patients with acute respiratory acidosis should be initially treated with HFNO over non-invasive ventilation. However, as the authors correctly note “the current evidence is insufficient on the use of HFNO in patients with hypercapnic respiratory failure”. Recommendation 1a should be more specific. I would suggest: “…clinicians use nasal oxygen rather than noninvasive ventilation for the initial treatment of hospitalized patients with acute hypoxemic respiratory failure.”	
3. The term “hospitalized” generally brings to mind patients admitted to the hospital and not necessarily those treated in the emergency department. As such, the target population should be defined early in the manuscript (i.e. in the	

abstract) so the reader clearly understands what "hospitalized" refers to. In the Target Audience and Patient Population section of the abstract, I would consider something like: "… the target patient population includes adult patients with acute respiratory failure treated in a hospital setting (including emergency department, hospital wards, step-down units, ICU…)"	
Reviewer 2	
1. Thank you for the opportunity to review this manuscript. The key questions in the guidelines are appropriate for the clinical context in which we need answers regarding the use of HFNC. They point to the weaknesses of current evidence as well as future research needs in the area.	
2. The search for data seems to be correct in relation to the databases analyzed, the biggest limitation, in my view, is the exclusion of studies that were not published in English.	
3. the methodology used to carry out the guidelines seems to me to be adequate, without any major problems, in my view, that prevent publication in the newspaper.	
4. Comparison between HFNC and NIV: there was a reduction in mortality from all causes and in the intubation rate, an effect carried by only one RCT (in the mortality outcome) and two RCTs (in the intubation outcome). Methodologically the guidelines indicate correct recommendations (low certainty in the recommendation and conditional recommendation in the intervention), however, I believe that they are quite optimistic for the level of knowledge we have on the subject. It is important for the authors to emphasize more emphatically in the body of the text with respect to the various limitations of such a recommendation, based on a few studies with very peculiar and distinct methodologies (at least on the intubation outcome). It is noted that when comparing HFNC and conventional oxygen therapy, there is no difference between the groups in the outcomes of mortality (4 RCTs and 1407 patients) and intubation (8 RCTs and 1694 patients). It does not make sense, from a physiological point of view, that the outcome with NIV is inferior to the outcome with oxygen therapy, which makes us infer, in the light of	

current knowledge, that the "superiority" of HFNC in comparison to NIV is due to the intrinsic peculiarities to studies that addressed the issue.	
5. The cost assessment is worthwhile, however, I consider it important to hear the opinion of the authors regarding its limitations, which is restricted to the United States scenario. In other countries, this cost assessment is certainly different.	
Reviewer 3	
1. High-flow nasal cannulae (HFNCs) have become a standard of care to deliver heated and humidified oxygen in several clinical situations for adults. It has several physiologic benefits over conventional oxygen therapy. It has been used to treat various causes of hypoxemic respiratory failure and post-extubation as both prophylaxis and treatment. However, the shreds of evidence are of low certainty, limiting the ability to draw conclusions or make recommendations. This manuscript has an in-depth review of all randomized controlled studies to confirm the clinical advantages of HFNC over other methods. The guidelines were well written with all the appropriate available evidence in the literature. The results were presented well, and it was easy to follow through. I agree with the authors on those recommendations. As they indicated, several studies(Maggiore et al. citation 33, Rittayamai et al. citation 39, Hernandez et al., Stephen et al., and Tiruvoipati et al.) seem to have a positive effect on the use of HFNC in the post-extubation setting.	
2. To select patients who would most likely benefit from HFNC in a post-extubation setting deserves further research. Some expert reviews try to propose the high-risk patient who may benefit, but it has not been validated in the prospective studies. (https://doi.org/10.1513/AnnalsATS.201707-548FR). This can be a potential clinical consideration.	
3. Overall, the manuscript is well written, scientifically sound with a good study design, analysis, and explanation of the results.	
Reviewer 4	
1. This manuscript describes a systematic review that was performed to provide clinical guidelines on	

appropriate use of high flow nasal oxygen among hospitalized patients for initial management of acute respiratory failure or post-extubation management of acute respiratory failure. This study is strengthened by the 29 RCTs and systematic reviews published between January 2000 and July 2020 using PubMed, Medline, NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects, and Health Technology Assessment Database that were included for analysis, as well as input from a broad range of stakeholders. The authors provided conditional, low-certainty recommendations for using HFNO over NIV for management of acute hypoxemic respiratory failure and HFNO over COT for management of post-extubation acute hypoxemic respiratory failure. However, I am concerned about pooling estimates across heterogeneous types of respiratory failure or across specific patient populations, and have several suggestions for improving the manuscript.	
2. The overall recommendations seem too broad when data support using 1) using noninvasive ventilation (NIV) in specific patient populations with specific diagnoses, and 2) only using high flow nasal oxygen (HFNO) in high-risk individuals post-extubation.	
3. Acute respiratory failure is quite broad and encompasses both hypoxemic and hypercarbic respiratory failure which have varying pathology and respond to therapies quite differently. Pooling estimates for different types of respiratory failure does not seem clinically appropriate. Similarly, many of the included studies were either pilot RCTs or investigated specific populations. Pooling estimates from such studies also does not seem clinically or scientifically appropriate. a. Did the authors attempt to perform meta-analyses? I suspect the heterogeneity of the included studies would preclude meta-analyses.	
4. The authors should more explicitly state how their manuscript contributes to the literature, when they cite a systematic review/meta-analysis published in 2020. a. Additionally, the JAMA manuscript demonstrates a mortality benefit for helmet	

ventilation over HFNO which the authors should rectify with the findings in the present study.	
5. There should be a table that lists all of the individual studies with the study characteristics, population, number of patients, P:F ratio, exposure, outcomes assessed/timing, etc. Maybe this should replace the current Table 2?	
6. I worry that the various types of COT included are quite different from one another, and as the amount of flow delivered increases, begins to approximate HFNO.	
7. Initial management – why did the authors classify hospital-acquired pneumonia as having a modest reduction with HFNO compared to both NIV and COT when both 95% CIs cross 0? The point estimate in and of itself should not be sufficient to make this assessment.	
8. Post-extubation – this is another example of several things I commented on previously – the authors state that all-cause mortality is potentially increased with HFNO. However, the 3 cited studies look at completely different populations, mortality is not statistically significantly different in any of the studies, and one of the studies is a non-inferiority study.	
9. I am confused by when the authors choose to state that an outcome is potentially increased or decreased when the 95% CI crosses 0 (e.g., mortality) vs when they do not (e.g., ICU LOS).	
10. I certainly think the HFNO vs COT comparison is biased by confounding by indication, but we would need to have data on P:F to fully understand this comparison.	
11. I think Figure 2 should be explained in a footnote or at the top, including indicating that the black dots are the point estimates for the comparison between the two and that the yellow bars are the 95% CIs. a. Why did the authors choose to show HFNO vs NIV for initial management and HFNO vs COT for post-extubation management? Why are all 4 comparisons not included? b. I think these displays could be larger and clearer. c. The outcomes in the figure should match the order they're described in the manuscript.	

d. It would make more sense to me to have HFNO on the top and then the comparator on the bottom.	
12. Page 5, line 150 – I think this was intended to read 'overview' rather than 'over'.	
13. Page 5, line 163 – I am not sure what the authors are referencing when they discuss that statistically significant findings are denoted with an asterisk – there is no corresponding table or figure.	
14. Patient Comfort – it is confusing to the reader that improvement is negative numbers in one study and positive numbers in other studies. The first study with negative numbers should be explained as to what is being measured.	

Appropriate Use of High Flow Nasal Oxygen in Hospitalized Patients for Initial or Post-Extubation Management of Acute Respiratory Failure: A Clinical Guideline from the American College of Physicians

Amir Qaseem, MD, PhD, MA, Itziar Etxeandia-Ikobaltzeta, PharmD, PhD, Nick Fitterman, MD, John W. Williams Jr., MD, MHS, & Devan Kansagara, MD, MCR for the Clinical Guidelines Committee of the American College of Physicians

Corresponding author:
A. Qaseem
190 N. Independence Mall West
Philadelphia, PA 19106
Email aqaseem@acponline.org

Word count: 4289

Date: 11/16/2020

Abstract

Description

The American College of Physicians (ACP) developed this guideline to provide clinical recommendations on the appropriate use of high flow nasal oxygen in hospitalized patients for initial or post-extubation management of acute respiratory failure. It is based on the best available evidence on the benefits and harms of high flow nasal oxygen, taken in the context of costs and patient values and preferences.

Methods

The ACP Clinical Guidelines Committee based these recommendations on a systematic review on the efficacy and safety of high flow nasal oxygen. The patient-centered health outcomes evaluated included all-cause mortality, hospital length of stay, 30-day hospital readmissions, hospital-acquired pneumonia, days of intubation/reintubation, intensive care unit (ICU) admission and ICU transfers, patient comfort, dyspnea, delirium, barotrauma, compromised nutrition, gastric dysfunction, functional independence at discharge, discharge disposition, and skin breakdown. We developed this guideline using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology.

Target Audience and Patient Population

The target audience is all clinicians and the target patient population includes hospitalized adult patients with acute respiratory failure.

Recommendations

Recommendation 1a: ACP suggests that clinicians use high flow nasal oxygen rather than noninvasive ventilation in hospitalized hypoxemic adults for the management of acute respiratory failure (conditional recommendation; low-certainty evidence).

Recommendation 1b: ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy in hospitalized hypoxemic adults with post-extubation acute respiratory failure (conditional recommendation; low-certainty evidence).

Introduction

High-flow nasal oxygen (HFNO) therapy is a relatively new type of noninvasive respiratory support that has been gaining widespread use for hospitalized patients in recent years. It involves the delivery of warm and humidified oxygen at a flow higher than the patient's inspiratory flow (up to 60 L/min) via a small nasal cannula. The purported benefits of HFNO compared to conventional oxygen therapy (COT) [low flow systems (nasal cannulae or masks) and high flow systems (masks)] and noninvasive ventilation (NIV) [continuous or bi-level positive airway pressure ventilation] include improved patient comfort, compliance (1) and physiological advantages, such as improved oxygenation and ventilation, reduced anatomical dead space, modest positive-end expiratory pressure, more efficient respiratory effort, reduced work of breathing, and secretion clearance (2-4). High flow nasal oxygen can be used as respiratory support in critically ill patients for a number of indications including respiratory failure or support post-extubation (1, 2).

Guideline Focus and Target Population

The purpose of this American College of Physicians (ACP) guideline is to present recommendations on the use of high flow nasal oxygen in hospitalized patients for initial or post-extubation management of acute respiratory failure. The Clinical Guidelines Committee (CGC) developed the recommendations, which are based on the best available evidence on the benefits and harms, patient values and preferences, and consideration of costs.

The target audience for this guideline is all clinicians and the target patient population includes hospitalized adult patients with acute respiratory failure. These recommendations are based on a systematic evidence review conducted by the Minneapolis VA Center for Care Delivery and Outcomes Research, funded by ACP (5).

Methods

Systematic Review of the Evidence

Details and methods for the supporting systematic evidence review are included in the accompanying paper (5) and in the Appendix. The CGC identified the key questions and convened a technical expert panel, comprised of clinical topic experts, clinicians, and epidemiologists to inform the evidence review and assist in refining the scope and key questions. Key questions included were:

Key Question 1: What is the comparative effectiveness of HFNO versus noninvasive ventilation or conventional oxygen therapy for hospitalized patients with acute respiratory failure?
Key Question 1a) Does comparative effectiveness of HFNO vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

Key Question 2: What are the harms of HFNO versus noninvasive ventilation or conventional oxygen therapy for hospitalized patients with acute respiratory failure?

Key question 2a) Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

Reviewers searched Medline, EMBASE, Cochrane, and CINAHL for randomized controlled trials (RCTs) and systematic reviews (as further source of RCTs) published in English from January 2000 through July 2020. They included studies that compared HFNO (humidified oxygen with flow rates ≥20 L/min) to NIV (continuous or bilevel positive airway pressure ventilation delivered through mask, nasal pillow, or helmet interface) or COT (oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask, etc.) in hospitalized patients with acute respiratory failure (defined as either SpO2 <90%, PaO2:FIO2 ratio ≤300, PaO2 ≤60 mmHg, or PaCO2 ≥45 mmHg). Studies that were included evaluated patients in hospital settings (including emergency departments, hospital wards, intermediate/step-down units, and intensive care units [ICU]) who were either hospitalized for acute respiratory failure or who developed acute respiratory failure post-extubation or post-surgery. Studies that assessed HFNO for oxygenation support before and during intubation were excluded. Non-randomized trials and observational studies were also excluded. Based on input from the CGC and technical expert panel, the reviewers stratified the primary analysis by indication: initial management of acute respiratory failure and post-extubation respiratory failure (defined as respiratory failure that develops after removal of endotracheal tube).

Main Outcomes

Committee members (clinicians and non-clinician public members) and the CGC Public Panel members were asked *a priori* to independently rate the importance of evaluated outcomes. Outcomes rated as critical included all-cause mortality, hospital length of stay, hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission and ICU transfers, and patient comfort. The remaining health outcomes were rated as important: delirium, 30-day hospital readmissions, barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury), compromised nutrition (enteral or parenteral nutrition), gastric dysfunction (placement of nasogastric tube, abdominal distension, nausea, or vomiting), functional independence at discharge, discharge disposition (home, assisted-living facility, nursing home, or long-term care hospital), and skin breakdown or pressure ulcers. All critical and important outcomes were considered in developing recommendations.

CGC members and technical expert panel members also agreed *a priori* upon thresholds to categorize the magnitude of effect for the following outcomes: all-cause mortality, hospital-acquired pneumonia, intubation, length of stay (ICU or hospital), and skin breakdown (Table 1).

Values and Preferences

ACP staff searched several databases (TRIP Medical Database, PubMed, Medline, EMBASE and CINAHL) through February 2020 to identify systematic reviews and individual studies on patient values and preferences regarding the use of high flow nasal oxygen. The development of this guideline also included perspectives, values, and preferences of two CGC members who

represent the public and a 7-member CGC Public Panel, who rated outcomes, provided input on their preferences among the intervention options via a direct choice exercise, and provided comments on the guideline and recommendations.

Costs

The CGC searched several databases (PubMed, Medline, NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) to identify literature on the costs of the interventions. Under the Medicare Inpatient Prospective Payment System, inpatient services are paid in episode of care bundles and not individually reimbursed, so the CGC used the Medicare Fee Schedule (outpatient) to approximate national average cost information according to the Medicare reimbursements fees.

Evidence to Recommendations

This guideline was developed by the CGC according to ACP's guideline development process, details of which can be found in ACP's methods papers (6, 7). The CGC used the GRADE tables in the accompanying systematic review (5) when reporting the evidence and graded the evidence and recommendations using GRADE methodology (8, 9) (Figure 1). The accompanying GRADE evidence-to-decision tables illustrate the evidence framework supporting the recommendations (Supplement).

Peer Review

The guideline underwent a peer review process through the journal and was posted online for comments from ACP Regents and ACP Governors, who represent internal medicine and its subspecialty physician members at the national and international levels. The CGC considered any comments before finalizing the guideline.

Summary of the Evidence

The evidence review identified 29 studies that met the inclusion criteria, of which 11 studies compared HFNO to NIV (10-20) and 21 studies (11, 14, 16, 21-38) compared HFNO to COT (3 studies used both as comparators). Table 2 provides an over of study characteristics. Eighteen studies took place in the ICU, 6 in the emergency department, and 5 in the hospital/ward/step down unit. Twenty studies assessed hypoxic respiratory failure, 10 of which included hypoxic, nonhypercapnic, 7 studies included patients with mixed hypoxic and hypercapnic respiratory failure, and 2 studies included hypercapnic respiratory failure. Underlying conditions in the studies included multiple diseases (n=19), followed by post-extubation (n=10), chronic obstructive pulmonary disease (n=3), immunocompromised patients (n=2), bronchoscopy (n=1), cardiogenic pulmonary edema (n=1), cystic fibrosis (n=1), and obesity (n=1). According to baseline PaO2/FIO2 ratio (<200) or SPO_2 (≤88%), patients in the included studies typically had at least moderate acute respiratory failure. Patients enrolled in the COT trials had a higher baseline mean SpO_2 (88%) compared those in the NIV trials (76%). Studies did not require patients to have failed any initial oxygen therapy prior to randomization. Treatment protocols and clinician/health system training varied among studies and were poorly reported. Findings that are statistically significant are denoted with "*".

Outcomes for Patients with Initial Management of Acute Respiratory Failure

Twenty-two studies reported outcomes for patients during initial management of acute respiratory failure. Eight RCTs (10-17) compared HFNO to NIV and 14 RCTs compared HFNO to COT (11, 14, 16, 21-31).

Critical Outcomes

All-Cause Mortality

Evidence showed that HFNO may result in a large reduction in all-cause mortality* for patients with hypoxic acute respiratory failure compared to NIV (low certainty; absolute risk difference [ARD], -15.8% [95% CI, -21.4% to -5.9%]) (11).

Evidence showed that HFNO may not reduce all-cause mortality for patients with hypoxic acute respiratory failure compared to COT (low certainty; ARD -0.8% [CI, -4.9% to 3.8%]) (11, 23, 27, 29).

Dyspnea

Evidence showed that there may not be a reduction in dyspnea among patients receiving HFNO compared to those receiving NIV (low certainty). Data could not be pooled. Two RCTs (10, 13) showed no difference in the short-term (mean change from baseline -0.1 vs. -0.9) or longer-term (standardized mean difference [SMD] 0.21 [CI, -0.12 to 0.54]) while 1 RCT (11) showed a higher percentage of patients with improvement in the short-term (ARD 17.3%, [CI, 3.7% to 30.9%]). Results varied among 4 small crossover trials: 2 trials (15, 16) showed little to no difference, 1 trial (14) reported short-term improvement, and 1 reported worsening (12).

Evidence showed that there may be a reduction in dyspnea among patients receiving HFNO compared to those receiving COT (low certainty). Not all data could be pooled. Pooled results from 4 trials (25-27, 31) showed an improvement based on scale scores (SMD, -0.56 [CI, -1.35 to 0.24]) and results from 3 trials (11, 21, 23) showed a higher percentage of patients with improvement in dyspnea or breathing (ARD 22.2% [CI, 13.3% to 31.1%]). Two RCTs (29, 30) showed little to no difference in short-term dyspnea based on scale scores (medians 2.3 to 3 vs. 2.6 to 3 on a 10-point scale, 10=most severe). Four small crossover studies showed little to no difference in short-term dyspnea (14, 16, 22, 28).

Hospital-Acquired Pneumonia

Evidence showed that HFNO may result in a modest reduction in hospital-acquired pneumonia among patients with hypoxic acute respiratory failure compared to NIV (low certainty; ARD -4.4% [CI, -7.0% to 3.7%]) (11).

Evidence showed HFNO may result in a modest reduction in hospital-acquired pneumonia amount among patients with hypoxic acute respiratory failure compared to COT (low certainty; ARD -4.8% [CI, -7.3% to 3.7%]) (11).

ICU Admissions

Evidence is very uncertain about the effect of HFNO on ICU admissions compared to NIV (insufficient) (10).

Evidence is very uncertain about the effect of HFNO on ICU admissions compared to COT (insufficient) (21, 23).

Intubation

Evidence showed that HFNO may result in a modest reduction in intubations* compared to NIV (low certainty; ARD -9.4% [CI, -15.2% to -1.6%]) (10, 11). Results did not vary by type of respiratory failure (hypoxic; hypoxic and/or hypercapnic).

Evidence showed that HFNO may not reduce intubation compared to COT (low certainty; ARD -0.4% [CI, -15.6% to 23.9%]) (11, 21, 23, 25-27, 29, 30). Results did not vary by type of respiratory failure (hypoxic; hypoxic and/or hypercapnic).

Length of Stay in the Hospital

Evidence showed that HFNO may not reduce hospital length of stay among patients with hypoxic and/or hypercapnic acute respiratory failure when compared to NIV (low certainty; MD 0.45 days [CI, -0.69 to 1.59]) (10, 17).

Evidence showed HFNO may not reduce hospital length of stay compared to COT (low certainty; medians ranged from 1 to 24 vs. 1 to 27 days) (23, 24, 27, 29).

Length of Stay in the ICU

Evidence is very uncertain about the effect of HFNO on ICU length of stay when compared to NIV (insufficient) (10, 11).

Evidence is very uncertain about the effect of HFNO on ICU length of stay when compared to COT (insufficient) (11, 24, 29).

Patient Comfort

Evidence showed that there may be an increase in comfort among patients receiving HFNO compared to those receiving NIV (low certainty). Data could not be pooled. One RCT (11) showed that HFNO increased comfort as assessed by an unmarked 100 mm visual analogue scale (VAS) (SMD -0.51 [CI,-0.78 to -0.24]) and another RCT (17) reported higher percentage of patients feeling comfort with HFNO than with NIV (ARD 21.4% [9.4 to 33.4]). One RCT (10) showed no difference based on a 5-point VAS (medians 2 vs. 2 on scale, 5=most discomfort). Among 4 crossover studies, 3 reported little to no difference (12, 15, 16) and 1 reported improvement in short-term patient comfort based on a 10-point numeric rating scale (NRS) (14).

Evidence showed that there may be an increase in comfort among patients receiving HFNO compared to those receiving COT (low certainty). Not all data could be pooled. Pooled data from 4 RCTs (11, 25-27) showed that HFNO increased comfort based on scale scores (SMD -0.61

[CI, -0.81 to -0.41]). One RCT (21) reported higher comfort based on a 5 point Likert scale (4 vs. 3 on a 5-point scale, 5=most comfort) while two others (29, 30) reported no difference in patient comfort on a 10-point scale (7.9 vs. 6.8 on a scale where 10=perfect and medians 3 vs. 3 on a scale where 10=worst). One RCT (23) showed a lower percentage of patients experiencing discomfort due to airway dryness (ARD -15.5% [CI, -30.8% to -0.2%]). Four small crossover studies reported little to no difference in short-term patient comfort (14, 16, 22, 28).

Important Outcomes

Skin Breakdown

Skin breakdown was not reported in studies comparing HFNO to NIV for the initial management of acute respiratory failure.

Evidence is very uncertain about the effect of HFNO on skin breakdown compared to COT (insufficient) (23, 27).

Intermediate Outcomes

One RCT reported higher rates of treatment escalation (defined as requiring a switch from HFNO to NIV or from NIV to HFNO) with HFNO when compared to NIV (10). Two trials reported higher rates of device intolerance in NIV compared to HFNO (13, 14).

Seven RCTs reported higher rates of treatment escalation for COT (to either HFNO or NIV) than HFNO (to NIV) (21, 23-25, 27, 29, 30). Six RCTs reported device intolerance but reporting was limited in the COT groups (14, 23, 25, 27, 29, 31).

Outcomes for Patients with Post-Extubation Acute Respiratory Failure

Ten studies reported outcomes for patients with post-extubation (including post-cardiothoracic surgery) acute respiratory failure. Three RCTs (18-20) compared HFNO to NIV, and 7 RCTs (32-38) compared HFNO with COT.

Critical Outcomes

All-Cause Mortality

Evidence showed that HFNO may increase all-cause mortality slightly when compared to NIV (low certainty; ARD 1.7% [CI, -1.3% to 5.7%]) (18-20). Results did not vary by type of respiratory failure (hypoxic; hypoxic, non-hypercapnic; hypercapnic).

Evidence showed that HFNO may not reduce all-cause mortality for patients with hypoxic acute respiratory failure when compared to COT (low certainty; ARD -0.1% [CI, -2.5% to 4.5%]) (32, 33, 36, 37).

Dyspnea

Evidence showed that there may not be a reduction in dyspnea among patients receiving HFNO compared to those receiving NIV (low certainty; ARD -2.4% [95% CI, -8.5% to 4.8%]) (20).

Evidence is very uncertain about the effect of HFNO on dyspnea compared to COT (35).

Hospital-Acquired Pneumonia

Evidence showed that HFNO may not reduce hospital-acquired pneumonia in patients with hypoxic acute respiratory failure compared to NIV (low certainty; ARD -1.5% [CI, -4.4% to 2.3%]) (18, 20).

Evidence showed that HFNO may not reduce hospital-acquired pneumonia in patients with hypoxic, nonhypercapnic acute respiratory failure compared to COT (low certainty; ARD -1.1% [95% CI, -2.0% to 2.2%]) (32).

ICU Admissions

No studies compared ICU admissions in patients with post-extubation acute respiratory failure for HFNO versus NIV or COT.

Reintubation

Evidence showed that HFNO may increase reintubations slightly compared to NIV (low certainty; ARD 2.0% [CI, -1.5% to 6.6%]) (18-20). Results did not vary by type of respiratory failure (hypoxic; hypoxic, non-hypercapnic; hypercapnic)

Evidence showed that HFNO may reduce reintubations slightly compared to COT (low certainty; ARD -3.9% [CI, -7.8% to 5.3%]) (32-38). Results did not vary by type of respiratory failure (hypoxic; hypoxic, non-hypercapnic; hypoxic and/or hypercapnic)

Length of Stay in the Hospital

Evidence is very uncertain about the effect of HFNO on hospital length of stay compared to NIV (insufficient) (18, 20).

Evidence is very uncertain about the effect of HFNO on hospital length of hospital compared to COT (insufficient) (32, 37).

Length of Stay in the ICU

Evidence showed that HFNO may not reduce ICU length of stay when compared to NIV (low certainty). Pooled data from 2 RCTs (18, 19) showed no difference (mean difference [MD], -0.98 days [CI, -1.99 to 0.03 days]) and a third trial (20) that could not be pooled also reported no difference in ICU length of stay based on median stay (medians 6 vs. 6 days).

Evidence showed that HFNO probably does not reduce ICU length of stay when compared to COT (moderate certainty). Pooled data from 5 RCTs showed little or no difference in length of stay (MD, 0.19 days [CI, -0.19 to 0.57 days) (33, 35-38). Another RCT (32) that could not be pooled also reported little to no difference in ICU length of stay between HFNO and COT (medians 6 vs. 6 days).

Patient Comfort

Evidence showed that there may not be an increase in comfort among patients receiving HFNO compared to those receiving NIV (low certainty). Data could not be pooled. One RCT (20) showed that HFNO made little to no difference in the percentage of participants reporting good comfort compared to NIV (ARD -1.6% [CI, -8.7% to 5.6%]). Another smaller study (19) found HFNO may increase comfort based on a 10-point scale where lower means better (SMD -0.75 [-1.38 to -0.12]).

Evidence showed that there may be an increase in comfort among patients receiving HFNO compared to those receiving COT (low certainty). Data could not be pooled. One RCT (33) showed that HFNO increased patient comfort based on a 10 point VAS where lower is better (SMD -0.70 [CI, -1.10 to -0.31) and showed lower discomfort related to interface with HFNO compared to COT (SMD -0.89 [-1.29 to -0.49]) (33). One RCT (36) showed a lower percentage of patients with discomfort related to dryness (ARD -31.5% [CI, -51.0 to -11.9%]) A third trial reported higher comfort with HFNO compared to COT on a 10-point scale (10=maximal discomfort) related to less dryness (medians 3 vs. 5) and interface (medians 3 vs. 7) (34). A fourth trial reported little to no difference in any measure of nasal, oral, or pharynx discomfort on a 10-point scale (38).

Important Outcomes

Skin Breakdown

Evidence showed that HFNO may result in a large reduction in skin breakdown compared to NIV (low-certainty; ARD -20.0% [CI, -23.7% to 2.3%]) (18-20).

Evidence is very uncertain about the effect of HFNO on skin breakdown compared to COT (insufficient) (35).

Intermediate Outcomes

Three trials reported mixed results for treatment escalation for HFNO compared to NIV (18-20). Five RCTs reported lower treatment escalation in patients with post-extubation acute respiratory failure compared to COT (RR, 0.43 [CI, 0.27 to 0.70]) (33-36, 38). Two trials also reported a higher rate of treatment or respiratory failure with COT compared to HFNO, but the studies did not clearly define subsequent treatment (32, 34).

Values and Preferences

No guidelines or systematic reviews were identified that assessed the relative importance of outcomes or patient values and preferences between HFNO and NIV. Feedback from the CGC public panel indicated a strong preference for the choice of HFNO over NIV for the initial management of acute respiratory failure, largely in part due to the mortality and intubation benefits (6 out of 6 respondents indicated that they preferred HFNO). For post-extubation management, three out of 6 respondents indicated they would prefer HFNO (most citing improved comfort as key factor in light of few other differences) and 3 said they were unsure.

No guidelines or systematic reviews were identified that assessed the relative importance of outcomes or patient values and preferences between HFNO and COT; however, 1 primary study was identified. A randomized crossover trial (39) conducted in a respiratory ICU in Thailand found that most (88.2%) of the recently extubated participants (n=17) preferred HFNO over COT (non-rebreather). The CGC public panel reported fewer preferences in the choice of HFNO over COT for the initial management of acute respiratory failure: Five out of 6 respondents indicated that they were unsure or had no preference and the remaining responded that s/he would prefer HFNO, citing a potential reduction in pneumonia. Four out of 6 respondents indicated that they would prefer of HFNO over COT for post-extubation acute respiratory failure; 1 responded no preference; and 1 responded unsure based on limited differences in outcomes but that reduced reintubation might sway the choice.

Costs

No studies were identified that reported on the costs of high flow nasal oxygen compared to NIV or COT in the United States. Indirect (outpatient) cost information from The Medicare national average monthly reimbursable rates were $41-$106 for COT, $185 for HFNO, and $1055 for NIV.

Multiple Chronic Conditions

None of the included studies compared HFNO with NIV or COT for acute respiratory failure in the setting of post lung transplantation, pulmonary embolism, pulmonary arterial hypertension, or asthma.

Areas of Inconclusive Evidence

Evidence was inconclusive on the use of HFNO versus COT for the initial management of acute respiratory failure. Overall, patients enrolled in the COT trials had lesser degrees of hypoxia than those enrolled in the NIV trials (baseline mean SpO_2 88% vs. 76%). Low-certainty evidence shows that HFNO may improve patient comfort, dyspnea, and result in a modest reduction in hospital-acquired pneumonia compared to COT but that it may make no difference for other clinical outcomes such as all-cause mortality, intubation, and hospital length of stay. There are additional cost and resource considerations: HFNO is more expensive than COT and widespread implementation of HFNO could be quite resource intensive. In light of these considerations, we do not believe the choice of HFNO over COT for the initial management of acute respiratory failure rises to the level of a clinical recommendation. However, most patients can use HFNO and there are usually no contraindications unless related to issues with fitting the nasal cannula.

Evidence was also inconclusive on the use of HFNO versus NIV for the management of post-extubation acute respiratory failure. Low-certainty evidence showed that HFNO may increase mortality and re-intubation slightly compared to NIV, and may make no difference in hospital-acquired pneumonia, ICU length of stay, patient comfort, and dyspnea though HFNO may reduce skin breakdowns by a large amount compared to NIV. Overall, effect sizes were inconsistent, small, and not statistically significant. Hence, evidence is inconclusive for or

against the use of HFNO over NIV for the management of post-extubation acute respiratory failure.

The current evidence is insufficient on the use of HFNO in patients with hypercapnic respiratory failure. Evidence on the use of HFNO is also insufficient for the following patient-centered outcomes: ICU admissions and length of stay for initial management of acute respiratory failure, hospital length of stay for post-extubation acute respiratory failure, or improvement in dyspnea for post-extubation acute respiratory failure compared to COT.

Areas of No Evidence

There were no studies that reported on the following patient-centered outcomes: discharge disposition, functional independence at discharge, or hospital readmissions. No studies reported on several potential harms including gastric dysfunction, compromised nutrition, delirium, or barotrauma. There was also no evidence on most intermediate outcomes, including respiratory rate, PaO2/FiO2 ration, SpO2, pH, PaO2, and PaCO2.

Recommendations

Figure 2 summarizes the recommendations and clinical considerations.

Recommendation 1a: ACP suggests that clinicians use high flow nasal oxygen rather than noninvasive ventilation in hospitalized hypoxemic adults for the management of acute respiratory failure (conditional recommendation; low-certainty evidence).

Rationale

Low-certainty evidence shows that there are benefits of using high flow nasal oxygen over NIV for the initial management of acute respiratory failure. There is a demonstrable improvement in clinically meaningful outcomes, including a reduction in mortality in patients with hypoxic, nonhypercapnic acute respiratory failure (low-certainty evidence). The reduction in mortality was large (ARD, -15.8%), but the evidence was limited to 1 trial of 216 patients. Low-certainty evidence also showed a modest reduction in intubations in patients with hypoxic and/or hypercapnic acute respiratory failure, a modest reduction in hospital-acquired pneumonia, and improvements in patient comfort. Most patients can use HFNO and there are usually no contraindications unless related to issues with fitting the nasal cannula. In addition, costs associated with using HFNO according to the Medicare national average monthly reimbursable rate are lower than NIV ($185 vs. $1055), although this cost information is limited to the outpatient setting.

Recommendation 1b: ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy in hospitalized hypoxemic adults with post-extubation acute respiratory failure (conditional recommendation; low-certainty evidence).

Rationale

Low-certainty evidence showed that HFNO may reduce re-intubation slightly compared to COT and low-certainty evidence showed that HFNO may improve patient comfort. Low-certainty

evidence also showed that HFNO did not perform worse than COT with regard to all-cause mortality, hospital-acquired pneumonia, and length of ICU stay, and although the magnitude did not pass the CGC's pre-determined thresholds, the direction of the effects for these outcomes consistently point towards a potential benefit.

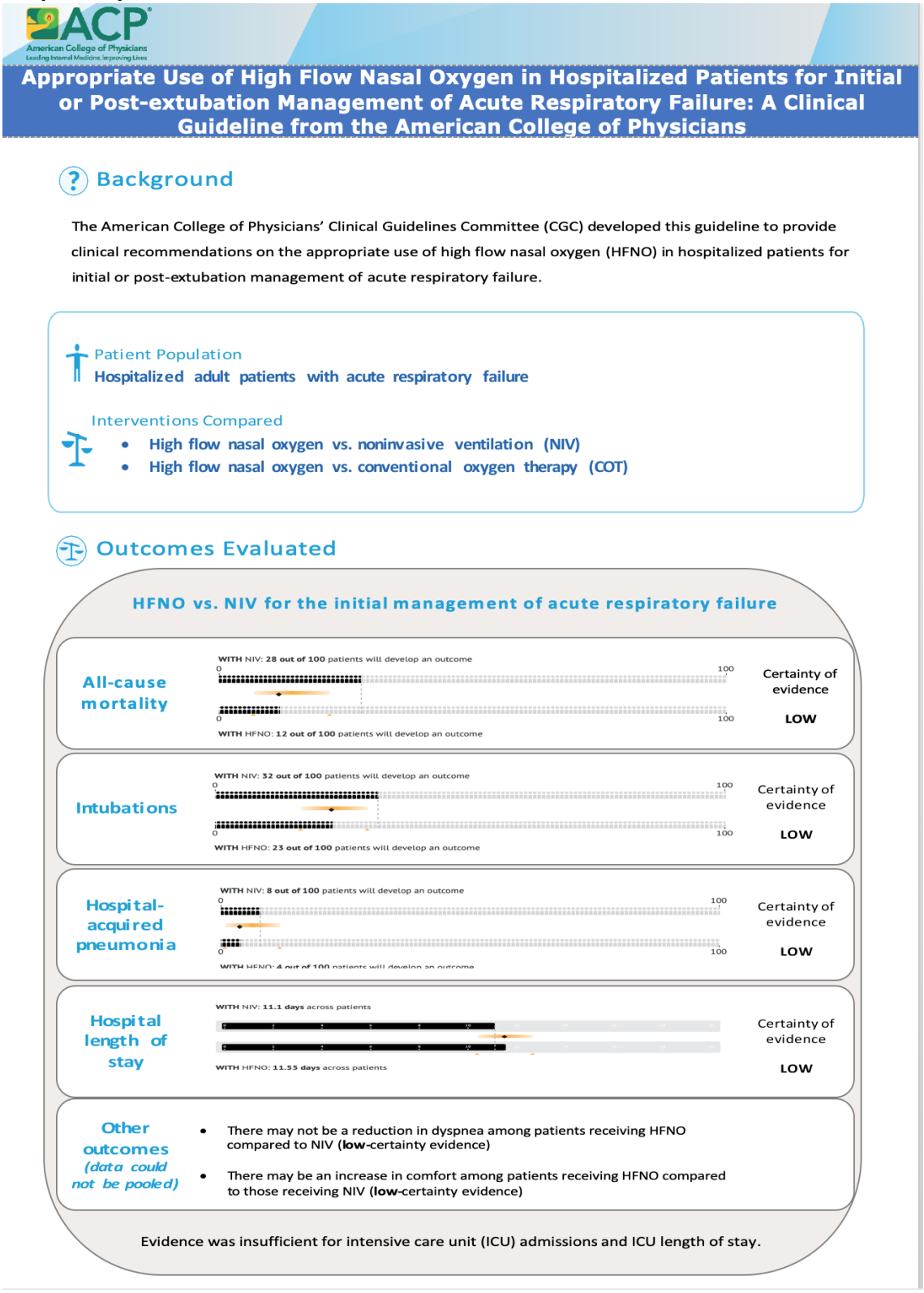
Clinical Considerations

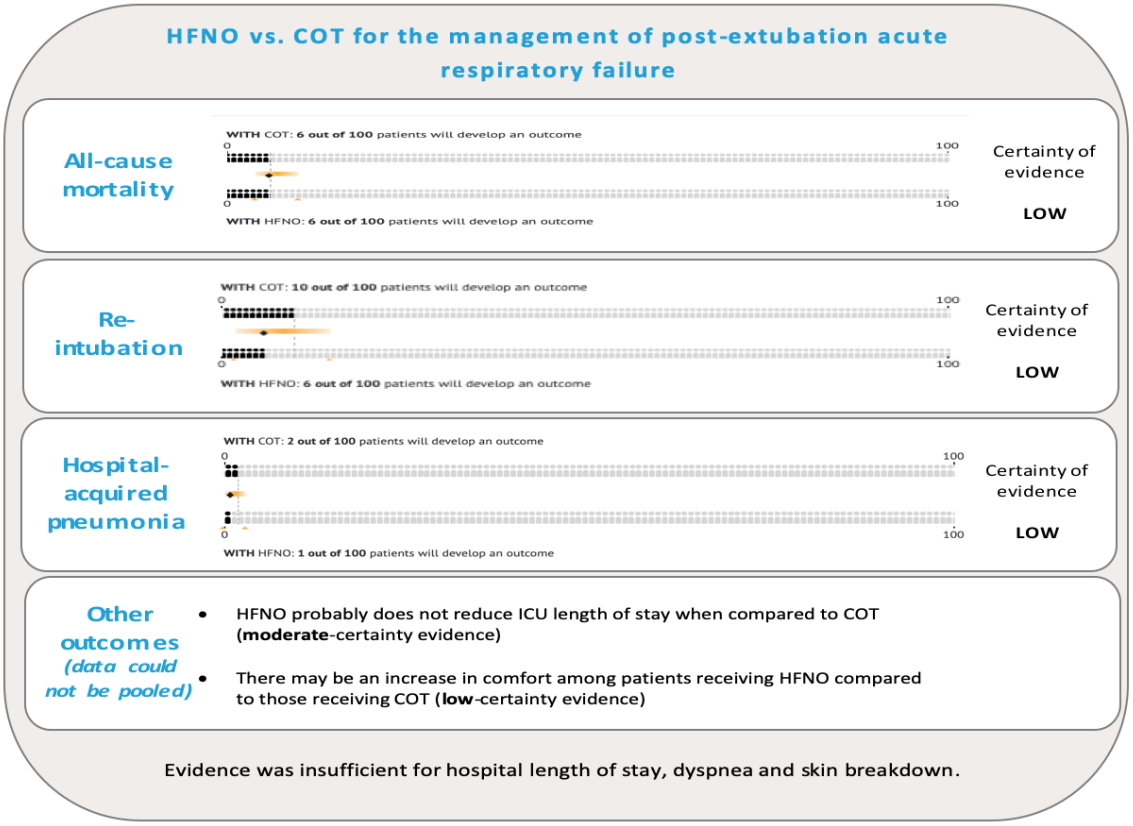
Most of the reviewed studies included patients with hypoxic respiratory failure and patients had at least moderate acute respiratory failure according to baseline PaO_2/FIO_2 ratio (<200) or SpO_2 (≤88%). Studies typically did not specify whether hypercapnic patients were excluded, and those that included patients with either hypoxic and/or hypercapnic acute respiratory failure did not specify the patient breakdown by type and did not stratify outcome reporting by type. Treatment effects did not differ significantly by clinical setting, disease indication, treatment duration, or type of acute respiratory failure, although data was limited for these comparisons. This guideline did not directly compare NIV versus COT, but another recent review found improved outcomes with NIV compared to COT (40). Few conclusions could be drawn from data on physiologic outcomes, though patients in the COT studies had lesser degrees of hypoxia than patients enrolled in the NIV studies. HFNO is an aerosol generating procedure and requires higher grades of personal protective equipment (respiratory protective devices) than routine procedures that do not involve aerosol generation (41).

Figure 1: Grading the certainty of evidence and strength of recommendations ACP clinical guidelines using GRADE

Grading Certainty of Evidence			
High	Confident that the true effect lies close to that of the estimate of the effect.		
Moderate	Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a sizeable possibility that it is substantially different.		
Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.		
Grading Strength of Recommendations			
Strength	**Balance of benefits and harms**	**Applicable Patient Population**	**Policy Implications**
Strong	Confidence that the benefits clearly outweigh risks and burden or vice versa.	Applies to most patients in most circumstances.	Only strong recommendations could be considered as quality indicators to guide the development of accountability, reporting, and payment programs.
Conditional	Benefits probably outweigh the risks and burden, or vice versa, but there is appreciable uncertainty	Applies to many patients, but may differ depending on circumstances or patients' values and preferences.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Quality indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Figure 2: Summary of the American College of Physicians Guideline on High Flow Nasal Oxygen in Hospitalized Patients for Initial or Post-extubation Management of Acute Respiratory Failure





Areas of Inconclusive Evidence

High flow nasal oxygen vs. conventional oxygen therapy for the initial management of acute respiratory failure.

Low-certainty evidence shows that HFNO may improve patient comfort, dyspnea, and result in a modest reduction in hospital-acquired pneumonia compared to COT but that it may make no difference for other clinical outcomes such as all-cause mortality, intubation, and length of stay in the hospital.

High flow nasal oxygen vs. conventional oxygen therapy for the initial management of acute respiratory failure.

Low-certainty evidence showed that HNFO may increase mortality and re-intubation slightly compared to NIV, and may make no difference in hospital-acquired pneumonia, ICU length of stay, patient comfort, and dyspnea though HNFO may reduce skin breakdowns by a large amount compared to NIV.

Values and Preferences

Values and preferences may vary according to individual patients. No relevant literature was identified that assessed patient values and preferences between HFNO and NIV. One small study reported a preference for HFNO over COT in recently extubated participants. The CGC Public Panel indicated a strong preference (6 out of 6 respondents) for the choice of HFNO over NIV for the initial management of acute respiratory failure, and most (4 out of 6) indicated a preference for HFNO over COT for post-extubation acute respiratory failure. There was more reported more variability and uncertainty in the responses for HFNO vs. COT for initial management and HFNO vs. NIV for post-extubation management.

500

Recommendations

RECOMMENDATION 1a: ACP suggests that clinicians use high flow nasal oxygen rather than noninvasive ventilation in hospitalized hypoxemic adults for the management of acute respiratory failure (conditional recommendation; low-certainty evidence).

RATIONALE: Low-certainty evidence shows that there is a demonstrable improvement in clinically meaningful outcomes, including a large reduction in mortality in patients with hypoxic, nonhypercapnic acute respiratory failure, a modest reduction in intubations in patients with hypoxic and/or hypercapnic acute respiratory failure, a modest reduction in hospital-acquired pneumonia, and improvements in patient comfort. Most patients can use HFNO and there are usually no contraindications unless related to issues with fitting the nasal cannula. In addition, costs associated with using HFNO are lower than NIV.

RECOMMENDATION 1b: ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy in hospitalized hypoxemic adults with post-extubation acute respiratory failure (conditional recommendation; low-certainty evidence).

RATIONALE: Low-certainty evidence showed that HFNO may reduce re-intubation slightly compared to COT and that HFNO may improve patient comfort. Low-certainty evidence also showed that HFNO did not perform worse than COT with regard to all-cause mortality, hospital-acquired pneumonia, and length of ICU stay, and although the magnitude did not pass the CGC's pre-determined thresholds, the direction of the effects for these outcomes consistently point towards a potential benefit.

Clinical Considerations

- Most of the reviewed studies included patients with hypoxic respiratory failure and patients had at least moderate acute respiratory failure according to baseline PaO2/FIO2 ratio (<200) or SpO2 (≤88%).
- Studies typically did not specify whether hypercapnic patients were excluded, and those that included patients with either hypoxic and/or hypercapnic acute respiratory failure did not specify the patient breakdown by type and did not stratify outcome reporting by type.
- Treatment effects did not differ significantly by clinical setting, disease indication, treatment duration, or type of acute respiratory failure, although data was limited for these comparisons.
- This guideline did not directly compare NIV versus COT, but another recent review found improved outcomes with NIV compared to COT in patients with acute hypoxemic respiratory failure (40).
- Few conclusions could be drawn from data on physiologic outcomes, though patients in the COT studies had lesser degrees of hypoxia than baseline physiologic parameters of patients enrolled in the NIV studies were worse than those enrolled in COT studies.
- HFNO is an aerosol generating procedure and requires higher grades of personal protective equipment (respiratory protective devices) than routine procedures that do not involve aerosol generation (41).

501

502 **Table 1: Thresholds for determining magnitude by outcome**

Outcome	Little or no effect	Small effect	Modest effect	Large effect
All-cause mortality	<1%	1-1.9%	2-4.9%	≥5%
Hospital-acquired pneumonia	<2%	2-3.9%	4-9.9%	≥10%
Intubation	<2%	2-3.9%	4-9.9%	≥10%
Length of stay	< 1 day	≥1 day	NA	≥ 3 day
Skin breakdown	<2%	2-3.9%	4-9.9%	≥10%

503

504 **Table 2: Study Characteristics**

Management	Risk of Bias	Acute respiratory failure *(# studies)*	Setting *(# studies)*	Patient Demographics *mean (range) [# studies] or (%) [# studies]*	Disease Indications *(# studies)*	Patient Comorbidities *(# studies)*
Initial Management of Acute Respiratory Failure *Comparison (total # studies)*						
HFNO vs. NIV (8)	Low (2) Moderate (6)	Hypoxic (5) *nonhypercapnic (3) + any (2)* Hypoxic and/or hypercapnic (3)	ED (1) ICU (4) Hospital (3)	Age: 63 (30-67) [7] Gender: 65% male (47-83%) [6] Race: 61% [1]	Multiple diagnoses (5) COPD exacerbation (1) Cystic fibrosis (1) (15) During bronchoscopy (1)	Chronic respiratory failure (1) COPD (2) CHF (3)
HFNO vs. COT (14)	Low (6) Moderate (8)	Hypoxic (11) *nonhypercapnic (4) + any (7)* Hypoxic and/or hypercapnic (2) Hypercapnic (1)	ED (5) ICU (7) Hospital (2)	Age: 68 (60-74) [12] Gender: 59% male (35-83%) [12] Race: 66% white; 79% European descent [2]	Multiple diseases (9) Cardiogenic pulmonary edema (1) COPD (1) Immunocompromised (2) Palliative care (1)	Chronic respiratory failure (3) COPD (4) CHF (6)
Post-extubation Management of Acute Respiratory Failure *Comparison (total # studies)*						
HFNO vs. NIV (3)	Low (2) Moderate (1)	Hypoxic (2) *nonhypercapnic (1) + any (1)* Hypoxic and/or hypercapnic (1)	ICU (3)	Age: 64 (64-76) [3] Gender: 65% male (64-66%) [2] Race: NR	Multiple diagnoses (1) COPD exacerbation (1) Post-cardiothoracic surgery patients (2)	COPD (2)
HFNO vs. COT (7)	Low (3) Moderate (4)	Hypoxic (5) *nonhypercapnic (3) + any (2)* Hypoxic and/or hypercapnic (2)	ICU (7)	Age: 60 (51-78) [7] Gender: 66% male (57-86%) [7] Race: NR	Multiple diagnoses (5) Obese (1) Post-cardiothoracic surgery (2)	Chronic respiratory failure (1) COPD (2) CHF (3)

505 CHF=congestive heart failure; COPD=chronic obstructive pulmonary disorder; COT=conventional oxygen therapy; HFNO=high flow nasal oxygen; NIV=noninvasive ventilation; NR = not reported

Appendix: Detailed methods

The Minneapolis VA Center for Care Delivery and Outcomes Research conducted the supporting evidence review. Details of the ACP guideline development process can be found in ACP's methods papers (6, 7). Disclosure of interests and management of any conflicts can be found at https://www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm.

Key Questions Addressed

Key Question 1: What is the comparative effectiveness of HFNO versus NIV or COT for hospitalized patients with ARF?

Key Question 1a: Does comparative effectiveness of HFNO vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

Key Question 2: What are the harms of HFNO versus NIV or COT for hospitalized patients with ARF?

Key Question 2a: Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

Search Strategy

Reviewers searched several databases for studies and systematic reviews published in English from January 2000 to July 2020.

Quality Assessment

Reviewers assessed risk of bias using a modified Cochrane approach (42) for RCTs.

Population Studied

Adults with acute respiratory failure (SpO_2 <90%, PaO_2:FIO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg)

Interventions Evaluated

High flow nasal oxygen (humidified oxygen with flow rates ≥20 L/min)

Comparators

Noninvasive ventilation (continuous or bilevel positive airway pressure ventilation [CPAP or BiPAP®]) and conventional oxygen therapy (e.g. oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask, etc.)

Outcomes

Outcomes rated as critical included all-cause mortality (in-hospital and the longest available through 30 days), hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission/ and ICU transfers, patient comfort, and hospital length of stay. The remaining health outcomes were rated as important: Delirium, 30-day hospital readmissions, barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury), compromised nutrition (enteral or parenteral nutrition), gastric dysfunction (placement of nasogastric tube, abdominal distension, nausea, or vomiting),

functional independence at discharge, discharge disposition (home, assisted-living facility, nursing home, or long-term care hospital), and skin breakdown or pressure ulcers.

Timing
Patients hospitalized for acute respiratory failure or who developed acute respiratory failure while hospitalized

Setting
Hospital (including hospital wards, intermediate/step-down units, and intensive care units) and emergency department

Target Audience
The target audience includes all clinicians

Target Patient Population
Hospitalized adult patients with acute respiratory failure

Public/Patient Involvement
The development of this guideline also included perspectives, values, and preferences of two non-physician CGC members who represent the public and a 7 member CGC Public Panel.

Peer Review
The supporting evidence review and guideline each underwent a peer review process through the journal. The guideline was posted online for comments from ACP Regents and ACP Governors, who represent internal medicine and its subspecialty physician members at the national and international level.

Notice: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to over-ride clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid five years after publication, or once an update has been issued.

Financial Statement: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Conflicts of Interest:
All financial and intellectual disclosures of interest were declared and potential conflicts were discussed and managed. Dr. Wilt was recused from chairing and from authorship and voting due to a moderate-level conflict (author of supporting evidence review). A record of disclosures of interest and management of conflicts of is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm.

APPROVED BY THE ACP BOARD OF REGENTS ON: Pending

Members of the ACP Clinical Guidelines Committee:
Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval:
†Timothy J. Wilt, MD, MPH, Chair (Tim.Wilt@va.gov)
*Devan Kansagara, MD, MCR, Vice Chair (kansagar@ohsu.edu)
*Pelin Batur MD, NCMP (baturp@ccf.org)
*Thomas G. Cooney, MD, MACP (cooneyt@ohsu.edu)
*Carolyn Crandall, MD, MS (ccrandall@mednet.ucla.edu)
*Nick Fitterman, MD (nfitterma@northwell.edu)
*Lauri A. Hicks, DO (lhicks@cdc.gov)
*Jennifer S. Lin, MD, MCR (Jennifer.S.Lin@kpchr.org)
*%Michael Maroto, JD, MBA (maroto@marotolaw.com)
*Reem A. Mustafa, MD, PhD, MPH (rmustafa@kumc.edu)
*Jeffrey A. Tice, MD (Jeff.Tice@ucsf.edu)
*%Janice Tufte (janicetufteconsulting@yahoo.com)
*Sandeep Vijan, MD, MS (svijan@umich.edu)
*John W. Williams Jr., MD, MHS (jwj.williams@duke.edu)

*Author
†Nonauthor contributor
%Non-physician public representative

Acknowledgements
The Clinical Guidelines Committee would like to acknowledge members of the ACP Guidelines Public Panel for their review and comments on the paper from a patient perspective: Cynthia Appley, Larry Curley, Ray Haeme, Billy Oglesby, James Pantelas, Missy Carson Smith, and Lelis Vernon.

Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190. N Independence Mall West, Philadelphia, PA 19106: email, aqaseem@acponline.org

Author affiliations:
A. Qaseem: American College of Physicians
I. Etxeandia-Ikobaltzeta: American College of Physicians
N. Fitterman: Northwell Health
J. Williams: Duke University School of Medicine, Durham Veterans Affairs Medical Center
D. Kansagara: Portland VA Medical Center

Current Addresses of Authors:
Amir Qaseem, MD, PhD, MHA
190 N. Independence Mall West, Philadelphia, PA 19106

Itziar Etxeandia-Ikobaltzeta, PharmD, PhD

1, Santa Margarita Hospital Street, Ground Floor 2, Office 1, Room 2, 20303 Irun, Gipuzkoa, Spain

Nick Fitterman, MD, MACP
270 Park Ave Huntington NY 11743

John W. Williams Jr., MD, MHS
200 Morris Street, 3rd Floor, Durham, NC 27701

Devan Kansagara, MD, MCR
3710 SW US Veterans Hospital Rd, Portland, OR 97239

Appropriate Use of High Flow Nasal Oxygen in Hospitalized Patients for Initial or Post-extubation Management of Acute Respiratory Failure: A Clinical Guideline from the American College of Physicians

SUPPLEMENT

Supplement Table 1. Evidence-to-Decision (EtD) Framework: Should high flow nasal oxygen (HFNO) vs. noninvasive ventilation (NIV) be used for initial management of acute respiratory failure?

Supplement Table 2. EtD Framework: Should HFNO vs. conventional oxygen therapy (COT) be used for initial management of acute respiratory failure?

Supplement Table 3. Should HFNO vs NIV be used for management of post-extubation acute respiratory failure?

Supplemental Table 4. Should HFNO vs. COT be used for management of post-extubation acute respiratory failure?

Supplement Table 1: Should HFNO vs. NIV be used for initial management of acute respiratory failure?

POPULATION:	Initial management of acute respiratory failure
INTERVENTION:	HFNO
COMPARISON:	NIV
MAIN OUTCOMES:	Intubation; All-cause mortality; Hospital-acquired pneumonia; intensive care unit (ICU) admissions; Length of stay, intensive care unit; Length of stay, hospital; Patient comfort (including related to airway dryness); Dyspnea; Hospital readmissions; Functional independence at discharge; Discharge disposition; Skin breakdown; Gastric dysfunction; Compromised nutrition; Delirium; Barotrauma

ASSESSMENT

JUDGEMENT

How Substantial Are The Desirable Anticipated Effects?
○ Trivial
○ Small
○ Medium
● **Large**
○ Varies
○ Don't know

How Substantial Are The Undesirable Anticipated Effects?
○ Large
○ Medium
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcome № of participants (studies)	Relative effect or Standardized mean difference	Anticipated Absolute effects (95% CI)*			Certainty
		NIV	HFNO	**Absolute risk difference (95% CI)**	
CRITICAL OUTCOMES					
All-cause Mortality № of participants: 216 (1 RCT) (11)	RR 0.44 (0.24 to 0.79)	28.2%	**12.4%** (6.8 to 22.3)	15.8% fewer (21.4 fewer to 5.9 fewer)	⨁◯◯ **LOW** ‡
Hospital-acquired Pneumonia № of participants: 216 (1 RCT) (11)	RR 0.46 (0.15 to 1.45)	8.2%	**3.8%** (1.2 to 11.9)	4.4% fewer (7.0 fewer to 3.7 more)	⨁◯◯ **LOW**§
Intubation № of participants: 420 (2 RCTs) (10, 11)	RR 0.71 (0.53 to 0.95)	32.4%	**23.0%** (17.2 to 30.8)	9.4% fewer (15.2 fewer to 1.6 fewer)	⨁◯◯ **LOW**†‡
ICU Admissions (yes/no) № of participants: 204 (1 RCT) (10)	RR 0.98 (0.73 to 1.32)	47.0%	**46.1%** (34.8 to 62)	-0.9% fewer (12.2 fewer to 15.0 more)	◯◯◯ **INSUFFICIENT**†‡**

Length of stay, hospital № of participants: 372 (2 RCTs) (10, 17)		The mean length of stay, hospital was **11.1** days	- The mean length of stay, hospital was **11.6** days	MD 0.45 days fewer (0.69 fewer to 1.59 more)	⊕◯◯ **LOW**†‡
Length of stay, ICU № of participants: 420 (2 RCTs) (10, 11)		The mean length of stay, intensive care unit was **8.3** days	The mean length of stay, intensive care unit was **7.7** days	WMD 0.64 days fewer (1.67 fewer to 0.39 more)	◯◯◯ **INSUFFICIENT**†‡**
Patient comfort, including related to airway dryness, based on VAS or % improved № of participants: 644 (7 RCTs) (10-12, 14-17)	1 trial (n=216) (11) reported HFNO improved comfort (SMD -0.51 [-0.78 to -0.24]) based on an unmarked 100 mm visual analogue scale (VAS) and 1 (n=168) (17) reported higher percentage of patients feeling comfort with HFNO (88.2% vs. 67.9%; ARD 21.4% [9.4 to 33.4]). 1 trial (n=204) (10) reported little to no difference in patient comfort based on a 5-point VAS (medians 2 vs. 2 on scale, 5=most discomfort). Among 4 crossover trials (n=56), 3 reported little to no difference (12, 15, 16) and 1 reported improvement in short-term patient comfort based on a 10-point numeric rating scale (NRS) (14).				⊕◯◯ **LOW**††‡‡
Dyspnea, based on VAS or Borg scale scores or % improved № of participants: 464 (7 RCTs) (10-16)	1 trial (n=177) (11) reported greater improvement in dyspnea short-term in patients allocated to HFNO compared with NIV (75.6% vs. 58.2%; ARD 17.3% [3.7 to 30.9]). 1 trial (n=180) (10) reported little to no difference in longer-term (SMD 0.21 [-0.12 to 0.54] dyspnea based on Borg. 1 trial (n=51) (13) reported little to no difference in short-term dyspnea based on 10-point VAS scale (Mean change from baseline -0.1 vs. -0.9). Among 4 crossover trials (n=56), 2 reported little to no difference based on VAS (15, 16), 1 reported worsening based on VAS (12) and 1 reported improvement in short-term dyspnea based on Borg (14).				⊕◯◯ **LOW**††‡‡
	IMPORTANT OUTCOMES				
Skin breakdown (facial pressure sore or nasal ulceration)	**NOT REPORTED**				

Explanations

† Downgraded two levels for large imprecision (very wide CIs) and/or sparse data and/or difficult to interpret based on the variability in the reporting of the effects

‡ Downgraded for imprecision (wide CIs)

§ Downgraded for study limitations, particularly high attrition

** Downgraded for indirectness, ICU stay possibly protocol driven

†† Downgraded due to inconsistency

‡‡ Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effect

§§ Downgraded to insufficient based on the enormity of the imprecision or difficult to interpret based on the variability in the reporting of the effects

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Insufficient ● **Low** ○ Moderate ○ High ○ No included studies	See Summary of Findings Table above.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No guidelines, systematic reviews, or studies were identified that assessed the relative importance of outcomes or patient values and preferences between HFNO and NIV. Feedback from the CGC public panel indicated a strong preference for the choice of HFNO over NIV for the initial management of acute respiratory failure, largely in part due to the mortality

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE

	See Summary of Findings Table above.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ● **Large savings** ○ Varies ○ Don't know	No studies were identified that reported on the costs of high flow nasal oxygen compared to noninvasive ventilation in the United States.

Table: National Average Medicare Monthly Reimbursable Rates for Noninvasive Respiratory Support Modalities (High Flow Nasal Oxygen vs. Noninvasive Ventilation)

Intervention	Medicare Billing Code	Monthly Medicare Rental Rate*
High Flow Nasal Oxygen	E1405 (O2/water vapor enriched with heated delivery)	$185
Noninvasive ventilation	E0466 (Home ventilator, any type, non-invasive interface)	$1,055

*Calculated as monthly average across 48 contiguous states. Fees vary by state, and by rural or non-rural status as well as contiguous/non-contiguous areas of the United States. Medicare does not directly provide a single national payment amount.
Source: https://www.cms.gov/medicaremedicare-fee-service-paymentdmeposfeescheddmepos-fee-schedule/dme20

663 **SUMMARY OF JUDGEMENTS**

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Medium	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Medium	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Insufficient	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Recommendation 1a: ACP suggests that clinicians use high flow nasal oxygen rather than noninvasive ventilation in hospitalized hypoxemic adults for the management of acute respiratory failure (conditional recommendation; low-certainty evidence).

Justification

Low-certainty evidence shows that there are benefits of using high flow nasal oxygen over NIV for the initial management of acute respiratory failure. There is a demonstrable improvement in clinically meaningful outcomes, including a reduction in mortality in

patients with hypoxic, nonhypercapnic acute respiratory failure (low-certainty evidence). The reduction in mortality was large (ARD, -15.8%), but the evidence was limited to 1 trial of 216 patients. Low-certainty evidence also showed a modest reduction in intubations in patients with hypoxic and/or hypercapnic acute respiratory failure, a modest reduction in hospital-acquired pneumonia, and improvements in patient comfort. Most patients can use HFNO and there are usually no contraindications unless related to issues with fitting the nasal cannula. In addition, costs associated with using HFNO according to the Medicare national average monthly reimbursable rate are lower than NIV ($185 vs. $1055), although this cost information is limited to the outpatient setting.

Research priorities

The current evidence is insufficient on the use of HFNO in patients with hypercapnic respiratory failure. Evidence on the use of HFNO is also insufficient for the following patient-centered outcomes for initial management of acute respiratory failure: ICU admissions and length of stay.

667

Supplement Table 2: Should HFNO vs. COT be used for initial management of acute respiratory failure?

POPULATION:	Initial management of acute respiratory failure
INTERVENTION:	HFNO
COMPARISON:	COT
MAIN OUTCOMES:	Intubation; All-cause mortality; Hospital-acquired pneumonia; ICU admissions; Length of stay, intensive care unit; Length of stay, hospital ; Patient comfort (including related to dryness); Dyspnea; Hospital readmissions; Functional independence at discharge; Discharge disposition; Skin breakdown; Gastric dysfunction; Compromised nutrition; Delirium; Barotrauma;

ASSESSMENT

JUDGEMENT

How Substantial Are the Desirable Anticipated Effects?
○Trivial
●Small
○ Medium
○ Large
○ Varies
○ Don't know

How Substantial Are the Undesirable Anticipated Effects?
○ Large
○ Medium
○ Small
●Trivial
○ Varies
○Don't know

RESEARCH EVIDENCE

Outcome № of participants (studies)	Relative effect or Standardized mean difference	Anticipated Absolute effects (95% CI)* COT	HFNO	**Absolute risk difference (95% CI)**	Certainty
CRITICAL OUTCOMES					
All-cause Mortality № of participants: 1407 (4 RCTs) (11, 23, 27, 29)	RR 0.97 (0.82 to 1.14)	27.2%	**26.3%** (22.3 to 31)	0.8% fewer (4.9 fewer to 3.8 more)	⨁◯◯ **LOW**†
Hospital-acquired Pneumonia № of participants: 200 (1 RCT) (11)	RR 0.44 (0.14 to 1.43)	8.5%	**3.7%** (1.2 to 12.2)	4.8% fewer (7.3 fewer to 3.7 more)	⨁◯◯ **LOW**§
Intubation № of participants: 1694 (8 RCTs) (11, 21, 23, 25-27, 29, 30)	Peto OR 0.98 (0.34 to 2.82)	26.5%	**26.1%** (10.9 to 50.5)	0.4% fewer (15.6 fewer to 23.9 more)	⨁◯◯ **LOW**†
ICU Admissions (yes/no) № of participants: 403 (2 RCTs) (21, 23)	RR 1.11 (0.58 to 2.12)	7.9%	**8.8%** (4.6 to 16.7)	0.9% more (3.3 fewer to 8.8 more)	◯◯◯ **INSUFFICIENT**†‡**

	Length of stay, hospital № of participants: 1267 (4 RCTs) (23, 24, 27, 29)	Four trials reported little to no difference in hospital length of stay based on medians (medians ranged from 1 to 24 vs. 1 to 27 days) (23, 27, 29) and/or p-values. (24)	⊕◯◯ **LOW***§*
	Length of stay, ICU № of participants: 1036 (3 RCTs) (11, 24, 29)	Two trials (n=976) (11, 29) found little or no difference in ICU length of stay (mean days NA; MD 0.41 days [-1.08 to 1.90]). 1 trial (n=60) reported little to no difference in ICU length (P=.20, no data reported). (24)	◯◯◯ **INSUFFICIENT** *†‡***
	Patient comfort, including comfort related to airway dryness, based on VAS or % improved № of participants: 1611 (12 RCTs total, some trials reported ≥1 measure of comfort) (11, 14, 16, 21-23, 25-30)	Pooled results from 4 trials (n=415) (11, 25-27) found HFNO improved comfort (SMD -0.61 [-0.81 to -0.41]) based on VAS. Results pertaining to patient comfort based on median or unclear (29) scale scores varied: 1 trial (n=100) (21) reported higher comfort based on a 5 point Likert scale (4 vs. 3, 5=most comfort, P=.04) while 2 trials (n=876) (29, 30) reported little to no difference in patient comfort on a 10-point scale (7.9 vs. 6.8, 10=perfect (29) and medians 3 vs. 3 ; 10=worst (30)). 1 trial (n=158) (23) reported a lower percentage of participants with discomfort related to dryness (29.8% vs. 45.3%; ARD -15.5% [-30.8 to -0.2]). 4 small crossover studies (n=62) (14, 16, 22, 28) reported little to no difference in short-term patient comfort.	⊕◯◯ **LOW**†††‡‡
	Dyspnea, based on VAS and Borg scale scores or % improved № of participants: 1799 (13 RCTs) (11, 14, 16, 21-23, 25-31)	Pooled results from 4 trials (n=258) (25-27, 31) found HFNO improved dyspnea (SMD -0.56 [-1.35 to 0.24]) based on VAS and Borg scales. 2 trials (n=876) (29, 30) reported little to no difference in short-term dyspnea based on median scale scores (medians 2.3-3 vs. 2.6-3 on a 10-point scale, 10=most severe). 3 trials (n=417) (11, 21, 23) reported a greater percentage of participants with improvement in dyspnea or improved breathing (78.0% vs. 55.8%; ARD 22.2% [13.3 to 31.1]). 4 small crossover studies (n=62) (14, 16, 22, 28) reported little to no difference in short-term dyspnea.	⊕◯◯ **LOW**†††‡‡
		IMPORTANT OUTCOMES	
	Skin breakdown (facial pressure sore or nasal ulceration) № of participants: 431 (2 RCTs) (23, 27)	Both trials reported no incidences of skin breakdown were observed with HFNO. For COT, one trial reported no incidences (23) and the other trial did not report this outcome (27).	◯◯◯ **INSUFFICIENT***§§*
	Explanations † Downgraded for imprecision (wide CIs) ‡ Downgraded for study limitations § Downgraded two levels for large imprecision (very wide CIs) and/or sparse data and/or difficult to interpret based on the variability in the reporting of the effects ** Downgraded for indirectness, ICU stay possibly protocol driven †† Downgraded due to inconsistency ‡‡ Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effect §§ Downgraded to insufficient based on the enormity of the imprecision or difficult to interpret based on the variability in the reporting of the effects		

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Insufficient ● **Low** ○ Moderate ○ High ○ No included studies	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No guidelines or systematic reviews were identified that assessed the relative importance of outcomes or patient values and preferences between HFNO and conventional oxygen therapy in patients undergoing initial management of acute respiratory failure; however, 1 primary study was identified. A randomized crossover trial (43) conducted in an ICU in France found that a larger number of subjects preferred HHFO2 over standard oxygen (16 vs 5; P .01), despite a relative noise induced by the device (nine subjects expressed no preference). The CGC public panel reported fewer preferences in the choice of HFNO over COT for the initial management of acute respiratory failure: Five out of 6 respondents indicated that they were unsure or had no preference and the remaining responded that s/he would prefer HFNO, both citing a potential reduction in pneumonia.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE

○ Favors the comparison ○ Probably favors the comparison ● **Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	See Summary of Evidence Table above.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ● **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No studies were identified that reported on the costs of high flow nasal oxygen compared to COT in the United States.

Table: National Average Medicare Monthly Reimbursable Rates for Noninvasive Respiratory Support Modalities (High Flow Nasal Oxygen vs. Conventional Oxygen Therapy)

Intervention	Medicare Billing Code	Monthly Medicare Rental Rate*
High Flow Nasal Oxygen	E1405 (O2/water vapor enriched with heated delivery)	$185
Conventional oxygen therapy	E1390 (O2 concentration, stationary)	$106
	E1392 (O2 concentration, portable)	$41

*Calculated as monthly average across 48 contiguous states. Fees vary by state, and by rural or non-rural status as well as contiguous/non-contiguous areas of the United States. Medicare does not directly provide a single national payment amount.
Source: https://www.cms.gov/medicaremedicare-fee-service-paymentdmeposfeescheddmepos-fee-schedule/dme20

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Medium	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Insufficient	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

No Recommendation

Justification

Evidence was inconclusive on the use of HFNO versus COT for the initial management of acute respiratory failure. Overall, patients enrolled in the COT trials had lesser degrees of hypoxia than those enrolled in the NIV trials (baseline mean SpO2 88% vs. 76%). Low-certainty evidence shows that HFNO may improve patient comfort, dyspnea, and result in a modest reduction in hospital-acquired pneumonia compared to COT but that it may make no difference for other clinical outcomes such as all-cause mortality, intubation, and hospital length of stay. There are additional cost and resource considerations: HFNO is more expensive than COT and widespread implementation of HFNO could be quite resource intensive. In light of these considerations, we do not believe the choice of HFNO over COT for the initial management of acute respiratory failure rises to the level of a clinical recommendation. However, most patients can use HFNO and there are usually no contraindications unless related to issues with fitting the nasal cannula.

Research priorities

The current evidence is insufficient on the use of HFNO in patients with hypercapnic respiratory failure. Evidence on the use of HFNO is also insufficient for the following patient-centered outcomes for initial management of acute respiratory failure: ICU admissions and length of stay.

677
678

Supplement Table 3: Should HFNO vs. NIV be used for management of post-extubation acute respiratory failure?

POPULATION:	post-extubation acute respiratory failure
INTERVENTION:	HFNO
COMPARISON:	NIV
MAIN OUTCOMES:	Intubation; All-cause mortality; Hospital-acquired pneumonia; ICU admissions; Length of stay, intensive care unit; Length of stay, hospital ; Patient comfort (including related to dryness); Dyspnea; Hospital readmissions; Functional independence at discharge; Discharge disposition; Skin breakdown; Gastric dysfunction; Compromised nutrition; Delirium; Barotrauma;

ASSESSMENT

JUDGEMENT

How Substantial Are The Desirable Anticipated Effects?
- **● Trivial**
- ○ Small
- ○ Medium
- ○ Large
- ○ Varies
- ○ Don't know

How Substantial Are The Undesirable Anticipated Effects?
- **● Trivial**
- ○ Large
- ○ Medium
- ○ Small
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcome № of participants (studies)	Relative effect or Standardized mean difference	Anticipated Absolute effects (95% CI)* NIV	Anticipated Absolute effects (95% CI)* HFNO	**Absolute risk difference (95% CI)**	Certainty
		CRITICAL OUTCOMES			
All-cause Mortality № of participants: 1476 (3 RCTs) (18-20)	RR 1.15 (0.88 to 1.51)	11.2%	**12.9%** (9.9 to 16.9)	1.7% more (1.3 fewer to 5.7 more)	⨁◯◯ **LOW§**
Hospital-acquired Pneumonia № of participants: 1434 (2 RCTs) (18, 20)	RR 0.90 (0.70 to 1.16)	14.7%	**13.2%** (10.3 to 17)	1.5% fewer (4.4 fewer to 2.3 more)	⨁◯◯ **LOW§**
Reintubation № of participants: 1476 (3 RCTs) (18-20)	RR 1.13 (0.90 to 1.43)	15.3%	**17.3%** (13.8 to 21.9)	2.0% more (1.5 fewer to 6.6 more)	⨁◯◯ **LOW§**
ICU Admissions (yes/no)	**NOT APPLICABLE**				

	Length of stay, hospital № of participants: 1434 (2 RCTs) (18, 20)	1 trial (n=604) (18) reported a lower hospital length of stay with HFNO (medians 23 vs. 26 days; MD -3 days [-6.8 to -0.8]). 1 trial (n=830) (20) reported little to no difference in hospital length of stay (medians 13 vs. 14 days).				◯◯◯ **INSUFFICIENT**† ††
	Length of stay, ICU № of participants: 1476 (3 RCTs) (18-20)	Pooled mean differences from 2 trials (18, 19) (n=646) found HFNO makes little or no difference in ICU length of stay (mean days NA; MD -0.98 days [-1.99 to 0.03]. 1 trial (n=830) reported little to no difference in ICU length of stay (medians 6 vs. 6 days)				⊕◯◯ **LOW**§
	Patient comfort, based on % improved or VAS № of participants: 872 (2 RCTs) (19, 20)	One large trial (n=748) (20) reported little to no difference in the percentage of participants reporting good comfort (51.3% vs. 52.9%; ARD -1.6 [-8.7 to 5.6]). One small trial (n=42) (19) found HFNO may improve comfort (SMD -0.75 [-1.38 to -0.12]) based on a 10-point scale where lower means better.				⊕◯◯ **LOW**††‡‡
	Dyspnea, based % improved № of participants: 752 (1 RCT) (20)	RR 0.96 (0.86 to 1.08)	60.4%	**58.0%** (52 to 65.3)	**2.4% fewer** (8.5 fewer to 4.8 more) 2.4% fewer (8.5 fewer to 4.8 more)	⊕◯◯ **LOW**§
	IMPORTANT OUTCOMES					
	Skin breakdown (facial pressure sore or nasal ulceration) № of participants: 1454 (3 RCTs)	Peto OR 0.15 (0.02 to 1.13)	24.3%	**4.6%** (0.6 to 26.6)	19.7% fewer (23.7 fewer to 2.3 more)	⊕◯◯ **LOW**‡††

Explanations

† Downgraded two levels for large imprecision (very wide CIs) and/or sparse data and/or difficult to interpret based on the variability in the reporting of the effects

‡ Downgraded for imprecision (wide CIs)

§ Downgraded for study limitations, particularly high attrition

** Downgraded for indirectness, ICU stay possibly protocol driven

†† Downgraded due to inconsistency

‡‡ Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effect

§§ Downgraded to insufficient based on the enormity of the imprecision or difficult to interpret based on the variability in the reporting of the effects

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE

○ Insufficient ● **Low** ○ Moderate ○ High ○ No included studies	See Summary of Findings Table above.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No guidelines, systematic reviews, or studies were identified that assessed the relative importance of outcomes or patient values and preferences between HFNO and NIV. Feedback from the CGC public panel indicated a variable preference for the choice of HFNO over NIV for post-extubation management, three out of 6 respondents indicated they would prefer HFNO (most citing improved comfort as key factor in light of few other differences) and 3 said they were unsure.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE

○ Favors the comparison ○ Probably favors the comparison **●Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○Favors the intervention ○ Varies ○ Don't know	See Summary of Findings Table above.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings **● Large savings** ○ Varies ○ Don't know	No studies were identified that reported on the costs of high flow nasal oxygen compared to noninvasive ventilation in the United States. **Table: National Average Medicare Monthly Reimbursable Rates for Noninvasive Respiratory Support Modalities (High Flow Nasal Oxygen vs. Noninvasive Ventilation)**

Intervention	Medicare Billing Code	Monthly Medicare Rental Rate*
High Flow Nasal Oxygen	E1405 (O2/water vapor enriched with heated delivery)	$185
Noninvasive ventilation	E0466 (Home ventilator, any type, non-invasive interface)	$1,055

*Calculated as monthly average across 48 contiguous states. Fees vary by state, and by rural or non-rural status as well as contiguous/non-contiguous areas of the United States. Medicare does not directly provide a single national payment amount.
Source: https://www.cms.gov/medicaremedicare-fee-service-paymentdmeposfeescheddmepos-fee-schedule/dme20

682

683

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Medium	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Medium	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Insufficient	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

No recommendation

Justification

Evidence was inconclusive on the use of HFNO versus NIV for the management of post-extubation acute respiratory failure. Low-certainty evidence showed that HFNO may increase mortality and re-intubation slightly compared to NIV, and may make no difference in hospital-acquired pneumonia, ICU length of stay, patient comfort, and dyspnea though HFNO may reduce skin breakdowns by a large amount compared to NIV. Overall, effect sizes were inconsistent, small, and not statistically significant. Hence, evidence is inconclusive for or against the use of HFNO over NIV for the management of post-extubation acute respiratory failure.

Research priorities

The current evidence is insufficient on the use of HFNO in patients with hypercapnic respiratory failure. Evidence on the use of HFNO is also insufficient for the following patient-centered outcome for post-extubation acute respiratory failure: hospital length of stay.

688

Supplemental Table 4: Should HFNO vs. COT be used for management of post-extubation acute respiratory failure?

POPULATION:	Post-extubation acute respiratory failure
INTERVENTION:	HFNO
COMPARISON:	COT
MAIN OUTCOMES:	Intubation; All-cause mortality; Hospital-acquired pneumonia; ICU admissions; Length of stay, intensive care unit; Length of stay, hospital ; Patient comfort (including related to dryness); Dyspnea; Hospital readmissions; Functional independence at discharge; Discharge disposition; Skin breakdown; Gastric dysfunction; Compromised nutrition; Delirium; Barotrauma;

ASSESSMENT

JUDGEMENT

How Substantial Are the Desirable Anticipated Effects?
○ Trivial
○ Small
●**Medium**
○Large
○ Varies
○ Don't know

How Substantial Are the Undesirable Anticipated Effects?
○ Large
○ Medium
○ Small
●**Trivial**
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcome № of participants (studies)	Relative effect or Standardized mean difference	Anticipated Absolute effects (95% CI)* COT	HFNO	Absolute risk difference (95% CI)	Certainty
		CRITICAL OUTCOMES			
All-cause Mortality № of participants: 782 (4 RCTs) (32, 33, 36, 37)	RR 1.01 (0.60 to 1.72)	6.2%	**6.3%** (3.7 to 10.7)	0.1% more (-2.5 fewer to 4.5 more)	⨁◯◯ **LOW**§
Hospital-acquired Pneumonia № of participants: 527 (1 RCT) (32)	RR 0.50 (0.13 to 1.97)	2.3%	**1.1%** (0.3 to 4.5)	1.1% fewer (2.0 fewer to 2.2 more)	⨁◯◯ **LOW**§
Reintubation № of participants: 1065 (7 RCTs) (32-36)	Peto OR 0.60 (0.23 to 1.61)	10.4%	**6.5%** (2.6 to 15.7)	3.9% fewer (7.8 fewer to 5.3 more)	⨁◯◯ **LOW**§
ICU Admissions (yes/no)	**NOT REPORTED**				

Length of stay, hospital № of participants: 587 (2 RCTs) (32, 37)		Study 1(32) Median 11 (IQR 6 to 15) Study 2(37) Mean 37.7	Study 1 Median 12 (IQR 6 to 16) Study 2 Mean 25.7	Study 1 MD 4 (-28 to 32) Study 2 MD 12 days (0.15 to 23.85)	◯◯◯ **INSUFFICIENT§§**
Length of stay, ICU № of participants: 1006 (6 RCTs) (32, 33, 35-38)	Pooled results from 5 trials (n=479) (33, 35-38) found HFNO makes little or no difference in ICU length of stay (approximately 6 days in each group; MD 0.19 [-0.19 to 0.57]. One trial not pooled (n=527) (32) reported little to no difference in ICU length of stay (medians 6 vs. 6 days).				⊕⊕◯ **MODERATE‡‡**
Patient comfort, including comfort related to dryness and interface, based on VAS or % improved № of participants: 324 (4 RCTs total, some trials reported ≥1 measure of comfort) (33, 34, 36, 38)	1 trial (n=105) (33) found HFNO improved comfort (SMD -0.70 [-1.10 to -0.31]) based on a 10- point VAS where lower is better. 1 trial (n=60) reported higher comfort or less dryness based on median scale scores. 1 trial (n=90) (36) reported a lower percentage of participants with discomfort related to dryness (38.3} % vs. 69.8%; ARD -31.5% [-51.0 to -11.9]). 2 trials (n=165) (33, 34) reported lower discomfort related to interface with HFNO versus COT (Trial 1 SMD -0.89 [-1.29 to -0.49]) (33) and Trial 2 medians 3 vs. 7 on a 10-point scale, 10=maximal discomfort, P<.001). (34) One trial (n=69) reported little to no difference in any measure of discomfort on a 10-point scale (nasal, oral, or pharynx) based on medians (38).				⊕◯◯ **LOW§**
Dyspnea, based Borg scale score № of participants: 155 (1 RCT) (35)	1 trial (35) reported little to no difference in short-term dyspnea (medians 1 vs. 0 on a 10-point scale, 10=maximal dyspnea).				◯◯◯ **INSUFFICIENT†§**
	IMPORTANT OUTCOMES				
Skin breakdown (facial pressure sore or nasal ulceration) № of participants: 527 (1 RCT) (35)	One trial (35) reported no incidences of skin breakdown were observed with HFNO but this outcome was not reported for the COT arm.				◯◯◯ **INSUFFICIENT*§§***

Explanations

† Downgraded for imprecision (wide CIs)

‡ Downgraded for study limitations

§ Downgraded two levels for large imprecision (very wide CIs) and/or sparse data and/or difficult to interpret based on the variability in the reporting of the effects

** Downgraded for indirectness, ICU stay possibly protocol driven

	†† Downgraded due to inconsistency ‡‡ Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effect §§ Downgraded to insufficient based on the enormity of the imprecision or difficult to interpret based on the variability in the reporting of the effects

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Insufficient ● **Low** ○ Moderate ○ High ○ No included studies	See Summary of Findings table above.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No guidelines or systematic reviews were identified that assessed the relative importance of outcomes or patient values and preferences between HFNO and COT; however, 1 primary study were identified. A randomized crossover trial (39) conducted in a respiratory ICU in Thailand found that most (88.2%) of the recently extubated participants (n=17) preferred HFNO over COT (non-rebreather). The CGC public panel reported a preference for HFNO preferences: Four out of 6 respondents indicated that they would prefer of HFNO over COT for post-extubation acute respiratory failure; 1 responded no preference; and 1 responded unsure based on limited differences in outcomes but that reduced reintubation might sway the choice.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	See Summary of Evidence Table above.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE
○ Large costs ● **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No studies were identified that reported on the costs of high flow nasal oxygen compared to COT in the United States.

Table: National Average Medicare Monthly Reimbursable Rates for Noninvasive Respiratory Support Modalities (High Flow Nasal Oxygen vs. Conventional Oxygen Therapy)

Intervention	Medicare Billing Code	Monthly Medicare Rental Rate*
High Flow Nasal Oxygen	E1405 (O2/water vapor enriched with heated delivery)	$185
Conventional oxygen therapy	E1390 (O2 concentration, stationary)	$106
	E1392 (O2 concentration, portable)	$41

*Calculated as monthly average across 48 contiguous states. Fees vary by state, and by rural or non-rural status as well as contiguous/non-contiguous areas of the United States. Medicare does not directly provide a single national payment amount.
Source: https://www.cms.gov/medicaremedicare-fee-service-paymentdmeposfeescheddmepos-fee-schedule/dme20

692 **S**

693

UMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Medium**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Medium	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Insufficient	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Recommendation 1b: ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy in hospitalized hypoxemic adults with post-extubation acute respiratory failure (conditional recommendation; low-certainty evidence).

Justification

Low-certainty evidence showed that HFNO may reduce re-intubation slightly compared to COT and low-certainty evidence showed that HFNO may improve patient comfort. Low-certainty evidence also showed that HFNO did not perform worse than COT with regard to all-cause mortality, hospital-acquired pneumonia, and length of ICU stay, and although the magnitude did not pass the CGC's pre-determined thresholds, the direction of the effects for these outcomes consistently point towards a potential benefit.

Research priorities

The current evidence is insufficient on the use of HFNO in patients with hypercapnic respiratory failure. Evidence on the use of HFNO is also insufficient for the following patient-centered outcomes for post-extubation acute respiratory failure: hospital length of stay and improvement in dyspnea (compared to COT).

698

References

1. Nishimura M. High-flow nasal cannula oxygen therapy in adults. Journal of intensive care. 2015;3(1):15-.
2. Papazian L, Corley A, Hess D, Fraser JF, Frat J-P, Guitton C, et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive care medicine. 2016;42(9):1336-49.
3. Möller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, et al. Nasal high flow reduces dead space. J Appl Physiol (1985). 2017;122(1):191-7.
4. Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care. 2013;58(10):1621-4.
5. PLACEHOLDER. Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: a systematic review Annals of Internal Medicine. 2020;xx(xx):xx-xx.
6. Qaseem A, Wilt TJ, Physicians ftCGCotACo. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians. Annals of Internal Medicine. 2019;171(5):354-61.
7. Qaseem A, Kansagara D, Lin JS, Mustafa RA, Wilt TJ, Physicians ftCGCotACo. The Development of Clinical Guidelines and Guidance Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods. Annals of Internal Medicine. 2019;170(12):863-70.
8. Schünemann H BJ, Guyatt G, Oxman A, eds.,. Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE Approach. Updated October 2013. Accessed at https://gdt.gradepro.org/app/handbook/handbook.html#:~:text=The%20GRADE%20handbook%20describes%20the,www.gradeworkinggroup.org on 24 February 2020.
9. GRADEpro GDT: GRADEpro Guideline Development Tool [software]. Hamilton, Ontario, Canada; McMaster University; 2015 (developed by Evidence Prime).
10. Doshi P, Whittle JS, Bublewicz M, Kearney J, Ashe T, Graham R, et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Ann Emerg Med. 2018;72(1):73-83 e5.
11. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185-96.
12. Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM, Tanzarella ES, et al. Physiological Comparison of High-Flow Nasal Cannula and Helmet Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure. Am J Respir Crit Care Med. 2020;201(3):303-12.
13. Saksitthichok B, Petnak T, So-Ngern A, Boonsarngsuk V. A prospective randomized comparative study of high-flow nasal cannula oxygen and non-invasive ventilation in hypoxemic patients undergoing diagnostic flexible bronchoscopy. J Thorac Dis. 2019;11(5):1929-39.
14. Schwabbauer N, Berg B, Blumenstock G, Haap M, Hetzel J, Riessen R. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). BMC Anesthesiol. 2014;14:66.
15. Sklar MC, Dres M, Rittayamai N, West B, Grieco DL, Telias I, et al. High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: a randomized crossover physiological study. Ann Intensive Care. 2018;8(1):85.
16. Vargas F, Saint-Leger M, Boyer A, Bui NH, Hilbert G. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respiratory Care; 2015.

17. Cong L, Zhou L, Liu H, Wang J**.** Original article outcomes of high-flow nasal cannula versunon-invasive positive pressure ventilation for patients with acute exacerbations of chronic obstructive pulmonary disease. International journal of clinical and experimental medicine. 2019;12(8):10863-7.
18. Hernandez G, Vaquero C, Colinas L, Cuena R, Gonzalez P, Canabal A, et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA. 2016;316(15):1565-74.
19. Jing G, Li J, Hao D, Wang T, Sun Y, Tian H, et al. Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: A pilot randomized controlled trial. Res Nurs Health. 2019;42(3):217-25.
20. Stephan F, Barrucand B, Petit P, Rezaiguia-Delclaux S, Medard A, Delannoy B, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A Randomized Clinical Trial. JAMA. 2015;313(23):2331-9.
21. Bell N, Hutchinson CL, Green TC, Rogan E, Bein KJ, Dinh MM**.** Randomised control trial of humidified high flow nasal cannulae versus standard oxygen in the emergency department. Emerg Med Australas. 2015;27(6):537-41.
22. Delorme M, Bouchard PA, Simon M, Simard S, Lellouche F**.** Effects of High-Flow Nasal Cannula on the Work of Breathing in Patients Recovering From Acute Respiratory Failure. Crit Care Med. 2017;45(12):1981-8.
23. Jones PG, Kamona S, Doran O, Sawtell F, Wilsher M**.** Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department: The HOT-ER Study. Respir Care. 2016;61(3):291-9.
24. Parke RL, McGuinness SP, Eccleston ML**.** A preliminary randomized controlled trial to assess effectiveness of nasal high-flow oxygen in intensive care patients. Respir Care. 2011;56(3):265-70.
25. Rittayamai N, Tscheikuna J, Praphruetkit N, Kijpinyochai S**.** Use of High-Flow Nasal Cannula for Acute Dyspnea and Hypoxemia in the Emergency Department. Respir Care. 2015;60(10):1377-82.
26. Spoletini G, Mega C, Pisani L, Alotaibi M, Khoja A, Price LL, et al. High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: A pilot randomized controlled trial. J Crit Care. 2018;48:418-25.
27. Makdee O, Monsomboon A, Surabenjawong U, Praphruetkit N, Chaisirin W, Chakorn T, et al. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Emergency Department Patients With Cardiogenic Pulmonary Edema: A Randomized Controlled Trial. Ann Emerg Med. 2017;70(4):465-72 e2.
28. Pilcher J, Eastlake L, Richards M, Power S, Cripps T, Bibby S, et al. Physiological effects of titrated oxygen via nasal high-flow cannulae in COPD exacerbations: A randomized controlled cross-over trial. Respirology. 2017;22(6):1149-55.
29. Azoulay E, Lemiale V, Mokart D, Nseir S, Argaud L, Pene F, et al. Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure: The HIGH Randomized Clinical Trial. JAMA. 2018;320(20):2099-107.
30. Lemiale V, Mokart D, Mayaux J, Lambert J, Rabbat A, Demoule A, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. Crit Care. 2015;19:380.
31. Ruangsomboon O, Dorongthom T, Chakorn T, Monsomboon A, Praphruetkit N, Limsuwat C, et al. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Relieving Dyspnea in

Emergency Palliative Patients With Do-Not-Intubate Status: A Randomized Crossover Study. Ann Emerg Med. 2019;18:18.

32. Hernandez G, Vaquero C, Gonzalez P, Subira C, Frutos-Vivar F, Rialp G, et al. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. JAMA. 2016;315(13):1354-61.
33. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190(3):282-8.
34. Song HZ, Gu JX, Xiu HQ, Cui W, Zhang GS**.** The value of high-flow nasal cannula oxygen therapy after extubation in patients with acute respiratory failure. Clinics (Sao Paulo). 2017;72(9):562-7.
35. Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF**.** Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI >/=30: a randomised controlled trial. Intensive Care Med. 2015;41(5):887-94.
36. Vourc'h M, Nicolet J, Volteau C, Caubert L, Chabbert C, Lepoivre T, et al. High-Flow Therapy by Nasal Cannulae Versus High-Flow Face Mask in Severe Hypoxemia After Cardiac Surgery: A Single-Center Randomized Controlled Study-The HEART FLOW Study. J Cardiothorac Vasc Anesth. 2020;34(1):157-65.
37. Cho JY, Kim HS, Kang H, Kim SH, Choe KH, Lee KM, et al. Comparison of Postextubation Outcomes Associated with High-Flow Nasal Cannula vs. Conventional Oxygen Therapy in Patients at High Risk of Reintubation: a Randomized Clinical Trial. J Korean Med Sci. 2020;35(25):e194.
38. Matsuda W, Hagiwara A, Uemura T, Sato T, Kobayashi K, Sasaki R, et al. High-Flow Nasal Cannula May Not Reduce the Re-Intubation Rate Compared With a Large-Volume Nebulization-Based Humidifier. Respir Care. 2020;65(5):610-7.
39. Rittayamai N, Tscheikuna J, Rujiwit P**.** High-flow nasal cannula versus conventional oxygen therapy after endotracheal extubation: a randomized crossover physiologic study. Respiratory care. 2014;59(4):485-90.
40. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. JAMA. 2020;324(1):57-67.
41. Jackson T, Deibert D, Wyatt G, Durand-Moreau Q, Adisesh A, Khunti K, et al. Classification of aerosol-generating procedures: a rapid systematic review. BMJ Open Respiratory Research. 2020;7(1):e000730.
42. Jp H, Altman D, Gotzsche P, Juni P, Moher D, Oxman A, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928-d.
43. Cuquemelle E, Pham T, Papon JF, Louis B, Danin PE, Brochard L**.** Heated and humidified high-flow oxygen therapy reduces discomfort during hypoxemic respiratory failure. Respir Care. 2012;57(10):1571-7.

Effectiveness and Harms of High-Flow Nasal Oxygen (HFNO) for Acute Respiratory Failure: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians

Running Title: Effectiveness and Harms of High-Flow Nasal Oxygen

Authors' full names:

Arianne K. Baldomero, MD, MS[1,2]; Anne C. Melzer, MD, MS[1,2]; Nancy Greer, PhD[3]; Brittany N. Majeski, BA[3]; Roderick MacDonald, MS[3]; Eric J. Linskens, BS[3]; and Timothy J. Wilt, MD, MPH[3,4]

Authors' affiliation(s):

[1]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA

[2]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

[3]Center for Care Delivery and Outcomes Research, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA

[4]Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Abstract word count: 290

Text word count: 4009

References: 80 (included)

Tables: 1 (included); **Figures:** 3 (included); **Box:** 1 (included)

Appendices: Tables: 4; Figures: 1 (separate document)

Supplementary Tables: 18; **Supplementary Figures:** 9 (separate document)

Corresponding author:

Arianne K. Baldomero, MD, MS

1 Veterans Drive, Pulmonary 111-N

Minneapolis, MN, USA

baldo004@umn.edu

ABSTRACT

Background: High-flow nasal oxygen (HFNO) use for treatment of adults with acute respiratory failure (ARF) has increased.

Purpose: To assess effectiveness and harms of HFNO versus noninvasive ventilation (NIV) or conventional oxygen therapy (COT) for the management of ARF in hospitalized adult patients.

Data Sources: English language searches of MEDLINE®, Embase, CINAHL, and Cochrane Library from January 2000 to July 2020; reference lists from systematic reviews.

Study Selection: Twenty-nine randomized controlled trials (RCTs) that evaluated HFNO versus NIV (k=11) or COT (k=21) in adults with ARF in a hospital setting.

Data Extraction: Data extraction by single investigator verified by a second; dual-investigator assessment of risk of bias; consensus determination of evidence certainty.

Data Synthesis: We reported results separately for HFNO vs. NIV and HFNO vs. COT and by initial management or post-extubation management. Compared to NIV, HFNO may reduce all-cause mortality, intubation hospital-acquired pneumonia and improve patient comfort in the initial management of ARF (low evidence certainty), but not as post-extubation management. Compared to COT, HFNO may reduce reintubation and treatment escalation and improve patient comfort in post-extubation management of ARF (low evidence certainty).

Limitations: Trials varied in populations enrolled, etiologies of ARF, and protocols used. Trial design, sample size, treatment/follow-up duration, and results reporting were often inadequate to accurately assess many outcomes. Treatment protocols, clinician/health system training, and cost and resource use were poorly characterized.

Conclusion: Compared to NIV, HFNO used as initial management for adults with ARF may improve several clinical outcomes. Compared to COT, HFNO used as post-extubation management may reduce reintubations and improve patient comfort. HFNO resulted in fewer harms than NIV or COT. Broad applicability, including required clinician and health system experience and resource use, is not well known.

Primary Funding Source: American College of Physicians

PROSPERO registration: CRD42019146691

INTRODUCTION

Acute respiratory failure (ARF) is generally defined as the new onset of clinically important hypoxia, hypercapnia, or both. Noninvasive respiratory treatment options for ARF vary by the etiology and severity, and include “conventional oxygenation therapy” (COT) – oxygen delivered through nasal cannula, simple face mask, air-entrainment mask, partial rebreathing mask, or non-rebreather mask, with maximum flow rate of approximately 15 L/min – and more advanced support modalities such as noninvasive ventilation (NIV). NIV encompasses continuous or bilevel positive airway pressure ventilation and requires specialized training and equipment to deliver. High-flow nasal oxygen (HFNO), a newer mode of noninvasive oxygen support, has been increasingly used in recent years, in part due to perceived benefits in comparison to COT and NIV. A comparison of the characteristics of COT, NIV, and HFNO is presented in the accompanying Box(1).

Compared to COT, HFNO is purported to provide additional support through washout of anatomic dead space(2), higher oxygen flow rates (up to 60 L/min)(3,4), generation of low level positive-end expiratory pressure (PEEP)(5-9), and higher concentrations of heated humidified oxygen (up to 100% FiO_2). Compared to NIV, which is typically delivered by full face mask in the acute setting, HFNO is delivered through a small, pliable nasal cannula, potentially improving clearance of secretions, patient comfort, and resource utilization. HFNO is considered to offer a number of physiologic advantages, such as improved oxygenation and ventilation(10,11). However the comparative benefits and harms of HFNO on clinical outcomes including mortality, need for intubation, hospital length of stay, patient comfort (12-14), clearance of airway secretions(15,16), and reduced work of breathing(13,17,18) are not well known.

The Minnesota Evidence Synthesis and Dissemination Center was commissioned by the American College of Physicians (ACP) to systematically review the evidence regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the management of ARF in hospitalized adult patients. This review was used by the ACP-Clinical Guidelines Committee (ACP-CGC) to develop a clinical practice guideline for the use of HFNO in hospitalized adults with ARF.

METHODS

Our protocol was developed with input from the ACP-CGC as well as an independent technical expert panel and registered in PROSPERO (CRD42019146691). Our full study protocol underwent additional peer review and was published(19). A summary of the protocol is presented in Appendix Table 1.

Data Sources and Study Selection

We searched multiple databases (January 2000-July 2020) for peer reviewed, English language, randomized controlled trials (RCTs) (Appendix Table 2). Abstracts and potentially eligible full text articles were independently reviewed by 2 investigators. We included parallel group and crossover studies of adult patients (age ≥18 years) with ARF in a hospital environment randomized to receive HFNO or either COT or NIV. We defined HFNO as delivery of humidified oxygen via nasal cannula at a flow rate ≥20 L/min. We excluded studies evaluating HFNO for oxygenation support before and during intubation and studies of pre-hospital HFNO. A study was included if ≥75% of enrollees met at least one criterion for ARF: SpO_2<90%, PaO_2:FIO_2 ratio≤300, PaO_2≤60 mmHg, or $PaCO_2$≥45 mmHg.

Outcome Measures

Critical outcomes defined by the ACP-CGC were: all-cause mortality (in-hospital and the longest available through 90 days), hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU) admission/transfers, patient comfort, and hospital length of stay. Important and intermediate outcomes are described in Appendix Table 1.

Data Extraction and Quality Assessment

Data extraction was completed by one reviewer and verified by a second. We assessed risk of bias using a modification of the Cochrane guidance for randomized trials(20). Individual elements were rated low, unclear, or high risk of bias. A study with unclear elements was considered moderate risk of bias.

Data Synthesis and Analysis

We examined clinical and methodological heterogeneity to determine appropriateness of quantitative synthesis. We pooled outcomes from clinically homogeneous studies using Comprehensive Meta Analysis V.3 or R. We calculated risk ratios (RR) or Peto odds ratios (OR) and corresponding 95% confidence intervals for categorical outcomes. The Peto method was applied when events were rare, particularly when trials reported zero events in one of the treatment arms(21). Mean and standardized mean differences (MD, SMD) were calculated for continuous outcomes. If there were at least 5 trials for a pooled analysis, the Hartung–Knapp–Sidik–Jonkman method for random-effects models was applied to calculate SMD for continuous outcomes and relative measures of effect for categorical outcomes with corresponding 95% CI(22). If there were fewer than 5 trials and no between-study variance (tau^2 at or near 0) data were meta-analyzed with a fixed-effects model(23). When there were no

events in a treatment arm, we used the treatment arm continuity correction. Absolute event rates and 95% CIs for the primary harm outcomes were pooled for each study group using the Freeman-Tukey double arcsine transformation(24). Heterogeneity was assessed using the I^2 statistic, Chi-squared test, and visual inspection of the forest plots. An I^2 statistic of 75% or greater may indicate substantial heterogeneity. We analyzed results separately for studies of initial management of ARF and studies of post-extubation ARF. We conducted subgroup analyses to explore potential causes of heterogeneity by clinical setting, disease indication, treatment duration, and type of ARF. If quantitative synthesis was not appropriate, findings were summarized narratively. We used a modification of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall certainty of evidence for critical outcomes as high, moderate, low, or insufficient(25,26). At the request of the ACP-CGC, we also assessed certainty of evidence for skin breakdown. The thresholds indicating level of magnitude for our critical outcomes were derived through input by our content experts and technical expert panel (Tables 1a and 1b).

Role of Funding Source

This review was funded by a contract with the American College of Physicians (ACP). A representative of the ACP provided technical support during the review and served as a liaison to the ACP-CGC and the technical expert panel. The ACP-CGC assisted in the development of key questions, study inclusion criteria, and outcome measures of interest but did not participate in data collection, analysis, or manuscript preparation.

RESULTS

Search results are shown in Appendix Figure 1. We identified 29 RCTs (in 32 articles)(27-58) which met inclusion criteria. An overview of included trials is presented in Appendix Table 3 and an overview of patient characteristics is presented in Appendix Table 4. Patients typically had at least moderate ARF according to baseline PaO_2/FIO_2 ratio (<200) or SPO_2 (≤88%). In the NIV parallel group studies, the baseline SpO2 weighted mean in the initial management trials was 76% while the baseline PaO_2/FIO_2 ratio weighted mean in the post-extubation trials was 198. In the COT parallel group studies, the baseline SpO2 weighted mean in the initial management trials was 88% while the baseline PaO_2/FIO_2 ratio weighted mean in the post-extubation trials was 227. Studies did not require patients to have failed an initial oxygen therapy prior to randomization though information was sparse on pre-randomization

oxygen treatments. Detailed study and treatment characteristics, risk of bias of individual studies, and outcomes data are reported in Supplementary Tables 1-10. We report results separately for studies comparing HFNO vs. NIV and HFNO vs. COT and by whether treatment was for initial management or post-intubation management of ARF. Treatment protocols varied by study based mostly on physiologic parameters, with most studies targeting SpO_2 levels ≥92% (range 88-95%). Information from crossover studies was limited to comfort and dyspnea outcomes in initial management. Subgroup analyses for both NIV and COT controls are presented in Supplementary Tables 11-14. The effect of treatments did not differ significantly by clinical setting, disease indication, treatment duration, or type of ARF, although for most outcomes there were few or no studies available for these comparisons. Data on physiologic outcomes were inadequate to derive conclusions due to variable types and timing of physiologic data reported (Supplementary Tables 15-18). The greatest difference in physiologic outcomes was in PaO_2/FiO_2 ratio, particularly in post-extubation management where post-treatment values were generally higher in NIV compared to HFNO (Supplementary Table 16) and in HFNO compared to COT (Supplementary Table 18).

HFNO vs. NIV

Initial Management of Acute Respiratory Failure

Eight studies (4 parallel design and 4 crossover studies) compared HFNO to NIV for initial management of ARF among patients with multiple diagnoses(32,34,35,49,54), chronic obstructive pulmonary disease(29), cystic fibrosis(50), and during bronchoscopy(48) (Appendix Tables 3 and 4). One of these studies reported outcomes on subgroups of patients with acute decompensated heart failure (36) and chronic obstructive pulmonary disease exacerbation or acute hypercapnic respiratory failure (57). Two were rated low risk of bias while 6 were rated moderate (Supplementary Table 2).

Critical Outcomes

Intubation

Pooled results from 2 RCTs (n=420) indicate that HFNO may reduce intubations by a moderate amount (20.1% vs. 30.7%; absolute risk difference [ARD] -9.4%, [-15.2, -1.6]) compared with NIV (RR 0.71 [0.53, 0.95]; I^2=0%; low evidence certainty) (Figures 1 and 2/Table 1a)(32,34).

All-cause Mortality

Results from 1 RCT (n=216) indicate that HFNO may reduce all-cause mortality by a large amount (12.3% vs. 28.2%; ARD -15.8% [-21.4, -5.9]) compared with NIV (RR 0.44 [0.24,

0.79]; low evidence certainty) (Figures 1 and 2/Table 1a)(34). The trial included patients with hypoxic ARF from multiple etiologies.

Hospital-acquired Pneumonia

One RCT (n=216) among adults with hypoxic ARF due to multiple etiologies evaluated hospital-acquired pneumonia (34). HFNO may reduce hospital-acquired pneumonia by a moderate amount 3.8% vs. 8.2%; ARD -4.4% [-7.0%, 3.7%]) compared to NIV (RR 0.46 [0.15, 1.45]; low evidence certainty) (Figure 1/Table 1a).

ICU Admissions and ICU Length of Stay

Few trials reported ICU admissions(32) or length of stay(32,34) (Supplementary Figure 1). Study protocol, rather than clinical outcomes, primarily determined ICU admission and length of stay. It is uncertain whether HFNO reduces ICU admissions or ICU length of stay (insufficient evidence) (Figure 1/Table 1a).

Hospital Length of Stay

Two RCTs (n=372) including patients with hypoxic and/or hypercapnic ARF reported hospital length of stay (Supplementary Figure 2)(29,32). HFNO may make little or no difference in hospital length of stay compared to NIV (MD 0.45 days [-0.69, 1.59]; I^2=0%; low evidence certainty) (Figure 1/Table 1a).

Patient Comfort and Dyspnea

Seven RCTs (n=644) reported comfort measures(29,32,34,35,49,50,54) and 7 RCTs (n=464) provided dyspnea measures(32,34,35,48-50,54), none of which could be pooled. HFNO may improve patient comfort but may make little or no difference in dyspnea compared to NIV (low evidence certainty) (Figure 1/Table 1a).

Important Outcomes

No trials comparing HFNO with NIV reported data on barotrauma, skin breakdown, discharge disposition, hospital readmissions, compromised nutrition, functional independence, or cost/resource utilization.

Intermediate Outcomes

Treatment escalation, defined as requiring a switch from HFNO to NIV or from NIV to HFNO, was rarely reported. One trial(32) suggested higher rates of device switching in HFNO to NIV than from NIV to HFNO. Two trials(48,49) reported higher rates of device intolerance in NIV vs. HFNO.

Post-extubation Management of Acute Respiratory Failure

Three parallel RCTs compared HFNO to NIV in post-extubation management of ARF(37,39,53). All were ICU trials in patients with multiple diagnoses, chronic obstructive

pulmonary disease exacerbation, or post-cardiothoracic surgery (Appendix Tables 3 and 4). Two trials were rated low risk of bias; 1 was rated moderate (Supplementary Table 2).

Reintubation

Three RCTs (n=1476) evaluated reintubation (37,39,53). HFNO may increase reintubations by a small amount (16.6% vs. 14.7%; ARD 2.0% [-1.5, 6.6]) compared with NIV (RR 1.13 [0.90, 1.43]; I^2=0%; low evidence certainty) (Figures 1 and 2/Table 1a).

All-cause Mortality

We pooled 3 RCTs (n=1476) that reported all-cause mortality(37,39,53). HFNO may increase all-cause mortality by a small amount (11.4% vs. 9.8%; ARD 1.7% [-1.3, 5.7]) compared to NIV (RR 1.15 [0.88, 1.51]; I^2=0%; low evidence certainty) (Figures 1 and 2/Table 1a).

Hospital-acquired Pneumonia

Two RCTs (n=1434) evaluated hospital-acquired pneumonia(37, 53). HFNO may make little to no difference in hospital-acquired pneumonia (12.3% vs. 13.6%; ARD -1.5% [-4.4, 2.3%]) compared to NIV (RR 0.90 [0.70, 1.16]; I^2=0%; low evidence certainty) (Figure 1/Supplementary Figure 3/Table 1a).

ICU Admissions

Not applicable.

ICU Length of Stay

Three RCTs (n=1476) reported ICU length of stay(37,39,53). In pooled results from 2 RCTs in medical patients (n=646), HFNO made little or no difference in ICU mean length of stay compared with NIV (MD -0.98 days [-1.99, 0.03]) (Supplementary Figure 2)(37,39). A third trial of post-cardiothoracic surgery patients(53) (n=830) only reported median length of stay and showed a similar benefit. HFNO may make little to no difference in ICU length of stay compared with NIV (low evidence certainty) (Figure 1/Table 1a).

Hospital Length of Stay

Two RCTs (n=1434) reporting hospital length of stay(37,53) were not pooled (data reported as means and medians). It is uncertain whether HFNO reduces hospital length of stay compared to NIV (insufficient evidence) (Figure 1/Table 1a).

Patient Comfort and Dyspnea

Two RCTs (n=872) provided patient comfort measures (39,53) but could not be pooled, and 1 trial reported dyspnea measures(53) (post-cardiothoracic surgery, n=752). One trial found slight improvement in comfort with HFNO(39) and 1 showed no difference(53). HFNO may make little or no difference in patient comfort compared to NIV (low evidence certainty) (Table

1a). HFNO may make little or no difference in dyspnea compared to NIV (58% vs. 60%; ARD -2.4% [-8.5 to 4.8]; low evidence certainty) (Figure 1/Table 1a).

Important Outcomes

Three trials (n=1454) comparing HFNO vs. NIV reported nasal/facial skin breakdown37,39,53). All 3 trials consistently showed significantly higher event rates in the NIV group; 2 trials reported no events in the HFNO groups(37,39) but 1 of the trials (n=604) reported that 42.9% of patients, all from the NIV group, had “nasal septum and skin trauma” resulting in discontinuation of NIV(37). The pooled skin breakdown event rate was 22.0% in NIV compared to 0.7% in HFNO (Peto OR 0.15 [0.02, 1.13]; I^2=88%) (Supplementary Figure 4). HFNO may reduce nasal/facial skin breakdown by a large amount (low evidence certainty). Reported findings for barotrauma, gastric dysfunction, and cost/resource utilization were inadequate to derive conclusions.

Intermediate Outcomes

Three trials (n=1150) reported rates of “treatment” or “respiratory” failure but did not report specific numbers of patients that were escalated to a different treatment. Results were mixed(37,39,53). As noted above, one trial reported intolerance due to skin trauma(37).

HFNO vs. COT

Initial Management of Acute Respiratory Failure

We included 14 trials comparing HFNO to COT for initial management of ARF among patients with multiple diseases(28,31,34,40,44,46,49,52,54), cardiogenic pulmonary edema(43), chronic obstructive pulmonary disease exacerbation(45), those who were immunocompromised(27,41), and in palliative care(47). Nine were parallel design RCTs and 5 were crossover studies. Eight studies enrolled fewer than 100 participants (Appendix Tables 3 and 4). Risk of bias was rated low for 6 studies and moderate for 8 (Supplementary Table 1b).

Intubation

We pooled 8 parallel design RCTs (n=1694) that evaluated intubation(27,28,33,40,41,43,46,52). HFNO may make little or no difference in intubation (8,1% vs. 7,6%; ARD -0.4% [-15.6, 23.9]) compared with COT (Peto OR 0.98 [0.34, 2.82]; I^2=12%; low evidence certainty) (Figures 1 and 3/Table 1b).

All-cause Mortality

We pooled 4 RCTs of hypoxic ARF (n=1407) that reported all-cause mortality(27,34,40,43). HFNO may make little or no difference in all-cause mortality (24.5% vs. 25.1%; ARD -0.8% [-4.9, 3.8) compared with COT (RR 0.97 [0.82, 1.14]; I^2=42%; low evidence certainty) (Figures 1 and 3/Table 1b).

Hospital-acquired Pneumonia

One RCT (n=200) evaluated hospital-acquired pneumonia in ICU patients with hypoxic ARF from multiple etiologies(34). HFNO may result in a moderate reduction in hospital-acquired pneumonia (3.8% vs. 8.5%; ARD -4.8% [-7.3%, 3.7%]) compared with COT (RR 0.44 [0.14, 1.43]; low evidence certainty) (Figure 1/Table 1b).

ICU Admissions

Two RCTs (n=403) reported ICU admissions(28,40). It is uncertain whether HFNO reduces ICU admissions compared to COT (insufficient evidence) (Figure 1/Supplementary Figure 5/Table 1b).

ICU Length of Stay

Three RCTs (n=1476) reported ICU length of stay(27,34,44) of which 2 trials of hypoxic ARF (n=976) were pooled(27,34). It is uncertain if HFNO reduces ICU length of stay (MD 0.41 days [-1.08, 1.90]; I^2=0%; insufficient evidence) (Figure 1/Supplementary Figure 6/Table 1b).

Hospital Length of Stay

Four RCTs (n=1267) reported hospital length of stay(27,40,43,44) which could not be pooled. HFNO may make little or no difference in hospital length of stay compared to COT (medians ranged from 1 to 24 vs. 1 to 27 days; low evidence certainty) (Figure 1/Table 1b).

Patient Comfort and Dyspnea

Twelve RCTs (n=1611) provided patient comfort measures(27,28,31,34,40,41,43,45,46,49,52,54). Four trials (n=415) provided data that permitted pooling. HFNO improved patient comfort based on visual analog scale (VAS) scores (SMD -.61 [-0.81, -0.41]; I^2=45%)(34,43,46,52) (Supplementary Figure 7). Results from the other 8 RCTs were mixed. Overall, HFNO may improve patient comfort compared with COT (low evidence certainty) (Table 1b). Thirteen RCTs (n=1799), including 4 crossover studies, provided dyspnea measures(27,28,31,34,40,41,43,45-47,49,52,54); 4 trials (n=258) could be pooled. HFNO provided moderate improvement in dyspnea compared to COT (SMD -0.56 [-1.35 to 0.24]; I^2=67%) (Supplementary Figure 8)(43,46,47,52). HFNO increased the percentage of individuals with improved dyspnea based on results from 3 trials that used different threshold criteria for defining improvement(28,34,40). Results from 9 studies that could not be pooled reported mixed results(27,28,31,34,40,41,45,49,54). Overall, HFNO may improve dyspnea compared with COT (low evidence certainty) (Figure 1/Table 1b).

Important Outcomes

Two trials (n=431) comparing HFNO vs. COT reported skin breakdown (facial pressure sore or nasal ulceration)(40, 43). Both trials reported no cases of skin breakdown in the HFNO

group. One trial reported no events in the COT group(40) while the other trial did not report skin breakdown in the COT group (insufficient evidence)(43). Other outcomes were rarely or not reported.

Intermediate Outcomes

Seven trials (n=1,503) comparing HFNO vs. COT reported treatment escalation from COT to either HFNO or NIV (4 studies) and from HFNO to NIV(27,28,40,41,43,44,46). Studies generally reported higher rates of treatment escalation for COT than for HFNO (Supplementary Figure 9). Six trials reported device intolerance to the assigned treatment(27,40,43,46,47,49). We were unable to derive conclusions due to limited reporting in the COT groups.

Post-extubation Management of Acute Respiratory Failure

Seven parallel group RCTs (n=1,065) compared HFNO with COT for post-extubation ARF. All were ICU trials in medical (mixed diagnoses)(38,42,51,56,58) and post-cardiothoracic surgery patients(30,55) (Appendix Tables 3 and 4). Three studies were rated low risk of bias and 4 moderate (Supplementary Table 2).

Reintubation

Based on pooled results from 7 RCTs (n=1065), HFNO may reduce reintubations by a small amount (4.7% vs. 8.3%; ARD -3.9% [-7.8%, 5.3%]) compared to COT (Peto OR 0.60 [0.23, 1.61]; I^2=40%; low evidence certainty) (Figures 1 and 3/Table 1b)(30,38,42,51,55,56,58).

All-cause Mortality

We pooled 4 RCTs of ICU patients with hypoxic ARF (n=782) that reported all-cause mortality (38,42,55,56). HFNO may make little or no difference in all-cause mortality (4.6% vs. 5.0%; ARD -0.1% [-2.5%, 4.5%]) compared with COT (RR 1.01 [0.60, 1.72]; I^2=0%; low evidence certainty) (Figures 1 and 3/Table 1b)

Hospital-acquired Pneumonia

One RCT (n=527) evaluated hospital-acquired pneumonia in the ICU in medical patients with post-extubation hypoxic (non-hypercapnic) ARF from multiple etiologies(38). HFNO may make little or no difference (1.1% vs. 2.3%; ARD -1.1% [-2.0%, 2.2%]) in hospital-acquired pneumonia compared with COT (RR 0.50 [0.13, 1.97]; low evidence certainty) (Figure 1/Table 1b).

ICU Admissions

Not applicable.

ICU Length of Stay

Six RCTs (n=1006) reported ICU length of stay (30,38,42,55,56,58) of which 5 (n=479) were pooled. Compared to COT, HFNO probably makes little or no difference in ICU length of

stay (approximately 6 days in each group; MD 0.19 [-0.19, 0.57]; moderate evidence certainty) (Figure 1/Supplementary Figure 6/Table 1b)(30,42,55,56,58).

Hospital Length of Stay

Two RCTs reported hospital length of stay; results could not be pooled as one reported medians and one reported means (38,56). It is uncertain whether HFNO reduces hospital length of stay compared to COT (insufficient evidence) (Figure 1/Table 1b).

Patient Comfort and Dyspnea

Four parallel design RCTs (n=324) provided patient comfort measures (42,51,55,58) which could not be pooled due to variation in measures reported. Three trials showed that HFNO resulted in improved patient comfort compared to COT and one reported little or no difference(58). HFNO may improve patient comfort compared with COT (low evidence certainty) (Table 1b). Only 1 parallel design RCT (n=155) reported dyspnea with little or no difference in median values(30). It is uncertain whether HFNO improves dyspnea compared to COT (insufficient evidence) (Figure 1/Table 1b).

Important outcomes

One trial reported no incidences of skin breakdown were observed with HFNO but this outcome was not reported for the COT arm (insufficient evidence)(38). No trials reported gastric dysfunction, hospital readmissions, compromised nutrition, or functional independence. Only 1 trial reported a measure of cost/resource utilization(42).

Intermediate outcomes

Five RCTs (n=479) reported treatment escalation from COT to either HFNO or NIV and HFNO to NIV (30,42,51,55,58). All trials reported lower treatment escalation in the HFNO vs. COT groups [6.3% vs. 18.5%; RR 0.43 [0.27, 0.70]) (Supplementary Figure 9). Two additional trials reported a higher rate of “treatment” or “respiratory” failure in the COT vs. HFNO group but ensuing treatment was not clearly defined(38,51). No RCTs comparing HFNO with COT reported device intolerance outcomes.

DISCUSSION

Our analysis of data from 29 RCTs comparing HFNO with NIV or COT found that compared to NIV, HFNO may reduce intubation, all-cause mortality, and hospital-acquired pneumonia, and improve patient comfort in the initial management of ARF. However, compared to NIV, HFNO may increase reintubations and mortality in post-extubation management of ARF. Compared to COT, HFNO may reduce reintubation and improve patient comfort in post-extubation management of ARF. Benefits of HFNO were less clear compared to COT in the

initial management of ARF. HFNO may reduce facial skin breakdown compared to NIV and results in fewer harms such as treatment escalation. Based on input from our technical expert panel and the ACP-CGC we analyzed results separately by whether treatment strategies were for initial or post-extubation management of ARF. Such patients are clinically distinct and may have different etiologies and severities of their ARF. For example, post-extubation ARF frequently result in reintubation, resulting in prolonged intubation duration and higher ICU mortality(59). Our results are generally consistent with past systematic reviews(1,60-76). However, we limited our inclusion criteria to hospitalized adults meeting criteria for ARF, included a broader scope of clinical conditions and settings, assessed HFNO against both NIV and COT, evaluated a more comprehensive list of key clinical outcomes, and updated our search through July 2020. We prioritized patient-centered outcomes such as intubation, mortality, pneumonia, length of hospitalization or length of ICU stay, rather than physiologic outcomes.

As respiratory treatment options vary by the etiology and severity of ARF, we analyzed results separately for NIV and COT. The baseline physiologic parameters of patients enrolled in the NIV trials were worse than those enrolled in the COT trials. For example, the baseline mean SpO_2 of the patients in initial management NIV parallel group trials was 76% compared to 88% in the COT trials. Additionally, 5 of the 21 (24%) COT trials versus 4 of the 11 (36%) NIV trials included patients with hypercapnic ARF. The intubation rates in NIV trials were higher compared to COT trials in both initial and post-extubation management of ARF, likely reflecting the higher severity of ARF in the NIV versus COT trials. Some trials included NIV as a comparator for causes of respiratory failure that are not recommended in NIV guidelines published by the European Respiratory Society and American Thoracic Society (77). However, national hospital discharge data indicate that many patients are treated with NIV for indications not recommended by these societies (78,79), such as hypoxemia due to pneumonia or hypoxemia of unclear etiology, while other patients having strong treatment recommendations are not treated with NIV (80). These data support that there may be an ongoing evidence gap in the use of ventilatory support strategies that this review can address.

We identified gaps in the existing literature that limited our conclusions and for which future research is needed. Trials varied in populations enrolled, etiology of ARF, and protocols used. When numerous causes of ARF were included in a single trial, results were often not stratified or sample sizes were too small to adequately evaluate outcomes across disease states or clinical settings. Studies often excluded patients with life-threatening comorbidities or at imminent risk of mechanical ventilation. No studies reported outcomes in patients with SARS

CoV-2 infection. Many studies used surrogate endpoints, such as physiologic outcomes, which may not reflect patient-centered outcomes such as mortality. Trial design, sample size, treatment/follow-up duration and results reporting were often inadequate to accurately assess our pre-specified outcomes. No RCTs evaluated delirium, compromised nutrition, functional independence at discharge, or discharge disposition. Finally, treatment protocols, clinician/health system training, and cost and resource use were poorly characterized. These represent a key part of the real-world utility of HFNO for a given health system.

In conclusion, compared to NIV, HFNO used as initial management for adults with ARF may improve several clinical outcomes. Compared to COT, HFNO used as post-extubation management may reduce reintubations and improve patient comfort. HFNO resulted in fewer harms than either NIV or COT. Broad applicability, including required clinician and health system experience and resource use, remain unknown.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge input and feedback on review scope, treatment categorization, critical outcomes, and draft findings from the members of the Technical Expert Panel: Charles Carpati, MD; Matthew G. Drake, MD; Andrew Dunn, MD, MPH, SFHM, MACP; and Robert C. Hyzy, MD.

Funding

The evidence review was commissioned by the American College of Physicians. The material is the result of work supported by and conducted at the Minneapolis VA Health Care System.

Dr. Baldomero was also supported, in part, by a National Institutes of Health National Center for Advancing Translational Sciences grant KL@TR002492 and UL1TR002494.

Reproducible Research Statement

Study Protocol: Baldomero AK, Melzer A, Greer N, et al. Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: A systematic review protocol. BMJ Open. 2020;10(2). [PMID: 32051320] doi: 10.1136/bmjopen-2019-034956

Statistical Code: Not available

Data Set: Supplementary Tables

DISCLOSURE

The materials presented here solely represent the views of the authors and do not represent the view of the U.S. Department of Veterans Affairs, the United States Government or the National Institutes of Health's National Center for Advancing Translational Sciences.

Current mailing address for AKB, ACM:

1 Veterans Drive, Pulmonary 111-N

Minneapolis, MN, USA

Current mailing address for all other authors:

One Veterans Drive (111-0)

Minneapolis, MN 55417

References

1. Drake MG. High-flow nasal cannula oxygen in adults: an evidence-based assessment. Ann Am Thorac Soc. 2018;15(2):145-155. [PMID: 29144160] doi: 10.1513/AnnalsATS.201707-548FR
2. Möller W, Feng S, Domanski U, et al. Nasal high flow reduces dead space. J Appl Physiol. 2017;122(1):191-197. [PMID:27856714] doi: 10.1152/japplphysiol.00584.2016
3. Ritchie JE, Williams AB, Gerard C, et al. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care. 2011;39(6):1103-10. [PMID:22165366] doi: 10.1177/0310057x1103900620
4. Sim MA, Dean P, Kinsella J, et al. Performance of oxygen delivery devices when the breathing pattern of respiratory failure is simulated. Anaesthesia. 2008;63(9):938-40. [PMID:18540928] doi: 10.1111/j.1365-2044.2008.05536.x
5. Parke RL, McGuinness SP**.** Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care. 2013;58(10):1621-4. [PMID:23513246] doi: 10.4187/respcare.02358
6. Parke RL, Eccleston ML, McGuinness SP**.** The effects of flow on airway pressure during nasal high-flow oxygen therapy. Respir Care. 2011;56(8):1151-5 doi: 10.4187/respcare.01106.
7. Groves N, Tobin A**.** High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care. 2007;20(4):126-31. [PMID:17931878] doi: 10.1016/j.aucc.2007.08.001
8. Parke R, McGuinness S, Eccleston M**.** Nasal high-flow therapy delivers low level positive airway pressure. Br J Anaesth. 2009;103(6):886-90. [PMID:19846404] doi: 10.1093/bja/aep280
9. Corley A, Caruana LR, Barnett AG, et al. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth. 2011;107(6):998-1004. [PMID:21908497] doi: 10.1093/bja/aer265
10. Tiruvoipati R, Lewis D, Haji K, et al. High-flow nasal oxygen vs high-flow face mask: A randomized crossover trial in extubated patients. J Crit Care. 2010;25(3):463-8. [PMID:19781896]. doi: 10.1016/j.jcrc.2009.06.050
11. Sztrymf B, Messika J, Mayot T, et al. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: A prospective observational study. J Crit Care. 2012;27(3):324.e9-13. [PMID:21958974] doi: 10.1016/j.jcrc.2011.07.075
12. Roca O, Riera J, Torres F, et al. High-flow oxygen therapy in acute respiratory failure. Respir Care. 2010;55(4):408-13. [PMID:20406507]
13. Rittayamai N, Tscheikuna J, Rujiwit P**.** High-flow nasal cannula versus conventional oxygen therapy after endotracheal extubation: A randomized crossover physiologic study. Respir Care. 2014;59(4):485-90. [PMID:24046462] doi: 10.4187/respcare.02397
14. Cortegiani A, Crimi C, Noto A, et al. Effect of high-flow nasal therapy on dyspnea, comfort, and respiratory rate. Crit Care. 2019;23(1):201. [PMID: 31167660] doi: 10.1186/s13054-019-2473-y
15. Williams R, Rankin N, Smith T, et al. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. Crit Care Med. 1996;24(11):1920-9. [PMID:8917046] doi: 10.1097/00003246-199611000-00025

16. Hasani A, Chapman TH, McCool D, et al. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. Chron Respir Dis. 2008;5(2):81-6. [PMID: 18539721]. doi: 10.1177/1479972307087190
17. Sztrymf B, Messika J, Bertrand F, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: A prospective pilot study. Intensive Care Med. 2011;37(11):1780-6. [PMID: 21946925] doi: 10.1007/s00134-011-2354-6
18. Lenglet H, Sztrymf B, Leroy C, et al. Humidified high flow nasal oxygen during respiratory failure in the emergency department: Feasibility and efficacy. Respir Care. 2012;57(11):1873-8. [PMID: 22417844] doi: 10.4187/respcare.01575
19. Baldomero AK, Melzer A, Greer N, et al. Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: A systematic review protocol. BMJ Open. 2020;10(2). [PMID: 32051320] doi: 10.1136/bmjopen-2019-034956
20. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928-d.
21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019.
22. IntHout J, Ioannidis JP, Borm GF**.** The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard Dersimonian-Laird method. BMC Med Res Methodol. 2014;14(1):25. [PMID: 24548571] doi: 10.1186/1471-2288-14-25
23. Veroniki AA, Jackson D, Bender R, et al. Methods to calculate uncertainty in the estimated overall effect size from a random-effects meta-analysis. Res Synth Methods. 2019;10(1):23-43. [PMID: 30129707] doi: 10.1002/jrsm.1319
24. Freeman MF, Tukey JW**.** Transformations related to the angular and the square root. Ann. Math. Statist. 1950:607-11.
25. McMaster University and Evidence Prime, Inc. *GRADEpro GDT: GRADEpro Guideline development tool*. Ontario, Canada, 2015.
26. Schünemann H, Brożek J, Guyatt G, et al. GRADE Handbook, 2019. Available: https://gdt.gradepro.org/app/handbook/handbook.html [Accessed 9 Oct 2019]
27. Azoulay E, Lemiale V, Mokart D, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: The HIGH randomized clinical trial. JAMA. 2018;320(20):2099-10. [PMID: 30357270] doi: 10.1001/jama.2018.14282
28. Bell N, Hutchinson CL, Green TC, et al. Randomised control trial of humidified high flow nasal cannulae versus standard oxygen in the emergency department. Emerg Med Australas. 2015;27(6):537-41. [PMID: 26419650] doi: 10.1111/1742-6723.12490
29. Cong L, Zhou L, Liu H, et al. Outcomes of high-flow nasal cannula versus non-invasive positive pressure ventilation for patients with acute exacerbations of chronic obstructive pulmonary disease. Int J Clin Exp Med. 2019;12(8):10863-7
30. Corley A, Bull T, Spooner AJ, et al. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI >/=30: A randomised controlled trial. Intensive Care Med. 2015;41(5):887-94. [PMID:25851385] doi: 10.1007/s00134-015-3765-6
31. Delorme M, Bouchard PA, Simon M, et al. Effects of high-flow nasal cannula on the work of breathing in patients recovering from acute respiratory failure. Crit Care Med. 2017;45(12):1981-8. [PMID: 28857852] doi: 10.1097/CCM.0000000000002693
32. Doshi P, Whittle JS, Bublewicz M, et al. High-velocity nasal insufflation in the treatment of respiratory failure: A randomized clinical trial. Ann Emerg Med. 2018;72(1):73-83 e5. [PMID: 29310868] doi: 10.1016/j.annemergmed.2017.12.006

33. Frat JP, Ragot S, Girault C, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: A post-hoc analysis of a randomised trial. Lancet Respir Med. 2016;4(8):646-52. [PMID: 27245914] doi: 10.1016/S2213-2600(16)30093-5
34. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185-96 [PMID:2598190] doi: 10.1056/NEJMoa1503326
35. Grieco DL, Menga LS, Raggi V, et al. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2020;201(3):303-12. [PMID:31687831] doi: 10.1164/rccm.201904-0841OC
36. Haywood ST, Whittle JS, Volakis LI, et al. HVNI vs NIPPV in the treatment of acute decompensated heart failure: Subgroup analysis of a multi-center trial in the ED. Am J Emerg Med. 2019;37(11):2084-90. [PMID: 30880040] doi: 10.1016/j.ajem.2019.03.002
37. Hernandez G, Vaquero C, Colinas L, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: A randomized clinical trial. JAMA. 2016;316(15):1565-74. [PMID: 27706464] doi: 10.1001/jama.2016.14194
38. Hernandez G, Vaquero C, Gonzalez P, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: A randomized clinical trial. JAMA. 2016;315(13):1354-61. [PMID: 26975498] doi: 10.1001/jama.2016.271132
39. Jing G, Li J, Hao D, et al. Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: A pilot randomized controlled trial. Res Nurs Health. 2019;42(3):217-25. [PMID: 30887549] doi: 10.1002/nur.21942
40. Jones PG, Kamona S, Doran O, et al. Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: The HOT-ER study. Respir Care. 2016;61(3):291-9. [PMID: 26577199] doi: 10.4187/respcare.04252
41. Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: A multicenter randomized trial. Crit Care. 2015;19:380. [PMID: 26521922] doi: 10.1186/s13054-015-1097-0
42. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190(3):282-8. [PMID: 25003980] doi: 10.1164/rccm.201402-0364OC
43. Makdee O, Monsomboon A, Surabenjawong U, et al. High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: A randomized controlled trial. Ann Emerg Med. 2017;70(4):465-72 e2 [PMID: 28601264] doi: 10.1016/j.annemergmed.2017.03.028
44. Parke RL, McGuinness SP, Eccleston ML**.** A preliminary randomized controlled trial to assess effectiveness of nasal high-flow oxygen in intensive care patients. Respir Care. 2011;56(3):265-70. [PMID: 21255498] doi: 10.4187/respcare.00801
45. Pilcher J, Eastlake L, Richards M, et al. Physiological effects of titrated oxygen via nasal high-flow cannulae in COPD exacerbations: A randomized controlled cross-over trial. Respirology. 2017;22(6):1149-55. [PMID: 28470831] doi: 10.1111/resp.13050
46. Rittayamai N, Tscheikuna J, Praphruetkit N, et al. Use of high-flow nasal cannula for acute dyspnea and hypoxemia in the emergency department. Respir Care. 2015;60(10):1377-82. [PMID: 26060321] doi: 10.4187/respcare.03837

47. Ruangsomboon O, Dorongthom T, Chakorn T, et al. High-flow nasal cannula versus conventional oxygen therapy in relieving dyspnea in emergency palliative patients with do-not-intubate status: A randomized crossover study. Ann Emerg Med. 2019;18:18. [PMID: 31864728] doi: 10.1016/j.annemergmed.2019.09.009
48. Saksitthichok B, Petnak T, So-Ngern A, et al. A prospective randomized comparative study of high-flow nasal cannula oxygen and non-invasive ventilation in hypoxemic patients undergoing diagnostic flexible bronchoscopy. J Thorac Dis. 2019;11(5):1929-39. [PMID: 31285886] doi: 10.21037/jtd.2019.05.02
49. Schwabbauer N, Berg B, Blumenstock G, et al. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: Effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). BMC Anesthesiol. 2014;14:66. [PMID: 25110463] doi: 10.1186/1471-2253-14-66
50. Sklar MC, Dres M, Rittayamai N, et al. High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: A randomized crossover physiological study. Ann Intensive Care. 2018;8(1):85. [PMID: 30187270] doi: 10.1186/s13613-018-0432-4
51. Song HZ, Gu JX, Xiu HQ, et al. The value of high-flow nasal cannula oxygen therapy after extubation in patients with acute respiratory failure. Clinics (Sao Paulo). 2017;72(9):562-7. [PMID: 29069260] doi: 10.6061/clinics/2017(09)07
52. Spoletini G, Mega C, Pisani L, et al. High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: A pilot randomized controlled trial. J Crit Care. 2018;48:418-25. [PMID: 30321833] doi: 10.1016/j.jcrc.2018.10.004
53. Stephan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: A randomized clinical trial. JAMA. 2015;313(23):2331-9. [PMID: 25980660] doi: 10.1001/jama.2015.5213
54. Vargas F, Saint-Leger M, Boyer A, et al. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respir Care. 2015; 60(10):1369-76. [PMID: 25944940] doi: 10.4187/respcare.03814
55. Vourc'h M, Nicolet J, Volteau C, et al. High-flow therapy by nasal cannulae versus high-flow face mask in severe hypoxemia after cardiac surgery: A single-center randomized controlled study-the heart flow study. J Cardiothorac Vasc Anesth. 2020;34(1):157-65. [PMID: 31230964] doi: 10.1053/j.jvca.2019.05.039
56. Cho JY, Kim H-S, Kang H, et al. Comparison of postextubation outcomes associated with high-flow nasal cannula vs. conventional oxygen therapy in patients at high risk of reintubation: a randomized clinical trial. J Korean Med Sci. 2020;35(25):e194.]PMID: 32597041] doi: 10.3346/jkms.2020.35.e194
57. Doshi PB, Whittle JS, Dungan II G, et al. The ventilatory effect of high velocity nasal insufflation compared to non-invasive positive pressure ventilation in the treatment of hypercapneic respiratory failure: a subgroup analysis. Heart Lung. 2020. [PMID: 32273085] doi: 10.1016/j.hrtlng.2020.03.008
58. Matsuda W. Hagiwara A, Uemura T, et al. High-flow nasal cannula may not reduce the re-intubation rate compared with large-volume nebulization-based humidifier. Respir Care. 2020;65(5):610-617. [PMID: 31992669] doi: 10.4187/respcare.07095
59. Thille A, Harrois A, Schortgen F, et al. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med. 2011;39(12):2612-8. [PMID: 21765357] doi: 10.1097/CCM.0b013e3182282a5a
60. Cheng LC, Chang SP, Wang JJ, et al**.** The impact of high-flow nasal cannula on the outcome of immunocompromised patients with acute respiratory failure: a systematic

review and meta-analysis. Medicina (Kaunas). 2019;55(10):16. [PMID: 31623276] doi: 10.3390/medicina55100693
61. Corley A, Rickard CM, Aitken LM, et al. High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev. 2017;5. [PMID: 28555461] doi: 10.1002/14651858.CD010172.pub2
62. Cortegiani A, Crimi C, Sanfilippo F, et al. High flow nasal therapy in immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. J Crit Care. 2019;50:250-6. [PMID: 30622042] doi: 10.1016/j.jcrc.2018.12.015
63. Helviz Y, Einav S**.** A systematic review of the high-flow nasal cannula for adult patients. Crit Care. 2018;22(1):71. [PMID: 29558988] doi: 10.1186/s13054-018-1990-4
64. Huang HB, Peng JM, Weng L, et al. High-flow oxygen therapy in immunocompromised patients with acute respiratory failure: A review and meta-analysis. J Crit Care. 2018;43:300-5. [PMID: 28968525] doi: 10.1016/j.jcrc.2017.09.176
65. Huang CC, Lan HM, Li CJ, et al. Use high-flow nasal cannula for acute respiratory failure patients in the emergency department: a meta-analysis study. Emerg Med Int. 2019. [PMID: 31737365] doi: 10.1155/2019/2130935
66. Kang H, Zhao Z, Tong Z**.** Effect of high-flow nasal cannula oxygen therapy in immunocompromised subjects with acute respiratory failure. Respir Care. 2020;65(3):369-376. [PMID: 31744865] doi: 10.4187/respcare.07205
67. Leeies M, Flynn E, Turgeon AF, et al. High-flow oxygen via nasal cannulae in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. Syst Rev. 2017;6(1):202. [PMID: 29037221] doi: 10.1186/s13643-017-0593-5
68. Liesching TN, Lei Y**.** Efficacy of high-flow nasal cannula therapy in intensive care units. J Intensive Care Med. 2017. [PMID: 28110612] doi: 10.1177/0885066616689043
69. Lin SM, Liu KX, Lin ZH, et al. Does high-flow nasal cannula oxygen improve outcome in acute hypoxemic respiratory failure? A systematic review and meta-analysis. Respir Med. 2017;131:58-64. [PMID: 28947043] doi: 10.1016/j.rmed.2017.08.005
70. Monro-Somerville T, Sim M, Ruddy J, et al.The effect of high-flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45(4):e449-e56. [PMID: 27611978] doi: 10.1097/CCM.0000000000002091
71. Ni YN, Luo J, Yu H, et al. Can high-flow nasal cannula reduce the rate of endotracheal intubation in adult patients with acute respiratory failure compared with conventional oxygen therapy and noninvasive positive pressure ventilation?: a systematic review and meta-analysis. Chest. 2017;151(4):764-75. [PMID: 28089816] doi: 10.1016/j.chest.2017.01.004
72. Ou X, Hua Y, Liu J, et al**.** Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. CMAJ. 2017;189(7):E260-E7. [PMID: 28246239] doi: 10.1503/cmaj.160570
73. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019;45(5):563-72. [PMID: 30888444] doi: 10.1007/s00134-019-05590-5
74. Tinelli V, Cabrini L, Fominskiy E, et al. High flow nasal cannula oxygen vs. conventional oxygen therapy and noninvasive ventilation in emergency department patients: a systematic review and meta-analysis. J Emerg Med. 2019;57(3):322-8. [PMID: 31421952] doi: 10.1016/j.jemermed.2019.06.033
75. Xu Z, Li Y, Zhou J, et al. High-flow nasal cannula in adults with acute respiratory failure and after extubation: a systematic review and meta-analysis. Respir Res. 2018;19(1):202. [PMID: 30326893] doi: 10.1186/s12931-018-0908-7

76. Zhu Y, Yin H, Zhang R, et al**.** High-flow nasal cannula oxygen therapy versus conventional oxygen therapy in patients after planned extubation: a systematic review and meta-analysis. Crit Care. 2019;23(1):180. [PMID: 31101127] doi: 10.1186/s13054-019-2465-y
77. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50:1602426. [PMID: 28860265] doi: 10.1183/13993003.02426-2016
78. Mehta AB, Douglas IS, Walkey AJ. Evidence-based utilization of noninvasive ventilation and patient outcomes. Ann Am Thorac Soc. 2017;14(11):1667-1673. [PMID**:** 28541747] doi: 10.1513/AnnalsATS.201703-208OC
79. Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: a population-based study. Ann Am Thorac Soc. 2013;10(1):10-17. [PMID: 23509327[doi: 10.1513/AnnalsATS.201206-034OC
80. Kulkarni VT, Kim N, Dai Y, et al. Hospital variation in noninvasive positive pressure ventilation for acute decompensated heart failure. Circ Heart Fail. 2014;7(3):427-433. [PMID: 24633829] doi: 10.1161/CIRCHEARTFAILURE.113.000698

Box. Comparison of key characteristics of conventional oxygen therapy (COT), noninvasive ventilation (NIV), and high flow nasal oxygen (HFNO)

	Conventional Oxygen Therapy	Noninvasive Ventilation	High Flow Nasal Oxygen
Interface	Multiple (nasal cannula, reservoir cannula, OxyMask, non- or partial rebreathing mask, Venturi mask, simple mask)	Tightly fitted mask (most common), nasal pillows, helmet*	Flexible silicone nasal cannula (most common), can be adapted to face mask, tracheostomy
Flow Rate	Up to 15 LPM of oxygen	Up to 120 LPM mixed air and oxygen	20 to 60 LPM mixed air and oxygen
FiO_2	FiO_2 varies by interface, flow rate of patient inhalation; maximum approximately 60%	Set FiO_2 up to 100%	Set FiO_2 up to 100%
Heat/Humidification	Rare	Yes	Yes
Positive Pressure	No	Yes	Likely†
Ventilatory Support	No	Yes‡	Yes‡

FiO_2: fractional inspired concentration of O_2, LPM: liters per minute
*rarely used in the United States
† Likely delivers some positive end-expiratory pressure as a result of high flow rate
‡ NIV in bilevel modes delivers ventilatory support similar to invasive ventilation. HFOT likely provides some ventilatory support through turbulent gas mixing, generation of positive end-expiratory pressure.

744
745

Table 1. Certainty of Evidence

1a. HFNO vs NIV

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	NIV			
Initial management of acute respiratory failure population trials						
Intubation: 420 (2 RCTs) [32,34]	RR 0.71 (0.53 to 0.95)	**20.1%** (14.9 to 25.8)	30.7% (24.6 to 37.2)	-9.4% (-15.2 to -1.6)	Low†‡	HFNO may reduce intubations by a moderate amount
All-cause Mortality: 216 (1 RCT) [34]	RR 0.44 (0.24 to 0.79)	**12.3%** (6.6 to 19.3)	28.2% (20.1 to 37.0)	-15.8% (-21.4 to -5.9)	Low‡	HFNO may reduce all-cause mortality by a large amount
Hospital-acquired Pneumonia: 216 (1 RCT) [34]	RR 0.46 (0.15 to 1.45)	**3.8%** (0.8 to 8.4)	8.2% (3.7 to 14.1)	-4.4% (-7.0 to 3.7)	Low§	HFNO may reduce hospital-acquired pneumonia by a moderate amount.
ICU Admissions (yes/no): 204 (1 RCT) [32]	RR 0.98 (0.73 to 1.32)	**46.2%** (36.6 to 55.8)	47.0% (37.3 to 56.9)	-0.9% (-12.2 to 15.0)	Insufficient†‡**	It is uncertain if HFNO reduces ICU admissions.
Length of stay, ICU: 420 (2 RCTs) [32,34]		**Mean (days) 7.3** (3.3 to 11.2)	Mean (days) 8.3 (3.9 to 12.3)	MD -0.64 days (-1.67 to 0.39)	Insufficient†‡**	It is uncertain if HFNO reduces ICU admissions.
Length of stay, hospital: 372 (2 RCTs) [29,32]		**Mean (days) 11.8** (6.8 to 18.0)	Mean (days) 11.6 (6.0 to 18.3)	MD 0.45 days (-0.69 to 1.59)	Low†‡	HFNO may make little or no difference in hospital length of stay.
Patient comfort, including related to dryness, based on VAS or % improved: 644 (7 RCTs) [29,32,34,35,49,50,54]	One trial (n=216) [34] reported HFNO improved comfort (SMD -0.51 [-0.78 to -0.24]) based on VAS and 1 (n=168) [29] reported greater comfort with HFNO (88.2% vs. 67.9%; ARD 21.4% [9.4 to 33.4]). One trial (n=204) [32] reported little to no difference in patient comfort based on VAS (medians 2 vs. 2 on a 5-point scale, 5=most discomfort). Among 4 crossover trials (n=56), 3 reported little to no difference [35, 50, 54] and 1 reported improvement with HFNO in short-term patient comfort based on VAS [49].				Low†††‡	HFNO may improve patient comfort.

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	NIV			
Dyspnea, based on VAS or Borg scale scores or % improved: 464 (7 RCTs) [32,34,35,47-50,54]	One trial (n=177) [34] reported greater improvement in dyspnea short-term in patients allocated to HFNO compared with NIV (75.6% vs. 58.2%; ARD 17.3% [3.7 to 30.9]). One trial (n=180) [32] reported little to no difference in longer-term (SMD 0.21 [-0.12 to 0.54] dyspnea based on Borg. 1 trial (n=51) [48] reported little to no difference in short-term dyspnea based on 10-point VAS scale (Mean change from baseline -0.1 vs. -0.9). Among 4 crossover trials (n=56), 2 reported little to no difference based on VAS,[50, 54] 1 reported worsening based on VAS, [35] and 1 reported improvement in short-term dyspnea based on Borg with HFNO. [49]				Low†††‡‡	HFNO may make little or no difference in dyspnea.
Skin breakdown (facial pressure sore or nasal ulceration):	**Not reported**					
Post-extubation acute respiratory failure population trials						
Reintubation: 1476 (3 RCTs) [37,39,53]	RR1.13 (0.90 to 1.43)	**16.6** (13.9 to 19.4)	14.7 (12.2 to 17.4)	2.0% (-1.5 to 6.6)	Low§	HFNO may increase reintubations by a small amount
All-cause Mortality: 1476 (3 RCTs) [37,39,53]	RR 1.15 (0.88 to 1.51)	**11.4%** (9.1 to 13.9)	9.8% (7.7 to 12.2)	1.7% (-1.3 to 5.7)	Low§	HFNO may increase all-cause mortality by a small amount
Hospital-acquired Pneumonia: 1434 (2 RCTs) [37,53]	RR 0.90 (0.70 to 1.16)	**12.3%** (9.9 to 14.8)	13.6% (11.2 to 16.1)	-1.5% (-4.4 to 2.3)	Low§	HFNO may make little to no difference in hospital-acquired pneumonia
ICU Admissions (yes/no)	**Not applicable**					
Length of stay, ICU: 1476 (3 RCTs) [37,39,53]	Pooled mean differences from 2 trials [35, 37] (n=646) found HFNO made little or no difference in ICU length of stay (mean days NA; MD -0.98 days [-1.99 to 0.03]. One trial (n=830) reported little to no difference in ICU length of stay (medians 6 vs. 6 days)				Low§	HFNO may make little to no difference in ICU length of stay

Outcome: Population № of participants (studies) References	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	NIV			
Length of stay, hospital: 1434 (2 RCTs) [37,53]	One trial (n=604) [35] reported a lower hospital length of stay with HFNO (medians 23 vs. 26 days; MD -3 days [-6.8 to -0.8]). One trial (n=830) [51] reported little to no difference in hospital length of stay (medians 13 vs. 14 days).				Insufficient§††	It is uncertain if HFNO reduces hospital length of stay.
Patient comfort, based on % improved or VAS: 872 (2 RCTs) [39,53]	One large trial (n=748) [51] reported little to no difference in the percentage of participants reporting good comfort (51.3% vs. 52.9%; ARD -1.6 [-8.7 to 5.6]). One small trial (n=42) [37] found HFNO may improve comfort (SMD -0.75 [-1.38 to -0.12]) based on VAS.				Low†††‡	HFNO may make little or no difference in patient comfort.
Dyspnea, based on % improved: 752 (1 RCT) [53]	RR 0.96 (0.86 to 1.08)	**58%** (53 to 63)	60% (55 to 65)	-2.4% (-8.5 to 4.8)	Low§	HFNO may make little or no difference dyspnea.
Skin breakdown (facial pressure sore or nasal ulceration): 1454 (3 RCTs) [37,39,53]	Peto OR 0.15 (0.02 to 1.13)	**0.7%** (0.09 to 1.7)	22.0% (19.0 to 25.1)	-20.0% (-23.7 to 2.3)	Low‡††	HFNO may reduce skin breakdowns by a large amount

ARD=absolute risk difference; CI=confidence interval; HFNO=high flow nasal oxygen; ICU=intensive care unit; MD=mean difference; NA=not available; NIV=noninvasive ventilation; OR=odds ratio; RCT=randomized controlled trial; RR=risk ratio; SMD=standardized mean difference; VAS=visual analog scale

GRADES of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Thresholds for determining magnitude by outcome
Intubation: Little or no effect: <2%; Small effect: 2-3.9%; Moderate effect: 4-9.9%; Large effect ≥10%
All-cause mortality: Little or no effect: <1%; Small effect: 1-1.9%; Moderate effect: 2-4.9%; Large effect: ≥5%
Pneumonia: Little or no effect: <2%; Small effect: 2-3.9%; Moderate effect: 4-9.9%; Large effect: ≥10%
Length of Stay: Little or no effect: <1 day; Small effect: ≥1 day; Moderate effect: NA; Large effect: ≥3 day
Skin breakdown: Little or no effect: <2%; Small effect: 2-3.9%; Moderate effect: 4-9.9%; Large effect: ≥10%

753 * Absolute risk differences were calculated in GRADEpro (gradepro.org) and are based on the relative magnitude of an effect and baseline risk (control event rate).
754 Absolute event rates were calculated with Freeman-Tukey double arcsine variance-stabilizing transformation

Explanations

† Downgraded for study limitations, particularly moderate attrition and/or unclear allocation concealment

‡ Downgraded two levels based on results derived from one trial (n=216) and imprecision, difficult to determine if there is a definitive benefit based on only a single study.

§ Downgraded two levels for imprecision (very wide CIs) and/or difficult to interpret based on the variability in the reporting of the effects

****** Downgraded for indirectness, ICU stay possibly protocol driven

†† Downgraded due to inconsistency

‡‡ Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effects

1b. Certainty of Evidence: HFNO vs COT

Outcome: Population № of participants (studies) references	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	COT			
Initial management of acute respiratory failure population trials						
Intubation: 1694 (8 RCTs) (27,28,34,40,41,43,46,52)	Peto OR 0.98 (0.34 to 2.82)	**8.1%** (0.2 to 23.5)	7.6% (0.0 to 25.4)	-0.4% (-15.6 to 23.9)	Low†‡	HFNO may make little or no difference in intubation
All-cause Mortality: 1407 (4 RCTs) (27,34,40,43)	RR 0.97 (0.82 to 1.14)	**24.5%** (21.4 to 27.7)	25.1% (21.9 to 28.5)	-0.8% (-4.9 to 3.8)	Low†‡	HFNO may make little or no difference in all-cause mortality
Hospital-acquired Pneumonia: 200 (1 RCT) (34)	RR 0.44 (0.14 to 1.43)	**3.8%** (0.8 to 8.4)	8.5% (3.6 to 15.1)	-4.8% (-7.3 to 3.7)	Low§	HFNO may result in a moderate reduction in hospital-acquired pneumonia
ICU Admissions (yes/no): 403 (2 RCTs) (28,40)	RR 1.11 (0.58 to 2.12)	**7.1%** (3.9 to 11.0)	6.7% (3.4 to 10.8)	0.9% (-3.3 to 8.8)	Insufficient†‡**	It is uncertain if HFNO reduces ICU admissions.
Length of stay, ICU: 1036 (3 RCTs) (27,34,44)	Two trials (n=976) (27,34) found little or no difference in ICU length of stay (mean days NA; MD 0.41 days [-1.08 to 1.90]). 1 trial (n=60) reported little to no difference in ICU length (P=.20, no data reported) (44).				Insufficient†‡**	It is uncertain if HFNO reduces ICU length of stay

Outcome: Population № of participants (studies) references	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	COT			
Length of stay, hospital: 1267 (4 RCTs) [27,40,43,44]	Four trials reported little to no difference in hospital length of stay based on medians (medians ranged from 1 to 24 vs. 1 to 27 days) [27,40,43] and/or p-values [44],				Low§	HFNO may make little or no difference in hospital length of stay
Patient comfort, including comfort related to dryness, based on VAS or % improved: 1611 (12 RCTs total, some trials reported ≥1 measure of comfort) [27,28,31,34,40,41,43,45,46,49,52,54]	Pooled results from 4 trials (n=415)[34,43 46,52] found HFNO improved comfort (SMD -0.61 [-0.81 to -0.41]) based on VAS. Results pertaining to patient comfort based on median or unclear [27] scale scores varied: One trial (n=100) [28] reported higher comfort based on VAS (4 vs. 3 on a 5-point scale, 5=most comfort, P=.04) while 2 trials (n=876) [27,41] reported little to no difference in patient comfort (7.9 vs. 6.8 on a 10-point scale, 10=perfect)[27] and medians 3 vs. 3 on a 10-point scale (10=worst)[41]. One trial (n=158) [40] reported a lower percentage of participants with discomfort related to dryness (29.8% vs. 45.3%; ARD -15.5% [-30.8 to -0.2]). Four small crossover studies (n=62) [31,45,49,54] reported little to no difference in short-term patient comfort.				Low†††‡	HFNO may improve patient comfort.
Dyspnea, based on VAS and Borg scale scores or % improved: 1799 (13 RCTs) [27,28,31,34,40,41,43,44-47,49,52 54]	Pooled results from 4 trials (n=258) [43,46,47,52] found HFNO improved dyspnea (SMD -0.56 [-1.35 to 0.24]) based on VAS and Borg scales. 2 trials (n=876) [27,41] reported little to no difference in short-term dyspnea based on median scale scores (medians 2.3 to3 vs. 2.6 to3 on a 10-point scale, 10=most severe). Three trials (n=417) [28,34,40] reported a greater percentage of participants with improvement in dyspnea or improved breathing (78.0% vs. 55.8%; ARD 22.2% [13.3 to 31.1]). Four small crossover studies (n=62) [31,45,49,54] reported little to no difference in short-term dyspnea.				Low†††‡	HFNO may improve dyspnea.
Skin breakdown (facial pressure sore or nasal ulceration): 431 (2 RCTs) [40,43]	Both trials reported no incidences of skin breakdown were observed with HFNO. For COT, one trial reported no incidences [40] and the other trial did not report this outcome. [43]				Insufficient§§	It is uncertain if HFNO reduces skin breakdown.
Post-extubation acute respiratory failure population trials						

Outcome: Population № of participants (studies) references	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	COT			
Reintubation: 1065 (7 RCTs) (30,38,42,51,55, 56,58)	Peto OR 0.60 (0.23 to 1.61)	**4.7%** (0.9 to 10.7)	8.3% (2.6 to 16.4)	-3.9% (-7.8 to 5.3)	Low§	HFNO may reduce reintubations by a small amount
All-cause Mortality: 782 (4 RCTs) (38,42,55, 56)	RR 1.01 (0.60 to 1.72)	**4.6%** (2.6 to 7.1)	5.0% (2.9 to 7.6)	-0.1% (-2.5 to 4.5)	Low§	HFNO may make little or no difference in all-cause mortality
Hospital-acquired Pneumonia: 527 (1 RCT) (38)	RR 0.50 (0.13 to 1.97)	**1.1%** (0.1 to 2.9)	2.3% (0.8 to 4.5)	-1.1% (-2.0 to 2.2)	Low§	HFNO may make little or no difference in hospital-acquired pneumonia
ICU Admissions (yes/no)	**Not applicable**					
Length of stay, ICU: 1006 (6 RCTs) (30,38,42,55, 56,58)	Pooled results from 5 trials (n=479) (30,42,55, 56,58) found HFNO makes little or no difference in ICU length of stay (approximately 6 days in each group; MD 0.19 [-0.19 to 0.57]. One trial not pooled (n=527) (38) reported little to no difference in ICU length of stay (medians 6 vs. 6 days).				Moderate‡	HFNO probably makes little or no difference in ICU length of stay
Length of stay, hospital: 587 (2 RCTs) (38, 56)		**Study 1[38]** Median 11 (IQR 6 to 15) **Study 2[56]** **Mean 37.7**	Study 1 Median 12 (IQR 6 to 16) Study 2 Mean 25.7	Study 1 MD 4 days (-28 to 32) Study 2 MD 12 days (0.15 to 23.85)	Insufficient§§	It is uncertain if HFNO improves hospital length of stay.

Outcome: Population № of participants (studies) references	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	COT			
Patient comfort, including comfort related to dryness and interface, based on VAS or % improved: 324 (4 RCTs total, some trials reported ≥1 measure of comfort) (42,51,55,58)	One trial (n=105) (42) found HFNO improved comfort (SMD -0.70 [-1.10 to -0.31]) based on VAS. One trial (n=60) (51) reported higher comfort or less dryness with HFNO based on median scale scores. One trial (n=90) (55) reported a lower percentage of participants with discomfort related to dryness with HFNO (38.3% vs. 69.8%; ARD -31.5% [-51.0 to -11.9]). Two trials (n=165) (42,51) reported lower discomfort related to interface with HFNO versus COT (Trial 1 SMD -0.89 [-1.29 to -0.49])(42) and Trial 2 medians 3 vs. 7 on a 10-point scale, 10=maximal discomfort, P<.001)(51). One trial (n=69) (58) reported little to no difference in any measure of discomfort on a 10-point scale (nasal, oral, or pharynx) based on medians.				Low§	HFNO may improve patient comfort.
Dyspnea, based Borg scale score: 155 (1 RCT) (30)	One trial reported little to no difference in short-term dyspnea (medians 1 vs. 0 on a 10-point scale, 10=maximal dyspnea).				Insufficient§§	It is uncertain if HFNO improves dyspnea.
Skin breakdown (facial pressure sore or nasal ulceration): 527 (1 RCT) (38)	One trial reported no incidences of skin breakdown were observed with HFNO but this outcome was not reported for the COT arm.				Insufficient§§	It is uncertain if HFNO reduces skin breakdown.

ARD=absolute risk difference; CI=confidence interval; COT=conventional oxygen therapy; HFNO=high flow nasal oxygen; ICU=intensive care unit; IQR=interquartile range; MD=mean difference; NA=not available; OR=odds ratio; RCT=randomized controlled trial; RR=risk ratio; SMD=standardized mean difference; VAS=visual analog scale

GRADES of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Insufficient certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Outcome: Population № of participants (studies) references	Relative effect or Standardized mean difference (95% CI)	Absolute event rates (95% CI)		Absolute risk difference (95% CI)*	Certainty	What happens
		HFNO	COT			

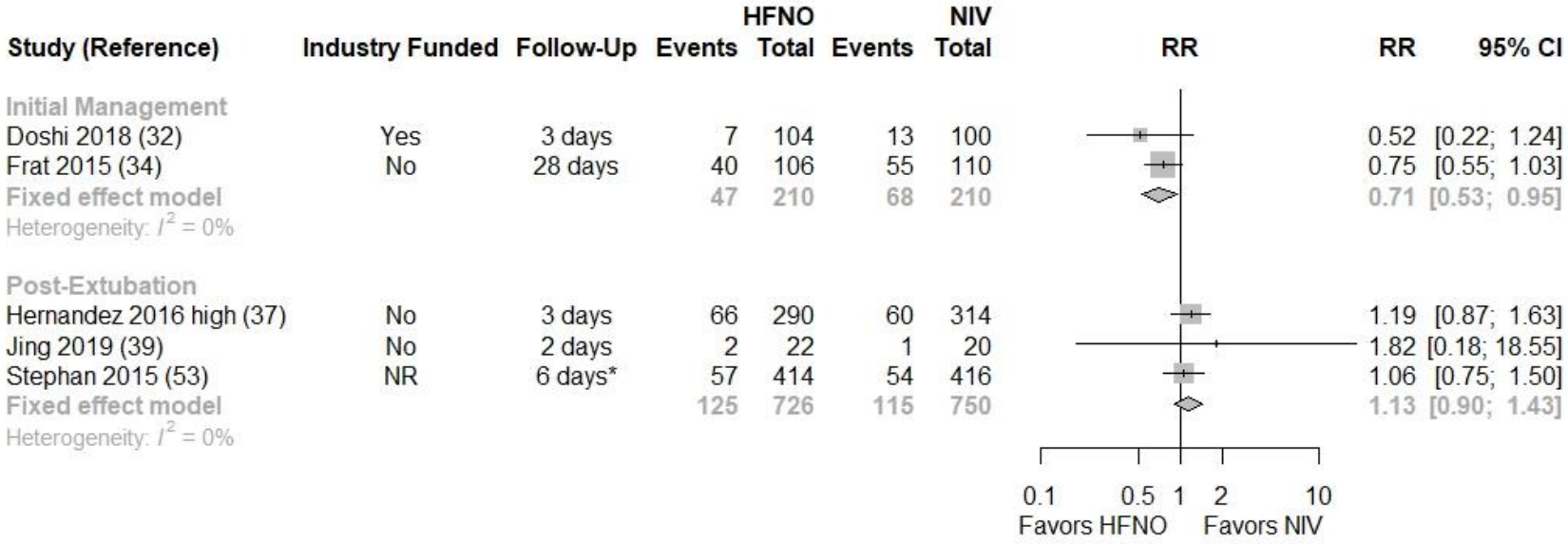
Thresholds for determining magnitude by outcome

Intubation: Little or no effect: <2%; Small effect: 2-3.9%; Moderate effect: 4-9.9%; Large effect ≥10%
All-cause mortality: Little or no effect: <1%; Small effect: 1-1.9%; Moderate effect: 2-4.9%; Large effect: ≥5%
Pneumonia: Little or no effect: <2%; Small effect: 2-3.9%; Moderate effect: 4-9.9%; Large effect: ≥10%
Length of Stay: Little or no effect: <1 day; Small effect: ≥1 day; Moderate effect: NA; Large effect: ≥3 day
Skin breakdown: Little or no effect: <2%; Small effect: 2-3.9%; Moderate effect: 4-9.9%; Large effect: ≥10%

* Absolute risk differences were calculated in GRADEpro (gradepro.org) and are based on the relative magnitude of an effect and baseline risk (control event rate).
Absolute event rates were calculated with Freeman-Tukey double arcsine variance-stabilizing transformation
Explanations
† Downgraded for imprecision (wide CIs)
‡ Downgraded for study limitations
§ Downgraded two levels for large imprecision (very wide CIs) and/or sparse data and/or difficult to interpret based on the variability in the reporting of the effects
** Downgraded for indirectness, ICU stay possibly protocol driven
†† Downgraded due to inconsistency
‡‡ Downgraded due to imprecision, difficult to interpret based on the variability in the reporting of the effect
§§ Downgraded to insufficient based on the enormity of the imprecision or difficult to interpret based on the variability in the reporting of the effects

Figure 2. Intubation and Mortality Plots for HFNO vs NIV

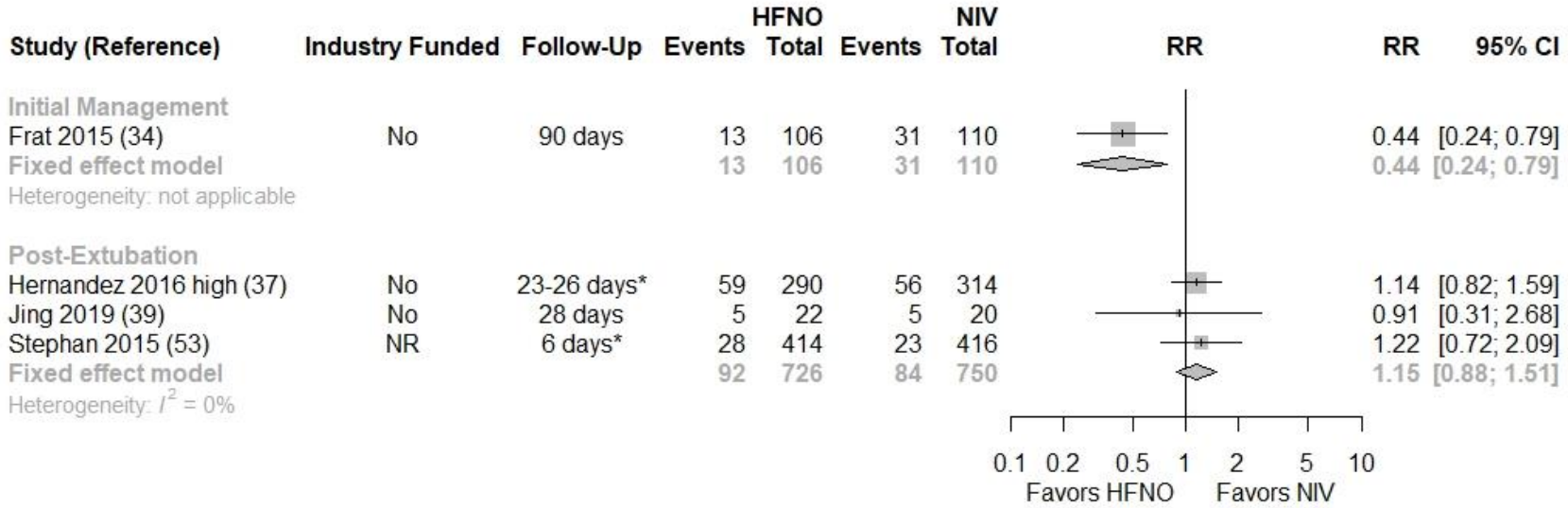
HFNO vs NIV: Intubation



CI=confidence interval; HFNO=high-flow nasal oxygen; ICU=intensive care unit; NIV=non-invasive ventilation; RR=risk ratio

*This is an estimated follow-up time based on the reported median ICU length of stay.

HFNO vs NIV: Mortality

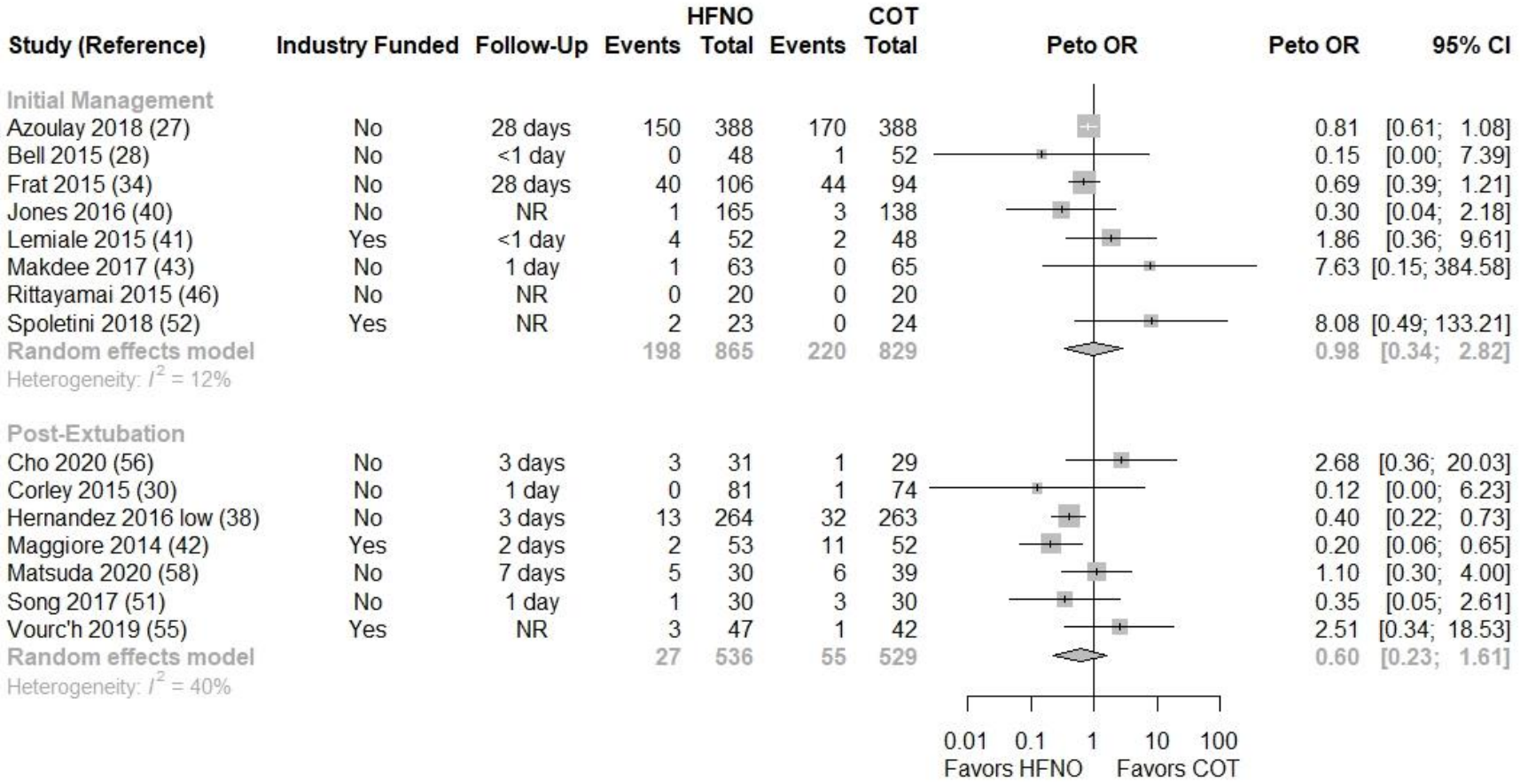


CI=confidence interval; HFNO=high-flow nasal oxygen; ICU=intensive care unit; NIV=non-invasive ventilation; RR=risk ratio

*These are estimated follow-up times based on the reported median hospital or ICU length of stay.

Figure 3. Intubation and Mortality Plots for HFNO vs COT

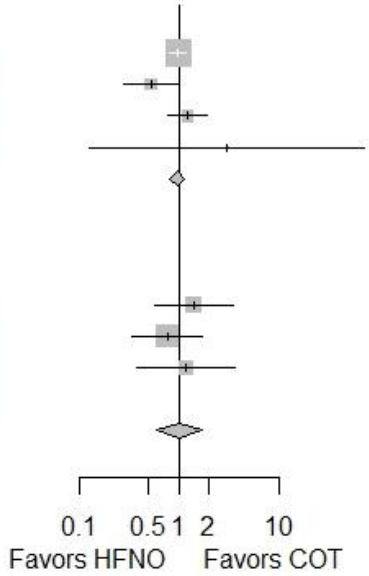
HFNO vs COT: Intubation



CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; OR=odds ratio; NR=not reported

HFNO vs COT: Mortality

Study (Reference)	Industry Funded	Follow-Up	HFNO Events	HFNO Total	COT Events	COT Total	RR	RR	95% CI
Initial Management									
Azoulay 2018 (27)	No	28 days	138	388	140	388		0.99	[0.82; 1.19]
Frat 2015 (34)	No	90 days	13	106	22	94		0.52	[0.28; 0.98]
Jones 2016 (40)	No	90 days	35	165	24	138		1.22	[0.76; 1.95]
Makdee 2017 (43)	No	7 days	1	63	0	65		3.03	[0.13; 71.85]
Fixed effect model			187	722	186	685		0.97	[0.82; 1.14]
Heterogeneity: I^2 = 42%									
Post-Extubation									
Cho 2020 (56)	No	32 days*	9	31	6	29		1.40	[0.57; 3.45]
Hernandez 2016 low (38)	No	11-12 days*	10	264	13	263		0.77	[0.34; 1.72]
Maggiore 2014 (42)	Yes	11 days*	6	53	5	52		1.18	[0.38; 3.62]
Vourc'h 2019 (55)	Yes	3 days*	0	47	0	43			
Fixed effect model			25	395	24	387		1.01	[0.60; 1.72]
Heterogeneity: I^2 = 0%									



CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; ICU=intensive care unit; RR=risk ratio

*These are estimated follow-up times based on the reported mean/median hospital or ICU length of stay.

Appendices

Appendix Table 1. Summary of Protocol

Key Questions:
1) What is the comparative effectiveness of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen for hospitalized patients?

1a) Does comparative effectiveness of high flow nasal oxygen vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

2) What are the harms of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen for hospitalized patients?

2a) Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

PICOTS	
Population:	Hospitalized adult patients with acute respiratory failure (ARF). ARF defined as SpO_2 <90%, PaO_2:FiO_2 ratio ≤300, PaO_2 ≤60 mmHg, or $PaCO_2$ ≥45 mmHg
Intervention:	High flow nasal oxygen (humidified, ≥20 L/min)
Comparators:	Noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen (e.g., simple, Venturi, or nonrebreather oxygen masks)
Outcomes:	Patient-Centered Outcomes *Critical Outcomes:* all-cause mortality (in-hospital and up to 90 days), hospital-acquired pneumonia, intubation/reintubation (days of intubation), ICU admissions/transfers (ICU days), patient comfort, hospital length of stay *Important Outcomes and Harms:* hospital readmissions (30 day) (e.g., all-cause, pneumonia), functional independence at discharge (e.g., scale scores, measures of independence/activities of daily living), discharge disposition, skin breakdown or pressure ulcers, gastric dysfunction, compromised nutrition (enteral or parenteral nutrition), delirium, barotrauma Intermediate Outcomes Respiratory rate, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, $PaCO_2$, treatment escalation, device intolerance Cost/resource utilization
Timing:	Hospitalization for ARF or development of ARF while hospitalized; immediate post-extubation; post-surgery. Exclude pre-intubation/pre-oxygenation and oxygenation support during intubation
Setting:	Hospital (including ICU, step-down units, hospital wards), emergency department
Study Design:	Randomized controlled trials (RCT), including crossover RCTs and cluster RCTs
Subgroups:	Patient characteristics: age, race, gender Disease/diagnosis (e.g. COPD, cardiogenic pulmonary edema, immunosuppressed, post-extubation, post-surgery; hypoxic vs. hypercapnic respiratory failure) Protocol/device settings (e.g., flow rate ≤30 vs. >30 L/min)

BiPAP=Bilevel Positive Airway Pressure; COPD=chronic obstructive pulmonary disease; CPAP=continuous positive airway pressure; ICU=intensive care unit

Databases Searched: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, and ClinicalTrials.gov

Appendix Table 2. Search Strategies

Ovid MEDLINE

1	(high flow nasal adj2 (cannula$ or oxygen$ or therap$ or insufflation$)).mp.
2	high flow therapy.mp
3	nasal high flow.mp.
4	high flow oxygen.mp.
5	(humidified high flow or humidified oxygen).mp.
6	HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
7	(Vapotherm or Optiflow or "Comfort Flo").ti,ab.
8	or/1-7
9	remove duplicates from 8
10	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
11	(random$ adj (enroll$ or assign$ or allocat$)).ti,ab.
12	((randomi#ed or controlled or clinical) adj2 trial$).ti,ab.
13	or/10-12
14	9 and 13
15	(meta-analy$ or metaanaly$ or meta analy$).ti,ab.
16	exp Meta-Analysis/
17	(systematic adj2 (review$ or overview$)).ti,ab.
18	(rapid review or meta synthesis or metasynthesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
19	or/15-18
20	9 and 19
21	limit 14 to english language
22	limit 21 to yr="1995 -Current"
23	limit 22 to "all child (0 to 18 years)"
24	limit 23 to "all adult (19 plus years)"
25	22 not 23
26	24 or 25
27	limit 20 to english language
28	limit 27 to yr="2015 -Current"
29	limit 28 to "all child (0 to 18 years)"
30	limit 29 to "all adult (19 plus years)"
31	28 not 29
32	30 or 31

Embase

1	(high flow nasal adj2 (cannula$ or oxygen$ or therap$ or insufflation$)).mp.
2	high flow therapy.mp.
3	nasal high flow.mp.

4	high flow oxygen.mp.
5	(humidified high flow or humidified oxygen).mp.
6	(HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
7	(Vapotherm or Optiflow or "Comfort Flo").ti,ab.
8	or/1-7
9	remove duplicates from 8
10	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
11	(random$ adj (enroll$ or assign$ or allocat$)).ti,ab.
12	((randomi#ed or controlled or clinical) adj2 trial$).ti,ab.
13	or/10-12
14	9 and 13
15	limit 14 to english language
16	limit 15 to yr="1995 -Current"
17	limit 16 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
18	limit 17 to (adult <18 to 64 years> or aged <65+ years>)
19	16 not 17
20	18 or 19
21	(neonat$ or pre-term or preterm or infant or pediatric).ti,ab.
22	20 not 21
23	limit 22 to (conference abstract or conference paper or "conference review" or editorial)
24	22 not 23
25	Limit 24 to (meta analysis or “systematic review”)

Cochrane Library

1	"high flow nasal" NEXT (cannula* OR oxygen* OR therap* OR insufflation*)
2	"high flow therapy" OR "nasal high flow" OR "high flow oxygen" OR "humidified high flow" OR "humidified oxygen"
3	HFNC OR HHFNC OR HFNT OR NHF OR HFNO OR HFOT OR HFNOT
4	Vapotherm OR Optiflow OR "Comfort Flo"
5	{OR #1-#4}
6	("randomized" OR "randomised" OR "controlled" OR "clinical") NEAR/2 trial
7	#5 AND #6 with Cochrane Library publication date Between Jan 1995 and May 2019
8	neonat* OR pre-term OR preterm OR infant OR pediatric OR paediatric OR newborn OR premature OR child* OR adolescen*
9	#7 NOT #8

CINAHL

1	high flow nasal cannula OR high flow nasal oxygen OR high flow nasal therapy OR high flow nasal insufflation

2 high flow therapy OR high flow oxygen OR nasal high flow

3 humidified high flow OR humidified oxygen

4 AB HFNC OR AB HHFNC OR AB HFNT OR AB NHF OR AB HFNO OR AB HFOT OR AB HFNOT

5 S1 OR S2 OR S3 OR S4

6 PT randomized controlled trial or controlled clinical trial

7 AB randomized

8 random* enroll* OR random* assign* OR random* allocat*

9 S6 OR S7 OR S8

10 S5 AND S9; Limiters: Published Date: 19950101-20191231; narrow by language; Narrow by subject age: all adult

Appendix Table 3. Overview of Included Trials and Papers*

Study Characteristic	Comparator				TOTAL
	COT vs. HFNO		NIV vs. HFNO		
	Initial Management	Post-extubation	Initial Management	Post-extubation	
Setting					
Emergency Department	5	0	1 (3)	0	**6 (8)**
ICU	7 (8)	7	4 (5)	3	**18 (19)†**
Hospital/Ward/Stepdown	2	0	3	0	**5**
ARF type					
Hypoxic	11 (12)	5	5 (6)	2	**20 (21)†**
Hypoxic, nonhypercapnic	4	3	3	1	**10†**
Hypercapnic	1	0	0	1	**2**
Hypoxic and/or hypercapnic	2	2	3 (5)	0	**7 (9)**
Indication‡					
Bronchoscopy	0	0	1	0	**1**
Cardiogenic pulmonary edema	1	0	0 (1)	0	**1 (2)**
COPD	1	0	1 (2)	1	**3 (4)**
Cystic Fibrosis	0	0	1	0	**1**
Immunocompromised	2 (3)	0	0 (1)	0	**2 (3)†**
Multiple Diseases	9	5	7	1	**19†**
Obese	0	1	0	0	**1**
Palliative Care	1				
Post-extubation	NA	7	NA	3	**10**
Post-surgery	NA	2	NA	1	**3**
Medical	NA	5	NA	2	**7†**
Treatment Duration					
< 6 hours	11	0	5	0	**14†**
≥ 6 hours	3 (4)	7	3 (6)	3	**15 (18)†**
Crossover Studies	5	0	4	0	**7†**
TOTAL # studies (papers)	**14 (15)**	**7**	**8 (11)**	**3**	**29 (32)†**

* Papers counted in ( )

† 3 studies (4 papers) had both COT and NIV as comparators.

‡ Some studies had more than 1 indication per study

ARF=acute respiratory failure; COPD=chronic obstructive pulmonary disease; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; ICU=intensive care unit; NIV=noninvasive ventilation

Appendix Table 4. Additional Study Characteristics and Patient Demographics

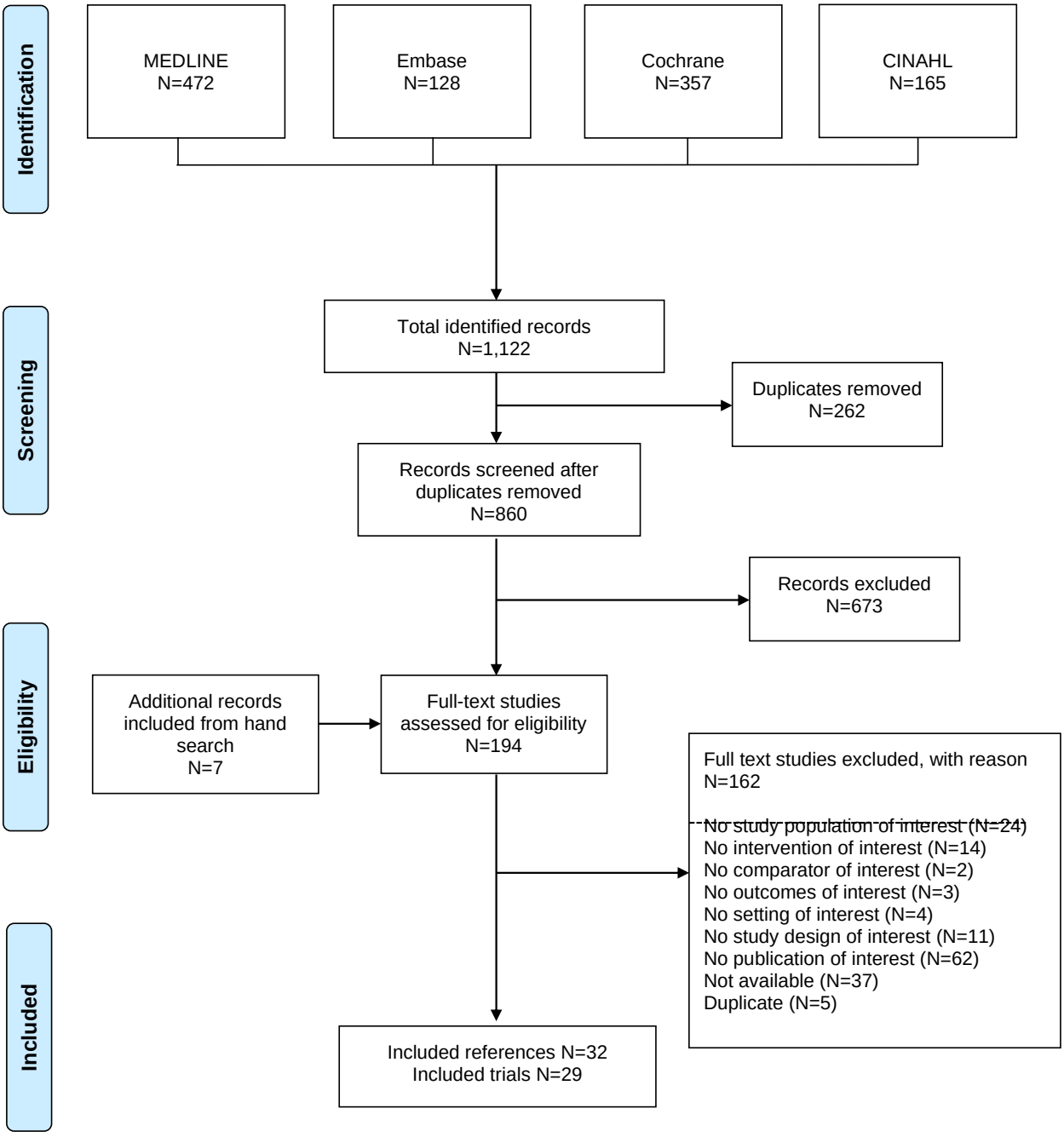
Study Characteristics	HFNO vs. COT		HFNO vs. NIV	
	Initial Management	Post-extubation	Initial Management	Post-extubation
Age (mean (range), # studies)	68 (60-74) 12 studies	60 (51-78) 7 studies	63 (30-67) 7 studies	64 (64-76) 3 studies
Gender (% male) (mean (range), # studies)	59 (35-83) 12 studies	66 (57-86) 7 studies	65 (47-83) 6 studies	65 (64-66) 2 studies
Race (%, # studies)	66% white; 79% European descent 2 studies	NR	61% white 1 study	NR
Comorbidities (%) (range, # studies)				
Chronic respiratory failure	10-31% 3 studies	NR	80% 1 study	NR
COPD	8-100% 4 studies	3-7% 3 studies	8-100% 2 studies	21-100% 2 studies
CHF	6-34% 6 studies	32% 1 study	6-8% 3 studies	NR
Comorbidity Index (score or range of scores, # studies)				
APACHE II	12-16.2 3 studies	7-23 5 studies	8-31 2 studies	10.5-11.1 2 studies
SAPS II	24.5-48.2 3 studies	26.5-43.5 2 studies	26-50.7 5 studies	28.9 1 study
Charlson Comorbidity Index	5 1 study	NR	NR	NR
Location (# trials)				
Europe	5	3	4	2
Australia/New Zealand	4	1	0	0
Southeast Asia	3	3	2	1
USA	1	0	1	0
Canada	1	0	1	0
Funding* (# trials)				
Industry	5	2	3	0
Received equipment, devices, and/or supplies from industry	8	1	3	0
Foundation	2	0	1	0
Government	3	3	1	1
University	1	3	0	0
Not reported	1	0	2	1
None	0	1	0	1
Sample Size (N) (# trials)				
≥500	1	1	0	2
100-500	5	2	3	0

<100	8	4	5	1
Risk of Bias (# trials)				
Low	9	3	2	2
Moderate	5	4	6	1
High	0	0	0	0
TOTAL # trials	**14**	**7**	**8**	**3**

*Some studies have multiple sources of funding

APACHE II=Acute Physiology and Chronic Health Evaluation II; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; NIV=noninvasive ventilation; NR=not reported; SAPS II= Simplified Acute Physiology Score

Appendix Figure 1. Literature Flow Diagram



Supplementary Material

Supplementary Table 1. Study Characteristics

Author, year **Country** **Funding** **Setting** **Special Population** **ARF Type** **Risk of Bias**	**Inclusion/Exclusion Criteria**	**Intervention** **Comparator** **Follow-up (primary outcome)**	**Demographics**
Azoulay, 2018 (27) France Funding: Government (industry provided supplies) Setting: ICU (32 hospitals – 24 university, 8 non-university) Special Population: Immunocompromised ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: ICU admission (recruited in ICU), age ≥18 years; AHRF with PaO_2 <60mmHg or SpO_2 <90% on room air, or tachypnea >30/min, or labored breathing, or respiratory distress; need for O_2 flow ≥6 l/min; known immunosuppression (defined by long-term or high-dose immunosuppressant drugs, solid organ transplantation, solid tumor requiring chemotherapy in last 5 years, hematologic malignancy at any time, or primary immune deficiency); written informed consent (patient or proxy) Exclusion: AIDS; imminent death; refused to participate (patient); anatomical factors precluding use of nasal cannula; hypercapnia indicating NIV ($PaCO_2$ ≥50 mmHg); isolated cardiogenic pulmonary edema indicating NIV, pregnancy or breastfeeding, absence of coverage by French health care insurance system; surgery within past 6 days	Intervention: HFOT (device not specified; Fisher & Paykel, France); initiated at 50 L/min and 100% FiO_2 with subsequent increase in flow rate to achieve SpO_2 ≥95%; maximum of 60 L/min; flow rate decreased if patient experienced discomfort (n=389 randomized, 388 analyzed) Comparator: COT (any device or combination of devices); flow set to achieve SpO_2 of ≥95%; HFOT used if conventional oxygen failed ("do not intubate" status) (n=389 randomized, 388 analyzed) Note: NIV used if patients were hypercapnic or with pulmonary edema. Treatment continued throughout ICU stay; patients received best standard of care according to local management protocols. Follow-up: 28 days (all-cause mortality)	N=776 Age (median): HFOT: 64 COT: 63 Race/ethnicity: NR Gender (% male): 66.6 Comorbidities (%): Chronic Respiratory Failure: 31.2 COPD: NR (included above) Congestive Heart Failure: 5.4 Comorbidity Index (Charlson): 5.0 Baseline characteristics: SpO_2: NR Respiratory Rate (breaths/min, median): HFOT: 33 COT: 32 PaO_2/FiO_2 ratio (median): HFOT: 136 COT: 128 pH: NR PaO_2: NR $PaCO_2$: NR

Bell, 2015 (28) Australia Funding: None (10 HFNO machines loaned by industry) Setting: ED (2 sites) Special Population: No ARF Type: Hypoxic Risk of Bias: Low	Inclusion: Adult patients (age >16) with shortness of breath who had both a respiratory rate >25 breaths per min and oxygen saturations <93%, as measured by treating ED nurse, for whom non-invasive or invasive ventilation was not felt to be immediately indicated Exclusion: Patients requiring immediate non-invasive ventilation or intubation; trauma patients; suspected pneumothorax; inability to provider consent (altered mental state, dementia, developmentally delayed, intoxicated, mental health/delirium)	Intervention: HFNO initiated at 50 L/min and FiO_2 30% (AIRVO$_2$, Optiflow) (n=48 randomized and analyzed) Comparator: COT includes standard nasal prongs or face mask (Venturi system or nonrebreather) (n=52 randomized and analyzed) Follow-up: 2 hours (reduction in respiratory rate by 20% or an escalation in ventilation requirements (HFNO, NIV, or intubation))	N=100 Age (mean): 74 Race/ethnicity: NR Gender (% male): 44 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 75 Congestive Heart Failure: 33 Comorbidity Index: NR Baseline characteristics (mean): SpO_2: 88.5 Respiratory Rate: 33 PaO_2/FiO_2 ratio: NR pH: 7.39 PaO_2: NR $PaCO_2$: NR
Cho, 2020 (56) Korea Funding: University Setting: ICU (single site) Special Population: Post-extubation; mechanically ventilated at high risk for reintubation following planned extubation ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: Adults requiring mechanical ventilation for >12 hours; suitable for extubation; high risk of reintubation based on age >65 yrs, APACHE II >12 on extubation day, BMI >30, poor expectoration or airway patency problem, difficult or prolonged weaning, or multiple comorbidities Exclusion: Patient or family member declined participation	Intervention: HFNC (AIRVO, Fisher & Paykel, New Zealand) immediately after extubation; FiO_2 maintained alongside previous setting of mechanical ventilation and adjusted so SpO_2 >90%; range of flow 30-60 L/min; maintained for 72 hours (switch to COT allowed after 72 hours) (n=31) Comparator: COT using nasal prongs or non-rebreather facemask; flow adjusted to target SpO_2 >90%; crossover to HFNC not allowed (n=29) Follow-up:72 hours for reintubation	N=60 Age (mean): 78 Race/ethnicity: NR Gender (% male): 63 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index: APACHE II HFNC: 13.3; COT: 10.7, P=.01 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: 19.9 PaO_2/FiO_2 ratio: 283.9 pH: 7.43 PaO_2: NR $PaCO_2$: 36.9

Cong, 2019 (29) China Funding: NR Setting: Hospital (single site) Special Population: COPD ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Moderate	Inclusion: Diagnosed with acute exacerbation of COPD according to national guidelines; admitted to ICU due to severe illness and were given ventilation therapy Exclusion: Unstable hemodynamics; unable to complete therapy; pneumonia; acute heart failure; bronchiectasis; asthma (as primary diagnosis); acute respiratory acidosis needing NIV; lung cancer and other complications	Intervention: HFNC via OH-60C High-flow non-invasive breathing therapeutic apparatus (n=84 randomized and analyzed) Comparator: NIPPV via ventilator Hamilton G5; ventilated by mouth and nose (n=84 randomized and analyzed) Follow-up: 12 hours and 5 days after treatment (blood gases); NR for comfort and hospital length of stay	N= 168 Age (mean): 67 Race/ethnicity (%): NR Gender (% male): 58 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 100 Congestive Heart Failure: NR Comorbidity Index: NR Baseline characteristics (mean): SpO_2: 77.5 Respiratory Rate: NR PaO_2/FiO_2 ratio: NR pH: 7.3 PaO_2: 53.6 $PaCO_2$: 72.5
Corley, 2015 (30) Australia Funding: Government Setting: ICU (# sites unspecified) Special Population: Post-surgery; post-extubation; obese (BMI ≥ 30) ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: ≥18 years of age, BMI ≥30 kg/m2, scheduled to undergo cardiac surgery on cardiopulmonary bypass Exclusion: Ventilation time >36 h, extubation onto NIPPV, requirement for tracheostomy, extubation as part of end-of-life treatment	Intervention: HFNC post-extubation (Optiflow, RT202 delivery tubing, RT050/051 nasal cannulae, MR850 heated humidifier; initiated at 35 L/min and titrated according to patient comfort (max of 50 L/min); minimum duration 8 hours with short breaks for nasal care or mobilization (n=81 randomized and analyzed) Comparator: COT post-extubation under direction of treating ICU consultant; delivered via nasal cannulae 2-4 L/min or simple face mask 6 L/min titrated to maintain SpO_2 ≥95% (or as consultant-directed) (n=74 randomized and analyzed) Goal: FIO_2 titrated to maintain SpO_2 ≥95%.	N= 155 Age (mean): 64 Race/ethnicity: NR Gender (% male): 74 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 7.1 Congestive Heart Failure: NR Comorbidity Index (APACHE II) (mean): 15 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: 17.0 PaO_2/FiO_2 ratio: 240.0 pH: NR PaO_2: NR $PaCO_2$: NR

		Follow-up: 1 and 5 days (atelectasis on chest X-ray)	
Delorme, 2017 (31) Canada Funding: NR Setting: Mixed (cardiac surgery ICU and cardiac and pulmonology departments) Special Population: No ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Low	Inclusion: Signs of acute and/or moderate respiratory distress, defined by a respiratory rate greater than 20 breaths/min associated with either hypoxemia (SPO_2 <90% with oxygen supplementation ≥3 L/min; "hypoxemic subgroup") or hypercapnia ($PaCO_2$ ≥45 mm Hg with a respiratory acidosis (pH <7.38); "hypercapnic subgroup") Exclusion: Contraindications for insertion of esophageal catheter; if patient presented severe and nonstable respiratory or cardiac disease deemed likely to be worsened by study protocol (acute coronary syndrome, nontreated pulmonary embolism, pneumothorax); patients at risk for imminent intubation	Intervention: HFNO via Airvo2 at 3 different flow rates (20, 40, 60 L/min) (n=12 received all 3 flow rates in randomized order) Comparator: COT. Includes 3 patients who received HFNO before inclusion (n=same 12 patients) Note: Washout of 10 minutes between each treatment period. FiO_2 adjusted to achieve SpO_2 of 88-92% in hypercapnic patients and 92-96% in hypoxic patients Follow-up: Every 15 min for four periods (Indexes of respiratory effort)	N=12 Age (mean): 69 Race/ethnicity: NR Gender (% male): 67 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index: NR Baseline characteristics (mean): SpO_2: 91 Respiratory Rate: 24 PaO_2/FiO_2 ratio: NR pH: 7.37 PaO_2: NR $PaCO_2$: 53.1
Doshi, 2018 (32) Haywood, 2019 (36) (Subgroup/special population: ADHF) Doshi 2020 (57) (Subgroup/special population: AECOPD or acute hypercapnic respiratory failure) US Funding: Industry Setting: ED (5 centers – 2 academic, 3 community)	Inclusion: Presenting to ED with respiratory compromise; age >18 years; clinical judgement of ARF requiring escalation to NIV or to maintain NIV if delivered to ED while receiving NIV Exclusion: Suspected drug overdose; cardiovascular instability; end-stage cancer; life expectancy <6 months; significant respiratory depression on presentation; Glasgow Coma Scale score <9; cardiac or respiratory arrest on presentation; need for emergency intubation; known or suspected cerebrovascular accident; known of suspected ST-segment elevation MI;	Intervention: HVNI (Precision Flow; Vapotherm, Inc.); initiated at 35 L/min, 35-37degC, and FiO_2 1.0; adjusted flow up to 40 L/min (n=116 randomized, n=104 treated; subgroup n=22) Comparator: NIV (Respironics Vision V60; Philips Healthcare) with oronasal mask; IPAP 10-20 cm H2O; EPAP 5-10 cm H2O; FiO_2 1.0 (n=112 randomized, n=100 treated; subgroup n=20) Note: Goal for HVNI and NIV was to decrease breathing rate to <25 breaths/min and optimize comfort; respiratory therapist at bedside for first 4 hours. Clinical management independent of intervention was	N=204 Age (mean): 64 Race/ethnicity: 61% White, 30% African American, 9% Other Gender (% male): 45 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index (APACHE II) (mean): 31.0 Baseline characteristics (mean): SpO_2: 93.3 Respiratory Rate (breaths/min): 30.3 PaO_2/FiO_2 ratio: NR pH: 7.34

Special Population: None ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Moderate	increased risk of pulmonary aspiration, agitation, or uncooperativeness Subgroup inclusion: 1) Discharge diagnosis of acute decompensated heart failure (ADHF) (Haywood 2019) 2) Discharge diagnosis of AECOPD or acute hypercapnic respiratory failure (Doshi 2020)	according to standard care at each facility; patients requiring ventilatory support beyond 72 hours were "reasoned to be in a long-term or progressive condition" Follow-up: 72 hours (treatment failure rate, arm failure rate [*ie,* decision to crossover to the alternate therapy]); blood samples at 0, 1, and 4 hours; disposition and length of stay at discretion of medical team	PaO_2: NR $PaCO_2$: 55.9 **ADHF subgroup (n=42)** Age (median): HVNI: 65 NIV: 60 Race/ethnicity: 45% White, 38% African American, 17% Other Gender (% male): 36 Comorbidity Index (APACHE II) (median): HVNI: 31.5 NIV: 29 Baseline characteristics: SpO_2 (median): HVNI: 95.5 NIV: 98.5 Respiratory Rate (breaths/min, median) HVNI: 33 NIV: 34 PaO_2/FiO_2 ratio (median): HVNI: 118 NIV: 153.5 pH (median): HVNI: 7.38 NIV: 7.33 PaO_2 (median): HVNI: 82 NIV: 116.5 $PaCO_2$ (median): HVNI: 42.5 NIV: 42.0 **AECOPD/hypercapnic ARF subgroup (n=65)** Age (median): HVNI: 65 NIV: 59

			Race/ethnicity: 65% White, 34% African American, 1% Other Gender (% male): 46 Comorbidity Index (APACHE II) (median): HVNI: 31.0 NIV: 29.0 Baseline characteristics: SpO_2 (median): HVNI: 96.5 NIV: 98.0 Respiratory Rate (breaths/min, median) HVNI: 32 NIV: 28 PaO_2/FiO_2 ratio (median): NR pH (median): HVNI: 7.33 NIV: 7.32 PaO_2 (median): HVNI: 98.5 NIV: 98.0 $PaCO_2$ (median): HVNI: 56.0 NIV: 64.6
Frat, 2015 (34) FLORALI Frat, 2016 (33) (Subgroup/special population: Immuno-compromised patients) France, Belgium Funding: Government (industry provided supplies/equipment) Setting: ICU (23 sites)	Inclusion: ≥18 years; met all 4 criteria: (1) respiratory rate >25 breaths/min, (2) PaO_2:FiO_2 ≤300 mmHg while breathing O_2 at ≥10L/min for ≥15 min, (3) $PaCO_2$ ≤45 mmHg, (4) absence of clinical history of underlying chronic respiratory failure Exclusion: $PaCO_2$ >45 mmHg, exacerbation of asthma or chronic respiratory failure, cardiogenic pulmonary edema, severe neutropenia, hemodynamic instability, use of vasopressors, Glasgow Coma Scale score ≤12 points, contraindications to	Intervention: HFOT (Optiflow, Fisher & Paykel Healthcare); heated, humidified oxygen via large-bore binasal prongs; initiated at 50 L/min and FiO_2 1.0; applied for ≥2 days (n=106) Comparators: a) COT; continuous through nonrebreather face mask at ≥10 L/min; applied until patient recovered or was intubated (n=96 randomized, 94 analyzed) b) NIV via facemask (Fisher & Paykel Healthcare) connected to ICU	N=310 Age (mean): 60 Race/ethnicity (%): NR Gender (% male): 71 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: 6.5 Comorbidity Index (SAPS II) (mean): 25.4 Baseline characteristics (mean): SpO_2: NR Respiratory Rate (breaths/min): 32.7

Special Population: None Subgroup analyses of 1) patients with PaO_2/FiO_2 ratio ≤200 at inclusion and 2) immunocompromised patients ARF Type: Hypoxic Risk of Bias: Low	NIV, urgent need for endotracheal intubation, do-not-intubate order, decision not to participate Immunocompromised post-hoc subgroup inclusion: Progressive solid or hematological cancer, acquired immunodeficiency syndrome, administration of immunosuppressive drugs, or steroids >0.3 mg/kg/day (prednisolone) for at least 1 month	ventilator; goal was tidal volume 7-10 mL/kg PBW with initial PEEP 2-10 cmH2O; minimal duration of 8 hours/day for ≥2 days during sessions ≥1 hour, high-flow oxygen therapy between sessions (n=111 randomized, 110 analyzed) Note: Goal was to maintain SpO_2 ≥92% Follow-up: 28 days (proportion of patients requiring endotracheal intubation)	PaO_2/FiO_2 ratio (mmHg): 155.4 pH: 7.43 PaO_2 (mmHg): 88.9 $PaCO_2$ (mmHg): 35.0 **PaO_2/FiO_2 ratio ≤200 subgroup (n=238)** Age (mean): 62 Race/ethnicity: NR Gender (% male): 67 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index (SAPS II) (mean): 26 Baseline characteristics (mean): Respiratory Rate (breaths/min): 33 SpO_2: NR PaO_2/FiO_2 ratio (mmHg): 125 pH: 7.43 PaO_2 (mmHg): 80 $PaCO_2$ (mmHg): 35 **Immunocompromised subgroup (n=82)** Age (mean): 62 Race/ethnicity: NR Gender (% male): 70 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index (SAPS II) (mean): 30 Baseline characteristics (mean): SpO_2: NR Respiratory Rate (breaths/min): 33

			PaO_2/FiO_2 ratio (mmHg): 148 pH: 7.44 PaO_2 (mmHg): 92 $PaCO_2$ (mmHg): 34
Grieco, 2020 (35) Italy Funding: Industry Setting: ICU (single site) Special Population: None ARF Type: Hypoxic, non-hypercapnic Risk of Bias: Low	Inclusion: Adult patients with AHRF, defined by: respiratory rate >25 breaths per min with acute-onset (<1 week) respiratory distress; need for supplemental oxygen to maintain SpO_2 >90%; evidence of pulmonary infiltrates in chest x-ray or CT scan; absence of history of chronic respiratory failure or moderate-to-severe cardiac insufficiency Exclusion: One or more of the following criteria: exacerbation of asthma or COPD; clinical evidence of cardiogenic pulmonary edema; acute respiratory failure occurring within 1 week after surgery; hemodynamic instability and/or shock; metabolic acidosis; Glasgow coma score <13; and/or facial anatomy contraindicating helmet or nasal cannula application	All patients received oxygen at a flow rate of 50 L/min via a nonrebreathing face mask at baseline for 15 mins. Then they all received the following two interventions in random order for 60 mins each: 1. HFNC administered via AIRVO 2 device or by a gas-compressed mechanical ventilator (EvitaXL or EvitaInfinity) through a heated humidifier (MR860). 2. NIV (helmet) delivered via dedicated device (Dimar); interface size chosen according to neck circumference; patients connected to a compressed-gas-based ventilator equipped with an NIV-dedicated module (EvitaXL or EvitaInfinity) through a bi-tube circuit with no humidification Follow-up: 1 hour (PaO_2/FiO_2 ratio)	N=15 Age (mean): 69 Race/ethnicity (%): NR Gender (% male): 60 Comorbidities (%): Chronic Respiratory Failure: 0% COPD: NR Congestive Heart Failure: NR Comorbidity Index (SAPS II) (median): 50.7 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: NR PaO_2/FiO_2 ratio: 187.3 pH: NR PaO_2: NR $PaCO_2$: 32.3
Hernandez, 2016 (38) Spain Funding: None (industry supplied equipment to 2 of the 7 ICUs) Setting: ICU (7 sites) Special Population: Mechanically ventilated at low risk for reintubation	Inclusion: Adult (≥18 years) patients receiving mechanical ventilation >12 hours; ready for scheduled extubation after tolerating SBT; meeting criteria for low risk of reintubation (age <65 years, absence of heart failure as primary indication for mechanical ventilation, absence of moderate-to-severe COPD, APACHE II <12 on day of extubation, BMI <30, absence of airway patency problems including high risk of developing laryngeal edema, ability to manage respiratory secretions, simple	Intervention: HFOT (Optiflow, Fisher & Paykel Healthcare) via nasal cannula immediately after extubation; initially set at 10 L/min, titrated upward in 5 L/min steps until patient discomfort; initial temperature 37°C (unless "too hot" for patient); FiO_2 regularly adjusted to target SpO_2 >92%; HFOT discontinued after 24 hours and patients received COT if needed (n=264 randomized and analyzed)	N=527 Age (mean): 51 Race/ethnicity: NR Gender (% male): 60.2 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 2.5% (mild) Congestive Heart Failure: NR Comorbidity Index (APACHE II) (median): 1) at ICU admission: 13.5 2) at extubation: 7

following planned extubation; post-extubation ARF Type: Hypoxic Risk of Bias: Low	weaning [proceed from initiation of weaning to successful extubation on 1st attempt without difficulty], <2 comorbidities, no prolonged mechanical ventilation [>7 days]) Exclusion: Do-not-resuscitate orders, tracheostomy, accidentally extubated or self-extubated, hypercapnic during SBT, pregnant	Comparator: COT; continuous, nasal cannula or nonrebreather facemask, flow adjusted to maintain SpO_2 >92% (n=263 randomized and analyzed) Note: 24 hours was standard ICU time; air source for HFOT not always available in wards Follow-up: 72 hours (reintubation); additional follow-up until hospital discharge; treated by medical, nursing, and respiratory therapy staff; rescue with NIV strongly discouraged	Baseline characteristics (mean): SpO_2: NR Respiratory Rate: NR PaO_2/FiO_2 ratio: 232.0 pH: 7.4 PaO_2: NR $PaCO_2$: 38.5
Hernandez, 2016 (37) Spain Funding: None Setting: ICU (3 sites) Special Population: Mechanically ventilated at high risk for reintubation following planned extubation; post-extubation ARF Type: Hypoxic Risk of Bias: Low	Inclusion: Adult (≥18 years) patients receiving mechanical ventilation >12 hours; ready for scheduled extubation after tolerating SBT; at least 1 criteria for high risk of reintubation (age >65 years, heart failure as primary indication for mechanical ventilation, moderate-to-severe COPD, APACHE II >12 on day of extubation, BMI >30, airway patency problems including high risk of developing laryngeal edema, inability to manage respiratory secretions, difficult or prolonged weaning [failing first attempt], ≥2 comorbidities, prolonged mechanical ventilation [>7 days]) Exclusion: Age <18 years, do-not-resuscitate orders, tracheostomy, accidentally extubated or self-extubated, hypercapnic during SBT, pregnant	Intervention: HFOT (Optiflow, Fisher & Paykel Healthcare) via nasal cannula immediately after extubation; initially set at 10 L/min, titrated upward in 5 L/min steps until patient discomfort; initial temperature 37°C (unless "too hot" for patient); FiO_2 regularly adjusted to target SpO_2 >92%; HFOT discontinued after 24 hours and patients received COT if needed (n=290 randomized, 288 included in per-protocol analysis) Comparator: NIV via full face mask BiPAP Vision, Respironics, Inc.) for 24 hours then COT via Venturi mask; PEEP/EPAP (initial: 5 cm H2O Protocol) and inspiratory pressure support/IPAP (initial: 10 cm H2O Protocol) adjusted to target respiratory rate of 25/min and adequate gas exchange (SaO_2=92% with pH=7.35); FiO_2 adjusted to maintain SpO_2 >92%; sedatives to increase tolerance not allowed (n=314 randomized, 312 included in per protocol analysis)	N=604 Age (mean): 65 Race/ethnicity: NR Gender (% male): 64.2 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 20.5 Congestive Heart Failure: NR Comorbidity Index (APACHE II) (median): 1) at ICU admission: 16 2) at extubation: 10.5 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: NR PaO_2/FiO_2 ratio: 192.5 pH: 7.4 PaO_2: NR $PaCO_2$: 40

		Note: 24 hours was standard ICU time; air source for HFOT not always available in wards Follow-up: 72 hours (reintubation); additional follow-up until hospital discharge; treated by medical, nursing, and respiratory therapy staff; rescue therapy with NIV not allowed in HFOT group	
Jing, 2019 (39) China Funding: Government Setting: ICU (single site) Special Population: COPD; post-extubation; hypercapnia ($PaCO_2$ ≥45) ARF Type: Hypercapnic Risk of Bias: Moderate	Inclusion: COPD patients who were intubated for exacerbation, with hypercapnia ($PaCO_2$ >45 mmHg) at the time of extubation, and met the "pulmonary infection control window" Exclusion: Tracheotomy; severe dysfunction of other organs, including heart, brain, liver, and renal failure; hemodynamic instability; facial injury, burns or deformities; uncooperative; copious secretions with weak cough ability; gastric over-distention, vomiting; untreated pneumothorax; rhinitis, nasal congestion, deformities or blockage; refuse to participate	Intervention: HFNC (Optiflow or AIRVO$_2$) using nasal cannulas chosen to be <50% of individual patients' nostrils' diameter). Temperature set at 37°C and FiO_2 adjusted to maintain O_2 saturation recorded by pulse oximetry at 88-92% (n=22 randomized and analyzed) Comparator: NIV (VPAP IIIST) with standard oral-nasal mask. IPAP initiated at 10-12 cmH20; EPAP at 4-5 cm$H_2$0. O_2 blended via port on mask and adjusted to maintain SpO_2 88-92% (n=20 randomized and analyzed) Follow-up: 3, 24, and 48 hours post-extubation (ABGs [pH, $PaCO_2$, PaO_2/FiO_2, vital signs, RR])	N=42 Age (mean): 76 Race/ethnicity (%): NR Gender (% male): NR Comorbidities (%): Chronic Respiratory Failure: NR COPD: 100 Congestive Heart Failure: NR Comorbidity Index (APACHE II) (mean): 11.1 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: 18.7 PaO_2/FiO_2 ratio: 244.7 pH: 7.45 PaO_2: NR $PaCO_2$: 53.4
Jones, 2016 (40) New Zealand Funding: Foundation Setting: ED (single site) Special Population: No	Inclusion: Subjects who had SpO_2 ≤ 92% on room air (≤90% if known chronic CO_2 retention) and a breathing frequency of ≥2 breaths/min either pre-hospital or upon arrival to the ED Exclusion: Patients who were intubated pre-hospital; required intubation or NIV immediately upon arrival; bullous lung disease; pneumothorax; facial	Intervention: HFNO delivered via Optiflow nasal interface connected to Airvo1 or Airvo2 humidifier. Initiated at 40 L/min, temperature 37°C, and FiO_2 0.28 (n=172 randomized, 165 analyzed) Comparator: COT via Hudson mask, Venturi device, or standard nasal prongs using wall oxygen titrated with a	N=303 Age (mean): 74 Race/ethnicity: 66% White, 0% Black, 34% Other Gender (% male): 48 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR

ARF Type: Hypoxic Risk of Bias: Moderate	abnormalities precluding the use of nasal prongs; facial or intracranial trauma; facial or trans-nasal neurosurgery (within 6 wks); epistaxis (within 2 wks); prior decision for palliative care only; had previously been enrolled	flow meter from 1-15 L/min (n=150 randomized, 138 analyzed) Goal: FIO_2 was titrated according to clinical need. Subjects with known chronic hypoxia had a target maximum SpO_2 of 93% or their last known resting oxygen saturation when well. Follow-up: NR (conversion to NIV or invasive positive-pressure ventilation). "Most participants had observations done" within the first 2 hours.	Comorbidity Index: NR "No. of comorbidities" (median, IQR) HFNO: 6 (4-9) COT: 7 (4-10) Does not state what comorbidities were counted Baseline characteristics (mean): SpO_2: 85.2 Respiratory Rate: 33 PaO_2/FiO_2 ratio: NR pH: NR PaO_2: NR $PaCO_2$: NR
Lemiale, 2015 (41) France Funding: Industry provided O_2 delivery devices and funds for study insurance and presentation of results. Setting: ICU (4 sites) Special Population: Immunocompromised ARF Type: Hypoxic Risk of Bias: Low	Inclusion: Consecutive immunocompromised patients admitted to ICU for ARF; over 18 years of age. ARF defined as onset of respiratory symptoms within 72 hours before ICU admission and either a need for oxygen greater than 6 L/min to maintain SpO_2 >95% or symptoms of respiratory distress (tachypnea >30/min, intercostal recession, labored breathing, and/or dyspnea at rest) Exclusion: Hypercapnia (>45 mmHg); mechanical ventilation before ICU admission; need for immediate NIV or IMV; patient refusal to participate	Intervention: HFNO used with heated humidified circuit; initiated at 40-50 L/min with FiO_2 1.0, then adjusted as needed to maintain SpO_2 ≥95% (n=53 randomized, 52 analyzed) Comparator: COT via Venturi mask; initial settings were FiO_2 60% (15 L/min), then adjusted as needed to maintain SpO_2 ≥95% (n=49 randomized, 48 analyzed) Goal: SpO_2 ≥95% Follow-up: 2 hours (need for NIV or IMV)	N=100 Age (median): HFNO: 59 COT: 65 Race/ethnicity: NR Gender (% male): 70 Comorbidities (%): Chronic Respiratory Failure: 11 COPD: NR Congestive Heart Failure: 6 Comorbidity Index (SAPS II) (median at ICU admission): HFNO: 42.0 COT: 37.5 Baseline characteristics (median): SpO_2: HFNO: 96 COT: 96 Respiratory Rate HFNO: 26 COT: 27

			PaO_2/FiO_2 ratio: HFNO: 128 COT: 100 pH: NR PaO_2: NR $PaCO_2$: NR
Maggiore, 2014 (42) Italy Funding: University, Industry Setting: ICU (2 sites) Special Population: Post-extubation ARF Type: Hypoxic Risk of Bias: Low	Inclusion: Mechanically ventilated >24 hours; successfully passed SBT, PaO_2/FiO_2 ≤300 at end of trial Exclusion: Age <18, pregnancy, tracheostomy, do-not-intubate status, planned use of NIV after extubation (≥3 failed SBT, $PaCO_2$ >45, RR >25 just before SBT)	Intervention: NHF (Optiflow, Fisher & Paykel Healthcare); 50 L/min; used for 48 hours or up to ICU discharge (n=53 randomized and analyzed) Comparator: COT via Venturi mask; used for 48 hours or up to ICU discharge (n=52 randomized and analyzed) Goal: FiO_2 adjusted to obtain SaO_2 of 92-98% (88-95% if compensated hypercapnia) Follow-up: 48 hours (PaO_2/FiO_2 ratio) Interface displacement NHF: 20 episodes (0.4/patient) COT: 89 episodes (1.7/patient) P<.001 Patients displacing interface NHF: 32.1% (17/53) COT: 55.8% (29/52) P=.01	N=105 Age (mean): 65 Race/ethnicity: NR Gender (% male): 64.8 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index (SAPS II) (mean): 43.5 Baseline characteristics (mean): SpO_2: NR Respiratory Rate (breaths/min): 23 PaO_2/FiO_2 ratio: 240.6 pH: NR PaO_2: 91.6 $PaCO_2$: 35.3
Makdee, 2017 (43) Thailand Funding: None (industry supplied equipment) Setting: ED (single site)	Inclusion: Age ≥18 years; diagnosis of cardiogenic pulmonary edema (history of acute dyspnea, bilateral rales, and signs of pulmonary congestion on initial chest x-ray); pulse oximetry reading <95% on room air; respiratory rate >24 breaths/min Exclusion: SpO_2 ≤90% or respiratory rate ≥35 breaths/min while on COT at	Intervention: HFNC (Optiflow; Fisher & Paykel Healthcare); initial flow at 35 L/min with maximum of 60 L/min to maintain O_2 saturation ≥95% (n=69 randomized, 63 analyzed) Comparator: COT via nasal cannula (n=51) or nonrebreather mask (n=14) (total n=67 randomized, 65 analyzed)	N=128 Age (mean): 70 Race/ethnicity: NR Gender (% male): 35.2 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 7.8 Congestive Heart Failure: NR

Special Population: Cardiogenic pulmonary edema ARF Type: Hypoxic Risk of Bias: Moderate	10 min after arrival in ED; need for immediate intubation or NIV; presence of myocardial infarction (cardiac chest pain with ECG change or increasing cardiac enzyme level), Glasgow Coma Scale score <13; hemodynamic compromise (blood pressure <90/60 mmHg); pregnancy; respiratory failure (respiratory rate >35 breaths/min, SPO_2 <90%, or signs of increased work of breathing); end-stage renal disease (estimated GFR<15 ml/min per 1.73 m^2 or dialysis), contraindications to use of equipment with positive airway pressure, concomitant pneumonia	Note: FiO_2 adjusted to maintain O_2 saturation ≥95%; 60-min protocol with modality continued at discretion of physician Follow-up: 1 hour (respiratory rate); other outcomes assessed at 24 hours and 7 days (mortality)	Comorbidity Index: NR Baseline characteristics (mean): SpO_2: 88.7 Respiratory Rate: 31 PaO_2/FiO_2 ratio: NR pH: NR PaO_2: NR $PaCO_2$: NR
Matsuda, 2020 (58) Japan Funding: Government (for manuscript preparation only) Setting: ICU (single site) Special Population: Post-extubation (mixed diagnoses) ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Moderate	Inclusion: Age ≥18 years; received conventional mechanical ventilation for >24 hours in the emergency department; successfully passed a SBT and $PaO_2/setFiO_2$ <300 mmHg within 3 hours before extubation Exclusion: Difficulty attaching the device safely, pregnancy, tracheostomy before enrollment, pneumothorax without drainage, do-not-intubate order	Intervention: HFNC; initial $setFiO_2$=0.4 and flow of 50 L/min; $setFiO_2$ adjusted to maintain SpO_2 of 88-95%; continued for up to 48 hours (n=32 randomized, 30 analyzed) Comparator: COT with large-volume nebulization-based humidifier; mask shaped to cover lower half of face; initial $setFiO_2$=0.4 and flow adjusted according to tidal volume; $setFiO_2$ adjusted to maintain SpO_2 of 88-95%; continued for up to 48 hours; O_2 therapy terminated or changed to normal nasal cannula if required $setFiO_2$ decreased to <0.3 (equipment limitation) (n=40 randomized, 39 analyzed) Follow-up: 1, 6, 24, and 48 hours; 5 and 7 days	N=72 randomized, data for 69 Age (mean): 71 Race/ethnicity: NR Gender (% male): 71 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 5.8 Congestive Heart Failure: NR Comorbidity Index (APACHE II) (mean): 23 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: 18.6 PaO_2/FiO_2 ratio: 220.8 pH: 7.46 PaO_2: 73.7 $PaCO_2$: 42.3
Parke, 2011 (44) New Zealand	Inclusion: Patients with mild to moderate hypoxemic respiratory failure (receiving ≥4 L/min oxygen via nasal cannula for ≥4 hours or ≥6 L/min via	Intervention: Humidified high flow oxygen via nasal high-flow (NHF) with initial flow 35 L/min. Used Optiflow, MR880 humidifier, RT241 heated	N=56 Age (mean): 64 Race/ethnicity: 78% European, 17.5% Pacific Island, 5% Other Other: 5%

Funding: Industry Setting: ICU Special Population: No ARF Type: Hypoxic Risk of Bias: Low	face mask for ≥2 hours) in cardiothoracic and vascular intensive care unit Exclusion: Patients requiring imminent mechanical ventilation	delivery tube, RT022 large/RT034 small, wide-bore nasal cannula. Flow and FiO_2 titrated to SpO_2 or SaO_2 ≥95% (n=30 randomized, 29 analyzed) Comparator: COT; humidified high flow oxygen via standard high-flow face mask. Used MR850 humidifier, RT308 heated delivery tube and air entrainer with an aerosol mask (Husdon RCI). Titrated to an SpO_2 or SaO_2 ≥95% (n=30 randomized, 27 analyzed). Follow-up: 30 min, 1 hour, 2 hours, and 4 hours (primary outcome not identified)	Gender (% male): 79 Comorbidities (%): NR Comorbidity Index (APACHE II) (mean): 12 Baseline characteristics (mean): SpO_2: 93 Respiratory Rate: 19.6 PaO_2/FiO_2 ratio: NR pH: 7.37 PaO_2: 75.0 $PaCO_2$: 42.5
Pilcher, 2017 (45) New Zealand Funding: Industry Setting: Hospital (not specified) (1 site) Special Population: COPD exacerbation ARF Type: Hypercapnic Risk of Bias: Low	Inclusion: Age ≥16; primary admission diagnosis of acute exacerbation of COPD; receiving oxygen therapy via standard nasal prongs (SNPs) Exclusion: None reported Note: Patients had been in hospital a median of 1 day prior to participation in study; 70 of 94 screened were excluded from study	All patients received oxygen via SNPs at same flow rate as study entry for 15 min prior to randomization to *order of receipt of treatments* Intervention: Nasal high flow cannula (AIRVO with Optiflow, Fisher & Paykel Healthcare) at 35 L/min at 37°C with supplemental oxygen titrated to SpO_2 on study entry Comparator: COT via SNPs (AirLife, CareFusion) with supplemental oxygen titrated to SpO_2 on study entry Note: Each treatment period followed by ≥15 min washout/observation with oxygen via SNP at baseline flow rate Follow-up: End of 2nd 30-min treatment period (with ≥15 min wash-out between and after; ~90 min total)	N=24 Age (mean): 70 Race/ethnicity: NR Gender (% male): NR Comorbidities (%): Chronic Respiratory Failure: NR COPD: 100 Congestive Heart Failure: NR Comorbidity Index: NR Baseline characteristics (mean): SpO_2: 94 Respiratory Rate: 21.8 PaO_2/FiO_2 ratio: NR pH: NR PaO_2: NR $PaCO_2$: 49
Rittayamai, 2015 (46)	Inclusion: Age ≥18 years; acute dyspnea with hypoxemia (>24	Intervention: HFNC (Optiflow; Fisher & Paykel Healthcare) at 35 L/min; FiO_2	N=40 Age (mean): 65

Thailand Funding: University Setting: ED (single site) Special Population: None ARF Type: Hypoxic Risk of Bias: Moderate	breaths/min and SpO_2 <94% on room air) Exclusion: Hemodynamic instability, need for NIV, chronic respiratory failure with long-term O_2 supplementation, decreased level of consciousness (Glasgow Coma Scale <13), lack of cooperation, pregnant	adjusted to achieve SpO_2 ≥94% within the first 5 min and continued for 1 hour (n=20 randomized and analyzed) Comparator: COT via nasal cannula or non-rebreathing mask at a flow of 3-10 L/min to achieve SpO_2 ≥94% for 1 hour (n=20 randomized and analyzed) Follow-up: 1 hour (dyspnea)	Race/ethnicity (%): NR Gender (% male): 37.5 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index (APACHE II) (mean): 15.1 Baseline characteristics (mean): SpO_2: 87.3 Respiratory Rate: 31.9 PaO_2/FiO_2 ratio: NR pH: NR PaO_2: NR $PaCO_2$: NR
Ruangsomboon, 2019 (47) Thailand Funding: Hospital Research and Development Fund (industry provided supplies) Setting: ED (single site) Special Population: Palliative care ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: Age ≥18 years; palliative status; known do-no-intubate status; presenting with hypoxemic respiratory failure (SpO_2<90% on room air, respiratory rate ≥30 breath/min, accessory muscle use, modified Borg scale score ≥4) Exclusion: Not able to cooperate; decreased level of consciousness (Kelly score <4 and not able to answer simple question); contraindications for positive airway pressure devices	All patients received standard treatment including COT, as required, before the trial Intervention: 60 min of HFNC (AIRVO-2, Fisher & Paykel); initial setting of 35 L/min adjusted to between 30 and 60 L/min to improve participant comfort; FiO_2 adjusted to achieve steady-state oxygen SpO_2 ≥95% Comparator: 60 min of COT by nasal cannula or nonrebreather mask; flow rate adjusted to achieve steady-state oxygen SpO_2 ≥95% Note: Initial 60 min treatment period followed immediately by crossover to 60 min of other treatment with initial 15 minutes being “active washout”; during trial all participants received standard treatments to alleviate respiratory distress including intravenous	N=48 (44 analyzed) Age (mean): 60.3 Race/ethnicity (%): NR White: Black: Other: Gender (% male): 44 Comorbidities (%): Chronic Respiratory Failure: 10% (chronic lung disease) COPD: NR Congestive Heart Failure: NR Comorbidity Index: NR Baseline characteristics: SpO_2: 89.2 Respiratory Rate: 33.4 PaO_2/FiO_2 ratio: NR pH: NR PaO_2: NR $PaCO_2$: NR

		morphine if needed; HFNC or COT continued after trial based on participant's preference Follow-up: 1 hour (dyspnea)	
Saksitthichok, 2019 (48) Thailand Funding: NR Setting: General ward or intermediate care unit (single site) Special Population: Bronchoscopy ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: Age ≥15; had hypoxemia; required FB for diagnosis of abnormal pulmonary lesions Exclusion: Not cooperative or complied with FB; had indication for intubation; decreased level of consciousness and/or unconscious; considered high risk for aspiration; had distorted maxillofacial structure not suitable for NIV or HFNC; rejected participation or withdrew from study Note: Patients who were unable to tolerate NIV or HFNC or who had SpO_2 ≤ 90% after randomization were excluded	Intervention: HFNC delivered through nasal cannula with AIRVO_2. Inspiratory flow rate was 40 L/min and FiO_2 was kept at 0.6 through 30 min post bronchoscopy (n=26 randomized and analyzed) Comparator: NIV with Phillips Respironics V60 machine and full-face mask. Bilevel positive airway pressure mode, with EPAP 5 cmH20 and IPAP ≥10 cmH20 or to achieve tidal volume of 8 mL/kg or at least 10 cmH_2O. FiO_2 was kept at 0.6 through 30 min post bronchoscopy (n=25 randomized and analyzed) Follow-up: 30 min after initiation of treatment, immediately after FB, 30 min after FB (lowest SpO_2 during FB)	N=51 Age (mean): 59 Race/ethnicity (%): NR Gender (% male): 55 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 7.8 Congestive Heart Failure ("Chronic heart diseases"): 5.9 Comorbidity Index (SAPS II) (mean): 27.8 Baseline characteristics (mean): SaO_2: 87.4 Respiratory Rate: 25.8 PaO_2/FiO_2 ratio: NR pH: 7.45 PaO_2: 54 $PaCO_2$: 32.9
Schwabbauer, 2014 (49) Germany Funding: Received 2 devices from Industry Setting: ICU (single site) Special Population: No ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: Patients with primary hypoxic respiratory failure (PaO_2 <55 mmHg on room air) of acute onset admitted to the ICU Exclusion: Clinical evidence for cardiac pulmonary edema; COPD and/or ventilatory failure; hemodynamic instability; contraindications to NIV; impaired consciousness or disorientation; inability to give informed consent	Each patient (n=14) underwent, in random order, three 30-min interventions (15-min washout period in between interventions with nasal cannula set to achieve SpO_2 ≥ 88%): 1. HFNC (OptiFlow, MR 850 active respiratory gas humidifier, setting "invasive ventilation") 2. COT via Venturi mask (Unomedical) 3. NIV (intensive care ventilators in the pressure support mode equipped with active respiratory gas humidifier (MR 850)	N=14 Age (mean): 60 Race/ethnicity: NR Gender (% male): NR Comorbidities (%): NR Comorbidity Index (SAPS II) (mean): 41.2 Baseline characteristics (mean): SpO_2: 93 Respiratory Rate: 28 PaO_2/FiO_2 ratio: NR pH: 7.47 PaO_2: 67

		Follow-up: 30 min (PaO_2)	$PaCO_2$: 36
Sklar, 2018 (50) Canada Funding: Foundation (industry provided equipment) Setting: Hospital ward (1 site) Special Population: Cystic fibrosis ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Moderate	Inclusion: >18 years; hospitalized; clinical indication for NIV at time of admission (at least 1 of a) respiratory rate >24/min or accessory muscle use, b) $PaCO_2$>45 mmHg from time of admission, c) nocturnal hypoventilation treated by NIV but requiring daytime NIV due to clinical worsening or d) diurnal hypercapnia); stabilized with NIV (respiratory therapists) medically optimized (treating physician) Exclusion: Active massive hemoptysis, pneumothorax with pleural drainage and persistent air leak, hemodynamic instability requiring vasopressors, uncooperative behavior, recent upper airway or esophageal surgery, skin or chest wall or abdominal trauma, declared pregnancy Note: Patients had been in hospital a median of 5 days and had been stabilized over a median of 3 days of NIV and medical therapy prior to enrollment; 60% of patients had used NIV at home	All patients received COT at baseline (mean 3 L/min) Intervention: 30 min of HFNT (AIRVO-2, Fisher & Paykel); maximum of 55 L/min as tolerated by patient; FiO_2 adjusted to achieve SpO_2 of ≥92% and temperature of 37°C or 34°C (patient preference) Comparator: NIV (3 systems based on availability – ResMed Stellar 150, ResMed VPAP III ST-A, or Respironics BiPAP Synchrony); 2 face masks (patient preference); FiO_2 adjusted to achieve SpO_2 of ≥92%; settings were those previously adjusted by respiratory therapy team Note: Each treatment period followed by 10 min washout with COT. All patients received standard therapy (antibiotics, nebulizer) at discretion of attending physician. Follow-up: End of 2nd 30-min treatment period (with 10 min wash-out between and after; ~80 min total)	N=15 Age (mean): 30 Race/ethnicity: NR Gender (% male): 47 Comorbidities (%): Chronic Respiratory Failure: 80 (12/15 report supplemental oxygen as outpatient) COPD: NR Congestive Heart Failure: NR Comorbidity Index: (APACHE II) (median): 8 Baseline characteristics (median): SpO_2: NR Respiratory Rate: 21 PaO_2/FiO_2 ratio: NR pH: 7.39 PaO_2: 64 $PaCO_2$: 53
Song, 2017 (51) China Funding: Government Setting: ICU (1 site) Special Population: Post-extubation	Inclusion: Patients with ARF (PaO_2 <60 mmHg, $PaCO_2$ >45 mmHg or both) admitted to ICU, mechanical ventilation ≥48 hours, ready for extubation after clinical weaning assessment, successfully passed SBT with 7 cmH2O of pressure support for 30-120 min Exclusion: Poor cooperation, tracheostomy, decreased level of	Intervention: HFNC (PT101AZ, Fisher & Paykel Healthcare); FiO_2 at 40%; flow level 60 L/min (adjusted down in 5- to 10- L/min decrements as oxygenation improved or stabilized) (n=30 randomized and analyzed) Comparator: COT with air entrapment mask (Jinlin Medical Appliances Factory); FiO_2 40%; flow rate 10 L/min (n=30 randomized and analyzed)	N=60 Age (mean): 69 Race/ethnicity: NR Gender (% male): 56.7 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index: (APACHE II): 12.6

ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Moderate	consciousness (Glasgow Coma Scale score ≤12), <18 years, pregnant	Note: Targeted SpO_2 94-98% if hypoxic respiratory failure, 88-92% if hypercapnic respiratory failure in both groups Follow-up: 24 hours (success rate of oxygen therapy, respiratory and hemodynamic parameters and discomfort)	Baseline characteristics (mean): SpO_2: 95.7 Respiratory Rate: NR PaO_2/FiO_2 ratio: 205.8 (calculated) pH: NR PaO_2: 82.3 $PaCO_2$: 41.9
Spoletini, 2018 (52) US Funding: Government, Industry (partial funding and equipment) Setting: ICUs (5) and Intermediate Care Units (2) Special Population: No ARF Type: Hypoxic and/or hypercapnic Risk of Bias: Moderate	Inclusion: Age ≥18 years, on acute NIV for anticipated time ≥24 hours due to acute or acute on chronic hypercapnic respiratory failure (pH <7.35 and pCO_2 >45 mmHg) or acute hypoxemic respiratory failure (PaO_2/FiO_2 <300, RR ≥24 breaths/min Exclusion: Contraindications to NIV (respiratory arrest, unable to fit mask, medically unstable, agitated/uncooperative, unable to protect airway, excessive secretions, organ failure [≥2 organs], recent upper airway or upper GI surgery, undrained pneumothorax, facial deformity, previous head/neck surgery), delirium, previous participation in the study, NIV initiation ≥48 hours prior to screening Note: Secondarily excluded patients who withdrew consent, underwent endotracheal intubation before first break, were weaned off NIV and O_2 therapy before the first break, received a different device per clinical team decision Criteria for restarting NIV and discontinuing breaks: worsening	Intervention: High-flow nasal therapy (Optiflow, Fisher & Paykel Healthcare); headed and humidified; initial flow rate of 35 L/min; flow rate and FiO_2 adjusted to maintain oxygenation (n=28 randomized, 23 analyzed) Comparator: COT, humidified via cold water system through nasal cannulae, Venturi, or non-rebreather facemasks; flow rate adjusted to maintain SpO_2 (n=26 randomized, 24 analyzed) Note: All patients received NIV in pressure support mode (Vision or V60 ventilator, Philips Respironics), initial PEEP at 4 cm H2O and PS of 4-8 cm H2O; adjusted by respiratory therapists to maintain target tidal volume of 6-8 ml/kg, RR≤24/min, and FiO_2 to maintain a targeted O_2 saturation adequate gas exchange (88-92% in hypercapnic patients or combined hypercapnic/hypoxemic, ≥92% in hypoxemic patients; orofacial mask (Free Motion RT040, Fisher & Paykel Healthcare). Study terminated early due to slow enrollment related to routine use of HFNO during breaks and loss of personnel for screening	N=47 Age (mean): 66 Race/ethnicity: NR Gender (% male): 38.3 Comorbidities (%): Chronic Respiratory Failure: NR COPD: 61.7 Congestive Heart Failure: 34.0 Comorbidity Index (APACHE II) (mean): 16.2 Baseline characteristics (mean): SpO_2: 95.9 Respiratory Rate (breaths/min): 26.4 PaO_2/FiO_2 ratio: 206.7 pH: 7.31 PaO_2: 96.1 $PaCO_2$: 57.6

	dyspnea uncontrolled by adjusting HFNT or COT settings, increased respiratory or heart rate by 15%, increased or decreased systolic blood pressure by 20%, drop in SpO_2 below target without recovery by increasing settings, request by patient or clinician	Follow-up: Through 6 breaks or until subject weaned off NIV (total time on and off NIV)	
Stéphan, 2015 (53) France Funding: NR Setting: ICU (6 sites) Special Population: Post cardiothoracic surgery; post-surgery; post-extubation ARF Type: Hypoxic Risk of Bias: Low Note: noninferiority study – hypothesis that HFNC was not inferior to NIV for preventing or resolving ARF after cardiothoracic surgery	Inclusion: Had undergone cardiothoracic surgery and met any of following criteria: 1) failure of SBT (SaO_2 <90% with 12 L of O_2 during a T-tube trial or PaO_2 <75 mmHg with FiO_2 ≥50% during low level pressure support) 2) successful SBT in patient with any of predefined risk factors for post-extubation ARF (BMI>30, left ventricular ejection fraction <40%, failure of previous extubation) 3) successful SBT followed by failed extubation (per defined criteria) Exclusion: Obstructive sleep apnea, tracheostomy, do-not-intubate status, delirium, nausea and vomiting, bradypnea, impaired consciousness, hemodynamic instability	Intervention: HFNC (37°C and 44mg H2O/L) (Optiflow, Fisher & Paykel Healthcare), initial flow rate 50L/min, initial FiO_2 50%, adjusted at physician discretion to maintain SaO_2 at 92-98% (n=414 randomized and analyzed) Comparator: NIV via bilevel positive airway pressure (BiPAP) with full face mask (BiPap Vision, Respironics or ICU ventilator in pressure-support mode with added PEEP); exchange filters for heat and moisture; pressure support started at 8 cm H2O and increased to achieve exhaled tidal volume of 8 mL/kg and respiratory rate <25/min; PEEP initially at 4 cm H2O; FiO_2 50%, adjusted to maintain SaO_2 at 92-98%; used initially for 2 hours then approximately 1 hour every 4 hours or more if needed; between BiPAP sessions patients received standard O_2 (nasal cannula, simple face mask, or nonrebreathing mask) to maintain SaO_2 at 92% or higher (n=416 randomized and analyzed) Note: All patients had active program of physiotherapy during post-operative period; respiratory therapists routinely visited each patient twice between 7 am and 7 pm (more often if needed). Nurse interventions for unplanned	N=830 (Demographics for entire study group; only those meeting inclusion criteria #1 or #3 met our definition of ARF) Age (mean): 64 Race/ethnicity: NR Gender (% male): 66.4 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Congestive Heart Failure: NR Comorbidity Index (SAPS II) (mean): 28.9 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: 23.1/min PaO_2/FiO_2 ratio: 199.5 pH: 7.39 PaO_2: NR $PaCO_2$: 38.9

		device adjustment (average over first 3 study treatment days): HFNO: 0.43 per patient, per day NIV: 0.28 per patient, per day Follow-up: Duration of ICU stay (treatment failure, switch to other study treatment, or premature study-treatment discontinuation)	
Vargas, 2015 (54) France Funding: Industry Setting: ICU (single site) Special Population: No ARF Type: Hypoxic Risk of Bias: Moderate	Inclusion: Patients with acute hypoxemic respiratory failure (PaO_2/FiO_2 ≤300 mmHg on oxygen and lung infiltrates by chest radiograph) admitted to the ICU Exclusion: <18 years of age, patients with tracheostomies, chronic retention of Co_2, respiratory acidosis (pH <7.35 and PaCo2 >45 mmHg), factors related to insertion of an esophageal catheter, excessive amounts of respiratory secretions, systolic blood pressure <90 mmHg, ventricular arrhythmia, encephalopathy or coma, life-threatening hypoxemia (PaO_2/FiO_2 <100 mmHg), decision to limit life-support treatments	All patients received the following 20-min interventions: 1. COT via high-FiO_2 non-rebreathing face mask (Hudson RCI/Telefex Medical). Goal was to achieve SpO_2 >90%. All patients received this intervention twice (first and last intervention). 2. HFNC (Optiflow, MR850 humidifier); 37°C via short wide-bore bi-nasal prongs) at 60 L/min 3. NIV via CPAP (BiPAP Vision at 5 cm H_2O) Note: COT was always delivered as the first and last intervention. HFNC and NIV were delivered in random order. Therefore, patients received 4 20-min interventions. Follow-up: 20 min (inspiratory muscle effort)	N=12 Age (mean): 65 Race/ethnicity: NR Gender (% male): 83 Comorbidities (%): Chronic Respiratory Failure: NR COPD: NR Heart Failure: 8 Immunosuppressed: 25 Comorbidity Index (SAPS II) (mean): 48.2 Baseline characteristics (mean): SpO_2: NR Respiratory Rate: NR PaO_2/FiO_2 ratio: 180.2 pH: NR PaO_2: NR $PaCO_2$: NR
Vourc'h, 2019 (55) France Funding: University and Industry	Inclusion: Admitted in ICU with severe hypoxemia (SpO_2 <96% with Venturi mask with FiO_2 of 50%) after extubation following scheduled CABG, age ≥18 years	Intervention: HFNC (Optiflow, Fisher & Paykel Healthcare) for 48 hours; FiO_2 100%, flow 45 L/min, 37°C (n=49 randomized, 47 in ITT analysis) Comparator: COT (HFFM) for 48 hours; non-rebreather mask (Hudson	N=90 Age (mean): 67 Race/ethnicity: NR Gender (% male): 85.6 Comorbidities (%): Chronic Respiratory Failure: NR

Setting: ICU (1 site) Special Population: Post-cardiothoracic surgery (coronary artery bypass surgery); post-extubation ARF Type: Hypoxic Risk of Bias: Low	Exclusion: Pregnancy, chronic respiratory failure, combined cardiac surgery, alteration of consciousness or requiring immediate intubation, surgical complications requiring reoperation, hemodynamic instability or ventricular arrhythmia, adults subject to legal protection, already participating in an interventional study on oxygenation	RCI), humidified oxygen, flow 15 L/min; no continuous positive airway pressure (n=49 randomized, 43 in ITT analysis) Note: FiO_2 (HFNC group) or gas flow (HFFM group) adjusted according to SpO_2; both devices switched for a 50% Venturi mask every 6 hours day and night; if SpO_2 >96% with Venturi mask, HFNC or COT suspended; if treatment failed, protocol advised considering NIV; decision to perform invasive ventilation after NIV failure was left to discretion of physician; all patients received physiotherapy twice per day Follow-up: 24 hours (PaO_2/FiO_2 ratio); to ICU discharge for other outcomes	COPD: 6% of HFNC group Congestive Heart Failure: 32.4 Comorbidity Index (SAPS II): 26.5 Baseline characteristics: SpO_2 (median): HFNC: 94.6 COT: 94 Respiratory Rate (mean): 21.5/min PaO_2/FiO_2 ratio (mean): 140 pH (mean): 7.4 PaO_2: NR $PaCO_2$ (mean): 40.2

ABG=arterial blood gas; ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of COPD; AHRF=acute hypoxemic respiratory failure; AIDS=acquired immunodeficiency syndrome; APACHE II=Acute Physiology and Chronic Health Evaluation II; ARF=acute respiratory failure; BiPAP=Bilevel Positive Airway Pressure; BMI=body mass index; CABG=coronary artery bypass surgery; COPD=chronic obstructive pulmonary disease; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=Emergency Department; EPAP=expiratory positive airway pressure; FB=flexible bronchoscopy; FiO_2=fraction of inspired oxygen; GFR=glomerular filtration rate; HFFM=high-flow face mask; HFNC=high flow nasal cannulae; HFNO=high-flow nasal oxygen; HFOT=high-flow oxygen therapy; HVNI=high-velocity nasal insufflation; ICU=intensive care unit; IPAP=inspiratory positive airway pressure; ITT=intention-to-treat; NHF=nasal high flow; NIPPV=non-invasive positive pressure ventilation; NIV=non-invasive ventilation; NR=not reported; O_2=oxygen; PEEP=positive end-expiratory pressure; PBW=predicted body weight; RR=respiratory rate; SAPS II=Simplified Acute Physiology Score; SBT=spontaneous breathing trial; SNP=standard nasal prong; SBT=spontaneous breathing trial

Physiologic measures: SpO_2: peripheral capillary oxygen saturation; PaO_2/FiO_2 ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide

Comorbidity Indexes: APACHE II (Acute Physiology and Chronic Health Evaluation II): measured during the first 24h; scores range from 0 to 71; higher score is associated with increased risk of hospital death; a score of 25% represents a predicted mortality of 50%; a score of >35% represents a predicted mortality of 80%; Charlson: predicts the 10-year mortality for a patient based on 19 categories of comorbidities; higher scores indicate greater comorbidity and higher risk of death; scores range from 19 to 114; SAPS II (Simplified Acute Physiology Score)=scores range from 0 to 163 with higher scores indicating more severe disease

Supplementary Table 2. Risk of Bias Assessment for Included Studies

Author, Year Setting Follow-up Comparator	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data*	Selective Reporting†	Overall Risk of Bias‡
Azoulay, 2018 (27) ICU 28 days COT	Low	Low—electronic system	High	High—No blinding of adjudication was performed for outcome assessments.	Low—<1% excluded from analysis (withdrew consent)	Low	Moderate
Bell, 2015 (28) ED 2 hours COT	Low—computer-generated	Low—opaque envelopes. Does not state that they were sealed.	High	Unclear—NR	Low—no loss to follow-up	Low	Low
Cho, 2020 (56) ICU Not specified COT	Unclear—NR	Unclear—randomized under supervision of a statistician	High	Unclear—NR	Low—no loss to follow-up	Low	Moderate
Cong, 2019 (29) Hospital 12 hours & 5 days NIV	Unclear—says "randomized" but no info on random sequence	Unclear—NR	High	Unclear	Low—no loss to follow-up	Unclear	Moderate
Corley, 2015 (30) ICU 1 & 5 days COT	Low—computerized	Low—numbered opaque envelopes. Does not state that they were sealed.	High	Low—assessors blinded to treatment allocation for primary outcome	High—stabilized or transferred patients not recorded in PaO_2/FiO_2 ratio outcome data	Low	Moderate
Delorme, 2017 (31) Hospital (Mixed) Every 15 min for four periods COT	Unclear—NR	Unclear—NR	High	Low—all signals treatment and data analysis performed with evaluator blinded to condition	Low—1 patient withdrew consent	Low	Low
Doshi, 2018 (32)	Low—computer generated	Low—envelopes (unclear if opaque)	High	Unclear—data analysis was independent	High—10-11% did not receive	Unclear—disposition not reported	Moderate

Author, Year Setting Follow-up Comparator	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data*	Selective Reporting†	Overall Risk of Bias‡
Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV					intervention (not eligible post-randomization or withdrew consent) and were not included in analysis		
Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	Low	Low—central, Web-based	High	Unclear—investigators unaware of study-group outcomes prior to analysis	Low—<1% excluded from analysis	Low	Low
Grieco, 2020 (35) ICU 1 hour NIV (helmet)	Low—software	Low—sealed envelopes	High	Unclear	Low—no loss to follow-up	Unclear	Low
Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	Low—random - number generator	Low—telephone call center	Unclear—investigators did not participate in clinical decisions	Unclear—statistical analyses were blinded	Low—no loss to follow-up	Low	Low
Hernandez, 2016 (37) (high risk patients) ICU	Low—random-number generator	Low—telephone call center	Unclear—investigators did not participate in clinical decisions	Unclear—NR	Low—0.7% (4/604) discontinued or lost to follow-up	Low	Low

Author, Year Setting Follow-up Comparator	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data*	Selective Reporting†	Overall Risk of Bias‡
72 hours for reintubation; to hospital discharge for other outcomes NIV							
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	Low—random number table	Unclear—NR	High	Unclear—NR	Low—no loss to follow up	Unclear	Moderate
Jones, 2016 (40) ED NR COT	Low—computer generated	Low—sealed opaque envelopes	High	Low—treatment allocation masked before analysis	High—participant experience survey response rate 52.2%	Unclear—added post hoc outcome (mech ventilation within 24 hours)	Moderate
Maggiore, 2014 (42) ICU 48 hours COT	Low—random-number generator	Low—opaque envelopes (assume sealed?)	High	Unclear—database monitored by 3rd party with no direct study involvement	Low—no loss to follow-up	Low	Low
Makdee, 2017 (43) ED 1 hour (respiratory rate); other outcomes assessed at 24 hours and 7 days COT	Unclear—NR	Low—sealed opaque envelopes	High	Unclear—data analysis was blinded	Low—6% not included in analysis (change in diagnosis or early termination of treatment)	Low	Low
Matsuda, 2020 (58) ICU 1, 6, 24, and 48 hours; 5 and 7 days COT (heated, humidified)	Low—computer generated	Low—independent staff	High	Unclear—NR	Unclear—4% not included in primary outcome analysis; only 29% with long-term discomfort data	High—disability and dysfunction specified in Methods but NR	Moderate

Author, Year Setting Follow-up Comparator	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data*	Selective Reporting†	Overall Risk of Bias‡
Parke, 2011 (44) ICU 30 min, 1 hour, 2 hours, and 4 hours COT (HFFM)	Low—random numbers table	Low—opaque, sealed envelopes	High	Unclear—NR	Low—7% with missing data	Unclear	Low
Pilcher, 2017 (45) Hospital End of 2nd treatment phase (~90 min) COT	Low—computer generated	Low—sealed opaque envelopes	High	Unclear—NR	Unclear—up to 4/24 (17%) lost for some outcomes	Low	Low
Rittayamai, 2015 (46) ED 1 hour COT	Unclear—not reported	Unclear—"blind envelope pull"	High	Unclear—NR	Low—1 withdrawal, 1 missing data (5%); both included in analysis	Low	Moderate
Ruangsomboon, 2019 (47) ED 1 hour COT	Low—computer generated	Low—sealed opaque envelopes	High	High	Low—92% (44/48) analyzed after 1st period	Low	Moderate
Saksitthichok, 2019 (48) Hospital (General ward or intermediate care unit) 30 min NIV	Low—minimization method with stratification factors	Unclear—NR	High	Unclear—NR	Low—no loss to follow-up	Unclear	Moderate
Schwabbauer, 2014 (49) ICU 30 min COT & NIV	Unclear	Unclear—NR	High	Unclear—NR	Unclear—all patients completed HFNO and COT phases; 29% did	Unclear	Moderate

Author, Year Setting Follow-up Comparator	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data*	Selective Reporting†	Overall Risk of Bias‡
					not complete NIV phase		
Sklar, 2018 (50) Hospital ward End of 2nd treatment phase (~80 min) NIV	Unclear—NR	Low—sealed opaque envelopes	Unclear—NR	Unclear—NR; de-identified data	Unclear—all completed study; 2/15 (13%) without CO_2 measures due to technical difficulties	Unclear—device for respiratory rate not available for all patients	Moderate
Song, 2017 (51) ICU 24 hours COT	Low—computer generated	Unclear—NR	High—not blinded	Unclear—NR	Unclear—not ITT analysis; 17% of COT group received HFNO	Low	Moderate
Spoletini, 2018 (52) ICUs (5) or Intermediate Care Units (2) Through 6 breaks or until off NIV COT	Low—computer generated	Low—opaque envelopes	High	Unclear—NR	High—13% not included in analysis	Low	Moderate
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	Low—computer generated	Low—opaque envelopes	High—not blinded	Unclear—NR	Low—all included in primary analysis	Unclear—little data for ARF subgroup	Low
Vargas, 2015 (54) ICU 20 min COT & NIV (CPAP)	Unclear	Unclear	High	Unclear	Unclear Table 2 missing data for several outcomes in final COT treatment	Unclear—protocol has some different elements (e.g., 30-min interventions, HFNC flow rate) and patient preference outcome not prespecified	Moderate

Author, Year Setting Follow-up Comparator	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data*	Selective Reporting†	Overall Risk of Bias‡
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	Low – computer generated by study statistician	Low—opaque envelopes	High—not blinded	Low—follow-up team blinded to randomization group	Low—8% withdrew consent after randomization	Low	Low

ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=Emergency Department; HFFM=high-flow face mask; HFNC=high flow nasal cannulae; ICU=intensive care unit; ITT=intention-to-treat; NHF=nasal high flow; NIV=non-invasive ventilation; NR=not reported

*Incomplete outcome data was rated high if more than 10% of participants randomized were not included in the analyses.

†Selective reporting was determined by comparing reported outcomes with outcomes specified in the Methods section. If a protocol paper was available, reported outcomes were compared with outcomes specified in the protocol.

‡Due to the nature of the intervention and comparator, blinding of study participants and study personnel was not feasible. This element was not considered in rating overall risk of bias. Studies were rated High risk of bias if 2 additional elements were rated high risk of bias. Studies were rated Low risk of bias if at least 3 elements were rated low and no additional elements were rated high. All other studies were rated Moderate risk of bias.

Supplementary Table 3. Treatment Characteristics

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Azoulay, 2018 (27) ICU 28 days COT	Did not receive treatment as randomized due to discomfort 3.1% (12/389)	NR	Flow Rate: 50 L/min. Goal to achieve SpO_2 ≥95. FiO_2: 100 Temperature: NR Duration: NR Flow rates decreased until discomfort resolved. COT used (Venturi mask) if HFNC generated significant discomfort or skin breakdown.	O_2 Flow Rate: NR. Goal to achieve SpO_2 ≥95 Duration: NR	6 hours after randomization Flow Rate (median, [IQR]): 50 L/min [50-60] FiO_2: 70 [60-90] Temperature: NR Duration: NR	6 hours after randomization O_2 Flow Rate (median [IQR]): 8 [6-15] Duration: NR		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Bell, 2015 (28) ED 2 hours COT	NR	NR	Flow Rate: 50 L/min. Titrated depending on patient's condition and response to treatment FiO_2: 30% Temperature: NR Duration: 2 hours	O_2 Flow Rate: NR. Titrated depending on patient's condition and response to treatment Duration: 2 hours	Flow Rate: NR. Flow was titrated to patient's work of breathing with aim to meet or exceed the patients' inspiratory flow demand FiO_2: NR Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR			✓
Cho, 2020 (56) ICU Not specified COT	NR	NR	Flow Rate: 30-60 L/min. Adjusted based on respiratory rate FiO_2: adjusted so SpO_2 >90% adjusted so SpO_2 >90% Temperature: NR Duration: 72 hours	O_2 Flow Rate: adjusted so SpO_2 >90% Duration: NR	Flow Rate: 38.1 L/min at 72 hours (maximum of 43.9 L/min) FiO_2: NR Temperature: NR Duration: NR	Flow Rate: 2.2 L/min at 72 hours (maximum of 4.0 L/min) Duration: NR		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Cong, 2019 (29) Hospital 12 hours & 5 days NIV	NR	NR	Flow Rate: 30-35 L/min FiO_2: NR Temperature: 37°C Duration: NR	IPAP: 10 cm H20 EPAP: 5 cm H20, increased after patient adapted FiO_2: Adjusted to ensure oxygen saturation Duration: NR	Flow Rate: 30-35 L/min FiO_2: NR Temperature: 37°C Duration (mean): 9.6 days	IPAP: 10 cm H20 EPAP: 5 cm H20, increased after patient adapted FiO_2: Adjusted to ensure oxygen saturation Duration (mean): 10.0 days			✓

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Corley, 2015 (30) ICU 1 & 5 days COT	NR	NR	Flow Rate: 35 to 50 L/min, titrated to patient comfort FiO_2: Titrated to maintain SpO_2 of ≥95% Temperature: 37°C Duration: Minimum of 8 hours with short breaks. HFNC discontinued prior to ward transfer as HFNC was not accepted on the ward. Not possible to extend ICU stay.	O_2 Flow Rate: 2-4 L/min (nasal cannulae) or 6 L/min (face mask) titrated to maintain SpO_2 of ≥95% Duration: NR	Flow Rate (mean): 45.7 L/min FiO_2: NR Temperature: NR Duration (mean): 10.9 hours	O_2 Flow Rate: NR Duration: NR			✓

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Delorme, 2017 (31) Hospital (Mixed) Every 15 min for four periods COT	NR	NR	Flow Rate: 20, 40, and 60 L/min (random order to each patient) FiO_2: Adjusted to achieve target SpO_2 of 88-92% in hypercapnic patients and 92-96% in hypoxemic patients Temperature: 37°C Duration: 15 min	O_2 Flow Rate: NR. Adjusted to achieve SpO_2 of 88-92% in hypercapnic patients and 92-96% in hypoxic patients Duration: 15 min	Flow Rate: NR FiO_2: NR Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR	N/A. Treatments only administered for 15 min		
Doshi, 2018 (32) Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV	NR	NR	Flow Rate: 35 L/min FiO_2: 1.0 Temperature: 35-37°C Duration: NR	IPAP: 10-20 cm H2O EPAP: 5-10 cm H2O FiO_2: 1.0 Duration: NR	Flow Rate (mean): 30 L/min FiO_2: 0.62 Temperature: 35°C Duration: NR	IPAP: 13 cm H2O EPAP 6 cm H2O FiO_2: 0.57 Duration: NR	□		

Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	NR	NR	***HFNC*** Flow Rate: 50 L/min FiO_2: 1.0 Temperature: NR Duration: ≥2 days to maintain SpO_2 ≥92	***COT*** O_2 Flow Rate: ≥10 L/min Duration: To maintain SpO_2 ≥92 ***NIV*** IPAP: NR PEEP: 2-10 cm H2O Pressure support: Goal to obtain expired tidal volume of 7-10 ml per kg of predicted body weight FiO_2: NR. Adjusted to maintain SpO_2 ≥92 Duration: 8 hours/day, ≥2 days, at least ≥1 hour per session	Initial Mean Settings ***HFNC*** Flow Rate: 48 L/min FiO_2: 0.82 Temperature: NR Duration: NR **Immuno-compromised subgroup** Flow Rate: 45 L/min FiO_2: 0.78 Temperature: NR Duration: at least 1 hour, with minimum duration of 8 hours per day within first 48 hours	Initial Mean Settings ***COT*** O_2 Flow Rate: 13 L/min Duration: NR ***NIV*** IPAP: NR PEEP: 5 cm H2O Pressure support: 8 cm of H2O FiO_2: 0.67 Duration: median 8 hours on day 1 and day 2 **Immuno-compromised subgroup** ***COT*** O_2 Flow Rate: 13 Duration: NR ***NIV*** IPAP: NR PEEP: 5 cm H2O Pressure support: 9 cm of H2O FiO_2: 0.67 Duration: medians of 9 hours on day 1 and 8 hours on day 2			

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Grieco, 2020 (35) ICU 1 hour NIV (helmet)	NR	NR	Flow Rate: 50 L/min FiO_2: Titrated to obtain an $SpO_2 \geq 92\%$ and $\leq 98\%$ in initial 15 mins, then kept unchanged for remaining 45 mins of study step Temperature: 37°C initially, diminished in case of discomfort Duration: 1 hour	IPAP: 8-10 cm H2O initially, then adjusted to permit peak inspiratory flow of 100-150 L/min, up to maximum of 20 cm H2O PEEP: 10-12 cm H2O; flow trigger was 2 L/min and increased in presence of autotriggering FiO_2: Titrated to obtain an $SpO_2 \geq 92\%$ and $\leq 98\%$ in initial 15 mins, then kept unchanged for remaining 45 mins of study step Duration: 1 hour	Flow Rate: 50 L/min FiO_2 (median): 0.50 Temperature: NR Duration: 1 hour	IPAP: NR PEEP: 10 cm H20 (12 patients) and 12 cm H2O (3 patients) Pressure support (median): 12 cm H2O FiO_2 (median): 0.50 Duration: 1 hour	N/A. Treatments only administered for 1 hour		

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	NR	NR	Flow Rate: 10 L/min titrated to patient discomfort FiO_2: Adjusted to achieve SpO_2>92% Temperature: 37°C Duration: 24 hours	O_2 Flow Rate: Adjusted to maintain SpO_2 >92% Duration: NR	12 hours after extubation Flow Rate: 30.9 L/min FiO_2: 0.32 Temperature: NR Duration: 24 hours	12 hours after extubation O_2 Flow Rate: NR FiO_2: 0.40 Duration: NR		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Hernandez, 2016 (37) (high risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes NIV	Adverse events requiring treatment discontinuation for 25% or more of the per-protocol time (18 hours) 0% (0/290)	Adverse events requiring treatment discontinuation for 25% or more of the per-protocol time (18 hours) 42.9% (135/314) Note: Total time under NIV was only 14 hours (IQR 8-23) due to "adverse events" (nasal septum and skin trauma)	Flow Rate: 10 L/min titrated to patient discomfort FiO_2: Adjusted to achieve SpO_2>92% Temperature: 37°C, titrated down to 31°C Duration: 24 hours	Flow Rate: IPAP: 10 cm H2O; adjusted to target a RR of 25/min and SaO_2 of 92% PEEP: 5 cm H2O; adjusted to target a RR of 25/min and SaO_2 of 92% Pressure support: 8 cm H2O adjusted to achieve exhaled tidal volume of 8 mL/Kg FiO_2: Adjusted to maintain SpO_2 >92% Duration: 24 hours, then COT with Venturi mask	12 hours post-extubation Flow Rate: 50 L/min FiO_2: 35 [30, 40] Temperature: NR Duration: NR	12 hours post-extubation IPAP: NR EPAP: NR Pressure support: NR FiO_2: 40 [35, 50] Duration (median): 14 hours		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	Discontinued intervention 4.5% (1/22) Note: This patient was transferred to other hospital after 25 hours of HFNC	Discontinued intervention 0% (0/20)	Flow Rate: NR FiO_2: Adjusted to maintain SpO_2 of 88-92% Temperature: 37°C Duration: At least 8 hours/day in 48 hours post-extubation	IPAP: Initiated at 10-12 cmH_20 EPAP: Started at 4-5 cmH_20 FiO_2: Adjusted to maintain SpO_2 of 88-92% Duration: at least 8 hours/day in 48 hours post-extubation	Flow Rate (mean): 52.4 FiO_2: 0.40 Temperature: NR Duration (mean): 63.6 hours	Flow Rate: 5.7 L/min IPAP: 11.4 cmH_2O EPAP: 4.6 cmH_2O FiO_2: NR Duration (mean): 97.9 hours			✓
Jones, 2016 (40) ED NR COT	Did not tolerate HFNO within 120 minutes 8.5% (14/165) Switched to COT 9.7% (16/165) Note: Includes 14 patients who did not tolerate HFNO	NR	Flow Rate: Starting at 40 L/min FiO_2: 0.28 Temperature: 37°C Duration: NR	O_2 Flow Rate: 1-15 L/min titrated according to clinical need Duration: NR	Flow Rate: NR FiO_2: NR Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR			✓

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Lemiale, 2015 (41) ICU 2 hours COT	NR	NR	Flow Rate: 40-50 L/min initially FiO_2: 100% initially, then adjusted to maintain SpO_2 of at least 95% Temperature: NR Duration: 2 hours	O_2 Flow Rate: 15 L/min initially FiO_2: 60% initially, then adjusted to maintain SpO_2 of at least 95% Duration: 2 hours	Flow Rate: NR FiO_2: NR Temperature: NR Duration: 2 hours	O_2 Flow Rate: NR Duration: 2 hours	N/A. Treatments only administered for 2 hours.		
Maggiore, 2014 (42) ICU 48 hours COT	NR	NR	Flow Rate: 50 L/min FiO_2: Adjusted to obtain SaO_2 of 92-98% (88-95% if compensated hypercapnia) Temperature: NR Duration: 48 hours or to ICU discharge	O_2 Flow Rate: NR. Adjusted to obtain SaO_2 of 92-98% (88-95% if compensated hypercapnia) Duration: 48 hours or to ICU discharge	Flow Rate: NR FiO_2: NR Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Makdee, 2017 (43) ED 24 hours to 7 days COT	1.6% (1/63) discontinued after 10 min because of severe discomfort	None reported	Flow Rate: 35 L/min FiO_2: 0.5; adjusted to maintain O_2 saturation ≥95% Temperature: NR Duration: 1 hour	O_2 Flow Rate: NR; adjusted to maintain O_2 saturation ≥95% Duration: 1 hour	Flow Rate: NR FiO_2: NR Temperature: NR Duration (median, (range)): 175 min (10-560)	O_2 Flow Rate: 3 L/min Duration: NR	✓		
Matsuda, 2020 (58) ICU 1, 6, 24, and 48 hours; 5 and 7 days COT (heated, humidified)	NR	NR	Flow Rate: 50 L/min FiO_2: 0.4 adjusted to maintain SpO_2 of 88-95% Temperature: NR Duration: up to 48 hours	O_2 Flow Rate: NR; adjusted according to tidal volume; maintained adjusted to maintain SpO_2 of 88-95% Duration: up to 48 hours	Flow Rate: NR FiO_2: NR Temperature: NR Duration (in those not reintubated) 0-24 hours: 7% 24-48 hours: 43% ≥48 hours: 43%	O_2 Flow Rate: 3 L/min Duration: (in those not reintubated) 0-24 hours: 28% 24-48 hours: 41% ≥48 hours: 18%	✓		
Parke, 2011 (44) ICU 30 min, 1 hour, 2 hours, and 4 hours COT (HFFM)	NR	NR	Flow Rate: Started at initial flow of 35 L/min FiO_2: Titrated to SpO_2 or SaO_2 ≥ 95% Temperature: 37°C Duration: NR	O_2 Flow Rate: NR. Titrated to SpO_2 or SaO_2 ≥ 95% Temperature: 31°C Duration: NR	Flow Rate: NR FiO_2: NR Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR			✓

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Pilcher, 2017 (45) Hospital End of 2nd treatment phase (~90 min) COT	NR	NR	Flow Rate: 35 L/min FiO_2: NR Temperature: 37°C Duration: 30 min	O_2 Flow Rate: NR Duration: 30 min	Flow Rate: 35 L/min FiO_2: NR Temperature: NR Duration: 30 min	O_2 Flow Rate: NR Duration: 30 min		✓	
Rittayamai, 2015 (46) ED 1 hour COT	5.0% (1/20) randomized did not receive intervention due to intolerance (data included for analysis)	NR	Flow Rate: 35 L/min FiO_2: Adjusted to achieve SPO_2 ≥94% in first 5 min Temperature: 37°C Duration: 1 hour	O_2 Flow Rate: 3-10 L/min adjusted to maintain SPO_2 ≥94% Duration: 1 hour	Flow Rate: 35.5 L/min FiO_2: 0.45 Temperature: NR Duration: NR	O_2 Flow Rate: 5.6 Duration: NR			✓
Ruangsomboon, 2019 (47) ED 1 hour COT	4.2% (2/48) could not tolerate HFNC due to discomfort	0% (0/48)	Flow Rate: 35 L/min FiO_2: Goal to achieve SpO_2 ≥95 Temperature: NR Duration: 60 min	O_2 Flow Rate: NR. Goal to achieve SpO_2 ≥95 Duration: 60 min	Flow Rate: 37.5 L/min FiO_2: 0.70 Temperature: 34.5 Duration: 60 min	O_2 Flow Rate: 8.7 Duration: 60 min	N/A. Treatments only administered for 1 hour.		

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Saksitthichok, 2019 (48) General ward or intermediate care unit 30 min NIV	All patients tolerated mode of oxygenation		Flow Rate: 40 L/min FiO_2: 0.60 Temperature: NR Duration: 30 min	IPAP: Level that achieved tidal volume of 8 ml/kg or at least 10 cmH_2O EPAP: 5 cmH_2O FiO_2: 0.60 Duration: 30 min	Flow Rate: 40 L/min FiO_2: NR Temperature: NR Duration: 30 min, then appropriate modes considered according to primary physicians	Flow Rate (mean): 38.6 L/min. IPAP (mean):12.3 cmH_2O. PEEP: 5 cmH_2O. Pressure support (mean): 7.3 FiO_2: NR Duration: 30 min, then appropriate modes considered according to primary physician			✓

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Schwabbauer, 2014 (49) ICU 30 min COT & NIV	Stopped intervention phase prematurely 0% (0/14)	Stopped intervention phase prematurely NIV 21.4% (3/14) COT 0% (0/14)	Flow Rate: NR FiO_2: NR Temperature: NR Duration: 30 min	**NIV:** IPAP: NR EPAP: NR FiO_2: NR Duration: 30 min **COT:** O_2 Flow Rate: NR Duration: 30 min	Flow Rate: 55 L/min FiO_2: 0.6 Temperature: NR Duration: 30 min	**NIV:** IPAP: NR PEEP: 5 cm H_2O Pressure support: Adjusted individually to achieve tidal volume of 6-8 ml/kg ideal body weight. FiO_2: 0.60 Duration: 30 min **COT:** O_2 Flow Rate: 15 L/min FiO_2: 0.60 Temperature: Room temperature with bubble humidification Duration: 30 min	N/A. Treatments only administered for 30 min		

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Sklar, 2018 (50) Hospital ward End of 2nd treatment phase (~80 min) NIV	NR	NR	Flow Rate: Up to 55 L/min FiO_2: Adjusted to achieve SpO_2 of at least 92% Temperature: 37°C or 34°C (patient preference) Duration: 30 min	IPAP: 14 EPAP: 6 FiO_2: Adjusted to achieve SpO_2 of at least 92% Duration: 30 min	Flow Rate (median): 45 L/min FiO_2 (median): 30 Temperature: NR Duration: 30 min	IPAP (median): 14 EPAP (median): 6 FiO_2: NR Duration: 30 min		✓	
Song, 2017 (51) ICU 24 hours COT	NR	NR	Flow Rate: 60 L/min adjusted downward. Targeted SpO_2 94-98% if hypoxic respiratory failure, 88-92% if hypercapnic respiratory failure in both groups FiO_2: 40% Temperature: NR Duration: NR	O_2 Flow Rate: 10 L/min. Targeted SpO_2 94-98% if hypoxic respiratory failure, 88-92% if hypercapnic respiratory failure in both groups FiO_2: 40% Duration: NR	Flow Rate: 36.8 L/min FiO_2: 40% Temperature: NR Duration: NR	O_2 Flow Rate: NR FiO_2: 40% Duration: NR		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings				Treatment Weaning Criteria		
			Protocol		Received				
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Spoletini, 2018 (52) ICUs (5) or Intermediate Care Units (2) Through 6 breaks or until off NIV COT	NR	NR	Flow Rate: 35 L/min initially, adjusted to maintain oxygenation FiO_2: NR. Adjusted to maintain oxygenation Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR	Flow Rate: 38.5 L/min FiO_2: 39.4% Temperature: NR Duration: 520 min	O_2 Flow Rate: 4.8 L/min FiO_2: 40.8% Duration: 370 min		✓	
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	NR	NR	Flow Rate: 50 L/min FiO_2: 50%, adjusted at physician discretion to maintain SaO_2 at 92-98% Temperature: 37°C Duration: NR	IPAP: NR PEEP: 4 cm H2O Pressure support: Starting at 8 cm H2O and increased to achieve 8 mL/kg and respiratory rate <25/min FiO_2: 50% initially, then adjusted to maintain SaO_2 of 92-98% Duration: 2 hours, then 1 hour every 4 hours	Flow Rate: NR FiO_2: NR Temperature: NR Duration (average per day over 3 days for entire study population): 6.4 hours	IPAP: NR PEEP: 4 cm H2O Pressure support: 8 cm H2O FiO_2: 50% Duration: 19.3 hours		✓	

Author, Year Setting Follow-up Comparator	Intolerance		Treatment Settings Protocol		Treatment Settings Received		Treatment Weaning Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Vargas, 2015 (54) ICU 20 min COT & NIV (CPAP)	NR	NR	Flow Rate: 60 L/min FiO_2: Same level as NIV Temperature: 37°C Duration: 20 min	**COT** O_2 Flow Rate: NR. Goal to achieve SpO_2 >90% Duration: 20 min **NIV (CPAP)** Pressure: 5 cm H_2O FiO_2: Same level as HFNC session Duration: 20 min	Flow Rate: 60 L/min FiO_2 (median): 0.61 Temperature: 37°C Duration: 20 min	**COT** O_2 Flow Rate: NR. Goal to achieve SpO_2 >90% FiO_2: 0.65 (first treatment); NR (last treatment) Duration: 20 min **NIV (CPAP)** Pressure: 5 cm H_2O FiO_2: 0.6 Duration: 20 min	N/A. Treatments only administered for 20 min		
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	NR	NR	Flow Rate: 45 L/min FiO_2: 100%; adjusted according to SpO_2 Temperature: 37°C Duration: 48 hours	O_2 Flow Rate: 15 L/min assuming this gas flow corresponded to an FiO_2 of 100%; adjusted according to SpO_2 Duration: 48 hours	Flow Rate: NR FiO_2: NR Temperature: NR Duration: NR	O_2 Flow Rate: NR Duration: NR		✓	

ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=Emergency Department; EPAP=expiratory positive airway pressure; FiO_2=fraction of inspired oxygen; HFFM=high-flow face mask; HFNC=high flow nasal cannulae; HFNO=high-flow nasal oxygen; ICU=intensive care unit; IPAP=inspiratory positive airway pressure;

IQR=interquartile range; N/A=not applicable; NIV=non-invasive ventilation; NR=not reported; O_2=oxygen; PEEP=positive end-expiratory pressure; SpO_2=peripheral capillary oxygen saturation

Supplementary Table 4. Patient-Centered Outcomes, Part 1

Author, Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean (SD) days unless indicated)		Length of Hospital Stay (mean (SD) days unless indicated)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Azoulay, 2018 (27) ICU 28 days COT	28 day 35.6% (138/388) RD -0.5% (95CI -7.3%, 6.3%) HR 0.98 (95%CI 0.8, 1.2), P=.94	28 day 36.1% (140/388)	N/A	N/A	Median [IQR] 8 [4-14] Mean difference 0.6 (95%CI -1.0, 2.2), P=.07	Median [IQR] 6 [4-13]	Median [IQR] 24 [14-40] Mean difference -2.0 (95%CI -7.3, 3.3), P=.60	Median [IQR] 27 [15-42]

Author, Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean (SD) days unless indicated)		Length of Hospital Stay (mean (SD) days unless indicated)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bell, 2015 (28) ED 2 hours COT	NR	NR	18.8% (9/48), P=.92 Time Assessed: NR Note: There were not standard ICU admission criteria across sites. All patients receiving HFNC at one hospital were required to be admitted to the high dependency unit due to staffing constraints on the ward.	19.2% (10/52) Time Assessed: NR	NR	NR	NR	NR
Cho, 2020 (56) ICU Not specified COT	29.0% (9/31), P=.46	20.7% (6/29)	N/A	N/A	14.7 (9.6), P=.78	13.8 (15.7)	37.7 (25.8), P=.05	25.7 (20.9)
Cong, 2019 (29) Hospital 12 hours & 5 days NIV	NR	NR	N/A	N/A	NR	NR	18.0 (6.2), P=.83	18.3 (7.0)
Corley, 2015 (30) ICU 1 & 5 days COT	NR	NR	N/A	N/A	38.7 (35.2) hours, P=.99	38.6 (23.9) hours	NR	NR

Author, Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean (SD) days unless indicated)		Length of Hospital Stay (mean (SD) days unless indicated)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Doshi, 2018 (32) Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV	NR	NR	46.2% (48/104)	47.0% (47/100)	3.3 (3.7) Mean difference -0.6 (95%CI -2.2, 1.0) **AECOPD/ hypercapnic ADF subgroup** Median: 1.8 P=.07	3.9 (4.1) **AECOPD/ hypercapnic ADF subgroup** Median: 2.5	6.8 (5.7) Mean difference 0.8 (95%CI -0.6, 2.2) **AECOPD/ hypercapnic ADF subgroup** Median: 4.4 P=.68	6.0 (4.4) **AECOPD/ hypercapnic ADF subgroup** Median: 5.0

Frat, 2015 (34) Frat, 2016 (33) (immune-compromised subgroup) ICU 28 days COT & NIV	Hospital mortality 11.3% (12/106) P<0.01 ICU mortality 11.3% (12/106) Overall P=.047 90 day 12.3% (13/106) Overall P=.02 PaO_2/FiO_2 ratio ≤200 subgroup ICU mortality 12.0% (10/83) Overall P=.03 90 day 13.3% (11/83)	Hospital mortality ***COT:*** 21.3% (20/94) ***NIV:*** 28.2% (31/110) ICU mortality ***COT:*** 19.1% (18/94) OR 1.85 (95%CI 0.8, 4.1) ***NIV:*** 24.5% (27/110) OR 2.6 (95%CI 1.2, 5.4) 90 day ***COT:*** 23.4% (22/94) HR 2.0 (95%CI 1.0, 4.0) ***NIV:*** 28.2% (31/110) HR 2.5 (95%CI 1.3, 4.8) PaO_2/FiO_2 ratio ≤200 subgroup ICU mortality ***COT:*** 21.6% (16/74) ***NIV:*** 28.4% (23/81) 90 day ***COT:***	N/A	N/A	Assessed at day 90 Survivors (n=93) 10.7 (15.8) Non-survivors (n=13) 14.9 (13.6) Overall P=.57 PaO_2/FiO_2 ratio ≤200 subgroup Survivors 10.0 (14.9) Non-survivors 15.9 (14.4) Overall P=.96	Assessed at day 90 ***COT*** Survivors (n=72) 9.1 (11.7) Non-survivors (n=22) 21.6 (19.9) ***NIV*** Survivors (n=79) 11.0 (11.6) Non-survivors (n=31) 15.7 (13.7) PaO_2/FiO_2 ratio ≤200 subgroup ***COT*** Survivors 8.3 (6.9) Non-survivors 18.1 (14.8) ***NIV*** Survivors 12.4 (13.1) Non-survivors 14.9 (13.2)	NR	NR

Author, Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean (SD) days unless indicated)		Length of Hospital Stay (mean (SD) days unless indicated)	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
	Overall P=.01 **Immuno-compromised subgroup** ICU mortality 15.4% (4/26) Overall P=.06 90 day 15.4% (4/26), Overall P=.046	27.0% (20/74) ***NIV:*** 32.1% (26/81) **Immuno-compromised subgroup** ICU mortality ***COT:*** 20.0% (6/30) ***NIV:*** 42.3% (11/26) 90 day ***COT:*** 26.7% (8/30) ***NIV:*** 46.2% (12/26)						
Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	Hospital 3.8% (10/264), P=.94 Mean Difference 1.2 (95%CI -2.5, 4.9)	Hospital 5.0% (13/263)	N/A	N/A	Median [IQR] days 6 [2–8] P=.29 Absolute difference 0 (95%CI -10, 24)	Median [IQR] days 6 [2–9]	Median [IQR] days 11 [6-15] P=.76 Absolute difference 4 (95%CI -28, 32)	Median [IQR] days 12 [6-16]
Hernandez, 2016 (37) (high risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes NIV	Hospital 20.3% (59/290), P=.94 Mean Difference -2.5 (95%CI -8.8, 3.8)	Hospital 17.8% (56/314)	N/A	N/A	Median [IQR] days 3 [2–7] Absolute difference 1 (95%CI -0.1, 2.1)	Median [IQR] days 4 [2–9]	Median [IQR] days 23 [14-46] Absolute difference -3 (95%CI -6.8, -0.8)	Median [IQR] days 26 [16-37]

Author, Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean (SD) days unless indicated)		Length of Hospital Stay (mean (SD) days unless indicated)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	28 day 22.7% (5/22), X^2=.036, P=.85	28 day 25% (5/20)	N/A	N/A	8.5 (3.5), Z=.827, P=.41	9.4 (4.8)	NR	NR
Jones, 2016 (40) ED NR COT	90 day 21.2% (35/165), P=.40 In-hospital 9.1% (15/165), P=.73	90 day 17.4% (24/138) In-hospital 8.0% (11/138)	4.8% (8/165), P=.60	3.6% (5/138)	NR	NR	Median [IQR] days 5 [2.8, 8.3], P=.43	Median [IQR] days 5.6 [2.8, 9.3]
Maggiore, 2014 (42) ICU 48 hours COT	At ICU discharge 11.3% (6/53) P=.77	At ICU discharge 9.6% (5/52)	N/A	N/A	11.7 (10.2), P=.44	10.4 (8.5)	NR	NR
Makdee, 2017 (43) ED 24 hours to 7 days COT	7 day 1.6% (1/63) Mean difference -1.6 (95%CI -4.7, 1.5)	7 day 0% (0/65)	NR	NR	NR	NR	Median (range) 1.1 (0.1, 27.6) Mean difference 0.1 (95%CI -0.9, 2.3)	Median (range) 1.2 (0.1, 17.4)
Matsuda, 2020 (58) ICU 1, 6, 24, and 48 hours; 5 and 7 days COT (heated, humidified	NR	NR	N/A	N/A	Within 7 days after extubation 4.4 (1.8) Mean difference 0.6 (95%CI -0.30, 1.46), P=.19	Within 7 days after extubation 3.8 (1.8)	NR	NR

Author, Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N)		ICU Admissions and/or Transfers (mean (SD) days unless indicated)		Length of Hospital Stay (mean (SD) days unless indicated)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Parke, 2011 (44) ICU 30 min, 1 hour, 2 hours, and 4 hours COT (HFFM)	NR	NR	N/A	N/A	Not significantly different between groups, P=.20		Not significantly different between groups, P=.11	
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	ICU 6.8% (28/414) Data for entire study population	ICU 5.5% (23/416)	N/A	N/A	Median [IQR] 6 [4, 10], P=.77 Data for entire study population	Median [IQR] 6 [4, 10] days	Median [IQR] 13 [9, 22], P=.59 Data for entire study population	Median [IQR] 14 [9, 20]
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	ICU 0% (0/47)	ICU 0% (0/43)	N/A	N/A	3.3 (2.4), P=.64 Mean Difference 0.2 (05%CI -0.7, 1.1)	3.1 (1.6)	NR	NR

ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; CI=confidence interval; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=Emergency Department; FB=flexible bronchoscopy; HFFM=high-flow face mask; HFNC=high flow nasal cannulae; HFNO=high-flow nasal oxygen; HR=hazard ratio; HVNI=high-velocity nasal insufflation; ICU=intensive care unit; IMV=invasive mechanical ventilation; NA=not applicable; NHF=nasal high flow; NIPPV=non-invasive positive pressure ventilation; NIV=non-invasive ventilation; NR=not reported; NS=not significant; O_2=oxygen; OR=odds ratio

Supplementary Table 5. Patient-Centered Outcomes, Part 2

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Azoulay, 2018 (27) ICU 28 days COT	NR	Received HFNC (did not receive treatment as randomized) 7.7% (30/389)	38.7% (150/388) Mean difference -5.1 (95%CI -12.3, 2.0) HR 0.85 (95%CI 0.7, 1.1), P=.17	43.8% (170/388)	NR	NR		✓	
Bell, 2015 (28) ED 2 hours COT	Escalation in ventilation therapy 4.2% (2/48), P=.02 2 patients escalated to NIV within 2 hours	Escalation in ventilation therapy 19.2% (10/52) 2 patients escalated to NIV, 7 patients escalated to HFNO, and 1 intubated.	0% (0/48)	1.9% (1/52)	NR	NR			✓
Cho, 2020 (56) ICU Not specified COT	NR	NR	9.7% (3/31), P=.61	3.5% (1/29)	NR	NR		✓	
Corley, 2015 (30) ICU 1 & 5 days COT	Required NIPPV w/in 24 hours 3.7% (3/81)	Required NIPPV w/in 24 hours 1.4% (1/74) Required HFNC 4.1% (3/74)	Required IPPV w/in 24 hours 0% (0/81)	Required IPPV w/ in 24 hours 1.4% (1/74)	NR	NR			✓

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Doshi, 2018 (32) Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV	Not responding to HVNI, received NIV 85.2% (23/27) **AECOPD/ hypercapnic ADF subgroup** Crossover to NIV 23.5% (8/34), P=.35	Not responding to NIV, received HVNI 35.3% (6/17) **AECOPD/ hypercapnic ADF subgroup** Crossover to HVNI 12.9% (4/31)	6.7% (7/104) (95%CI 2%, 12%) Risk difference -6% (95%CI -14%, 2%) **ADHF subgroup** 0% (0/22) **AECOPD/ hypercapnic ADF subgroup** 5.9% (2/34), P=.24	13.0% (13/100) (95%CI 6%, 20%) **ADHF subgroup** 0% (0/20) **AECOPD/ hypercapnic ADF subgroup** 16.1% (5/31)	NR	NR		✓	

Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	NR	NR	At day 28 37.7% (40/106), Overall P=.18 PaO_2/FiO_2 ratio ≤200 subgroup 34.9% (29/83), Overall P=.009 **Immuno-compromised subgroup** 30.7% (8/26), Overall P=.04	At day 28 ***COT:*** 46.8% (44/94) OR 1.45 (95%CI 0.8, 2.6) ***NIV:*** 50.0% (55/110) OR 1.7 (95%CI 1.0, 2.8) PaO_2/FiO_2 ratio ≤200 subgroup ***COT:*** 52.7% (39/74) OR 2.1 (95%CI 1.1, 3.9) ***NIV:*** 58.0% (47/81) OR 2.6 (95%CI 1.4, 4.8) **Immuno-compromised subgroup** ***COT*** 43.3% (13/30) OR 1.7 (95%CI 0.6, 5.2) ***NIV*** 65.4% (17/26) OR 4.3 (95%CI 1.3, 13.6)	NR	NR		✓	

Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	Postextubation respiratory failure 8.3% (22/264) Difference 6.1 (95%CI 0.7, 11.6); P=.03 Note: Rescue therapy with NIV was strongly discouraged	Postextubation respiratory failure 14.4% (38/263)	Reintubation within 72 hours 4.9% (13/264), P=.004 Absolute difference 7.2% (95%CI 2.5, 12.2) OR 0.3 (95%CI 0.2, 0.7) Sensitivity analysis Medical patients without respiratory failure 3.8% (5/132) Absolute difference -8.7% (95%CI -15.3, -2.2) OR 0.3 (95%CI 0.1, 0.8) Surgical patients 6.1% (8/131) Absolute difference -9.7% (95%CI -17.8, -20) OR 0.4 (95%CI 0.1, 0.9)	Reintubation within 72 hours 12.2% (32/263) Sensitivity analysis Medical patients without respiratory failure 12.5% (19/152) Surgical patients 15.8% (19/120)	NR	NR		✓	

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Hernandez, 2016 (37) (high risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes NIV	Postextubation respiratory failure 26.9% (78/290) Difference 12.9 (95%CI 6.6, ∞) Note: Rescue therapy with NIV was not allowed	Postextubation respiratory failure 39.8% (125/314)	Reintubation within 72 hours 22.8% (66/290) Difference (one-sided non-inferiority analysis) -3.7 (95%CI -9.1, ∞) OR 1.25 (95%CI 0, 1.74)	Reintubation within 72 hours 19.1% (60/314)	NR	NR		✓	
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	Required NIV w/in 48 hours post-extubation 4.5% (1/22) Post-extubation respiratory failure 13.6% (3/22)	Post-extubation respiratory failure 5.0% (1/20)	Reintubation w/in 48 hours post-extubation 9.1% (2/22), X^2=0.007, P=.93	Reintubation w/in 48 hours post-extubation 5.0% (1/20)	NR	NR		✓	
Jones, 2016 (40) ED NR COT	Mechanical ventilation within 24 hours (post hoc) 5.5% (9/165) (95%CI 2.8, 10.2) (n=9/165), P=.053 Note: Includes NIV and IMV	Mechanical ventilation within 24 hours (post hoc) 11.6% (16/138) (95%CI 7.2, 18.1) (n=16/138) Note: Includes NIV and IMV	0.6% (1/165), P=.33	2.2% (3/138)	NR	NR		✓	

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
		1 patient became apneic, 7 patients had decreased Glascow coma score (3 due to acute hypercapnia)							
Lemiale, 2015 (41) ICU 2 hours COT	NIV 11.5% (6/52) NIV or IMV 15.4% (8/52), P=.36	NIV 6.3% (3/48) NIV or IMV 8.3% (4/48)	Intubated 7.7% (4/52)	Intubated 4.2% (2/48)	NR	NR		✓	
Maggiore, 2014 (42) ICU 48 hours COT	Requiring any form of ventilator support 7.5% (4/53), P<.001 NIV 3.8% (2/53), P=.04	Requiring any form of ventilator support 34.6% (18/52) NIV 15.4% (8/52)	Reintubation within 48 hours 3.8% (2/53) P=.005 4 additional patients were reintubated after 48 hour study period	Reintubation within 48 hours 21.2% (11/52) (Includes 1 patient who went from NIV to invasive ventilation) 5 additional patients were reintubated after 48 hour study period	NR	NR		✓	
Makdee, 2017 (43) ED 24 hours to 7 days COT	Conversion to NIV within 24 hours 1.6% (1/63)	Conversion to NIV within 24 hours 4.6% (3/65)	Within 24 hours 1.6% (1/63) Mean difference -1.6 (95%CI	Within 24 hours 0% (0/65)	NR	NR		✓	

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
	Mean difference 3 (95%CI -3.1, 9.2)		-4.7, 1.5)						
Matsuda, 2020 (58) ICU 1, 6, 24, and 48 hours; 5 and 7 days COT (heated, humidified	NIV within 48 hours 0% (0/30) Reintubation or NIV within 48 hours 7% (2/30) OR 0.28 (95%CI 0.03-1.58), P=.17	NIV within 48 hours 8% (3/39) Reintubation or NIV within 48 hours 13% (5/39)	Within 48 hours 7% (2/30) OR 0.49 (95%CI 0.04, 3.28), P=.69 Within 7 days 17% (5/30) OR 1.10 (95%CI 0.24, 4.88), P>.99	Within 48 hours 13% (5/39) Within 7 days 15% (6/39)	NR	NR		✓	
Parke, 2011 (44) ICU 30 min, 1 hour, 2 hours, and 4 hours COT (HFFM)	Required NIV 10.3% (3/29), P=.10 Received COT (HFFM) 0% (0/29) “Success” (maintained on or weaned from assigned O_2 therapy w/in 24 hours of enrollment)	Required NIV 29.6% (8/27) Received NHF 18.5% (5/27) Note: Includes 1 who received NHF and NIV “Success” (maintained on or weaned from assigned O_2 therapy w/in 24 hours of enrollment) 55.6% (15/27)	NR	NR	NR	NR	N/A. Intubation not reported		

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
	90.0% (26/29), P=.006 "Failed" (worsening respiratory failure requiring change in respiratory-support device w/in 24 hours of study enrollment; determined by treating clinician) 10.3% (3/29), P=.006	"Failed" (worsening respiratory failure requiring change in respiratory-support device w/in 24 hours of study enrollment; determined by treating clinician) 44.4% (12/27)							
Rittayamai, 2015 (46) ED 1 hour COT	Conversion to NIV 0% (0/20)	Conversion to NIV 0% (0/20)	0% (0/20)	0% (0/20)	NR	NR			✓
Song, 2017 (51) ICU 24 hours COT	Treatment failure 10.0% (3/30), P=.012 Conversion to NIV 6.7% (2/30), P=.64	Treatment failure 36.7% (11/30) Conversion to NIV 3.3% (1/30) Conversion to HFNC 16.7% (5/30)	3.3% (1/30), P=.29	10.0% (3/30)	NR	NR		✓	
Spoletini, 2018 (52)	NR	NR	8.7% (2/23)	0% (0/24)	NR	NR			✓

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
ICUs (5) or Intermediate Care Units (2) Through 6 breaks or until off NIV COT									
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	Treatment failure (reintubation, switch to other study treatment or premature study-treatment discontinuation (patient request or medical reason) 28.7% (79/275), P=NS Data from inclusion criteria #1 and #3 patients	Treatment failure 27.2% (72/265)	Reintubation 13.8% (57/414) Data for entire study population	Reintubation 13.7% (54/416)	NR	NR		✓	

Author, Year Setting Follow-up Comparator	Treatment Escalation (not intubation) % (n/N)		Intubation % (n/N)		Intubation (mean # of days)		Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	NIV for treatment failure 27.7% (13/47), P=.007 Mean Difference -28 (95%CI -48, -9) NIV or intubation for treatment failure 34.0% (16/47) Received COT (HFFM) during first[t] hour 8.5% (4/47) Note: Unclear if these cases are also included in NIV cases above; these cases not included in pooled analysis	NIV for treatment failure 55.8% (24/43) NIV or intubation for treatment failure 58.1% (25/43) Received HFNC during first hour 2.3% (1/43)	Reintubation 6.4% (3/47), P=.75 Mean Difference 4 (95%CI -4.3, 12.4)	Reintubation 2.4% (1/42)	NR	NR	✓		

ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HFNO=high flow nasal oxygen; HVNI=high-velocity nasal insufflation; HFNC=high flow nasal cannula; HR=hazard ratio; ICU=intensive care unit; IMV= invasive mechanical ventilation; IPPV=intermittent positive-pressure ventilation; NIPPV= Non-invasive positive pressure ventilation NIV=non-invasive ventilation; N/A=not applicable; NHF=nasal high flow; NR=not reported; OR=odds ratio; VAS=visual analog scale

Supplementary Table 6. Patient-Centered Outcomes, Part 3

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Azoulay, 2018 (27) ICU 28 days COT	NR	NR	NR	NR	NR	NR	Patient Comfort (0 [severe discomfort] to 10 [perfect comfort]) Baseline 6.0 (n=388) 6 Hours 6.3 (n=321) 7 Days 7.9 (n=63) P NS (all time points) Data from plots Dyspnea (0 [none] to 10 [severe]) Baseline 5.6 (n=388) 6 Hours 4.6 (n=309) 7 Days 2.3 (n=61) P NS (all time points) Data from plots	Patient Comfort (0 [severe discomfort] to 10 [perfect comfort]) Baseline 6.0 (n=388) 6 Hours 6.3 (n=314) 7 Days 6.8 (n=49) Dyspnea (0 [none] to 10 [severe]) Baseline 5.4 (n=388) 6 Hours 4.2 (n=289) 7 Days 2.6 (n=47)

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bell, 2015 (28) ED 2 hours COT	ICU 18.8% (9/48), P=.92 Discharged from ED 10.4% (5/48), P=.63	ICU 19.2% (10/52) Discharged from ED 7.7% (4/52)	NR	NR	NR	NR	Patient Comfort Score (1-5; higher=very comfortable; assessed at 1-hour post commencement of O_2 therapy) (median, [IQR]) 4 [3-4], P=.035 % of patients who had reduction in Borg score w/in 2 hours of commencement of treatment 75.0% (36/48), P=.044	Patient Comfort Score (median, [IQR]) 3 [2-4] % of patients who had reduction in Borg score 55.8% (29/52)
Cong, 2019 (29) Hospital 12 hours & 5 days NIV	NR	NR	NR	NR	NR	NR	Patient comfort (% "feeling comfort," assessed by hospital-designed questionnaire. Time of assessment NR) 88.2%, P=.008	Patient comfort (% "feeling comfort," assessed by hospital-designed questionnaire. Time of assessment NR) 67.9%
Corley, 2015 (30) ICU 1 & 5 days COT	NR	NR	NR	NR	NR	NR	Dyspnea score (modified Borg scale; 0=no dyspnea, 10=maximal dyspnea) (median, [IQR]) 1-hour post extubation 1 [0, 2], P=.09 8 hours post extubation 1 [0, 3], P=.008 Authors report that difference is not clinically relevant	Dyspnea score (median, [IQR]) 1-hour post extubation 0 [0, 2] 8 hours post extubation 0 [0, 1]

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Delorme, 2017 (31) Hospital (Mixed) Every 15 min for four periods COT	NR	NR	NR	NR	NR	NR	Comfort (VAS scale) (median, [IQR]) Assessed after 15 min 20 L/min: 9 [8, 9] 40 L/min: 8 [7, 9] 60 L/min: 8 [7, 9], P=.28 Dyspnea (modified Borg scale) (median, [IQR]) 20 L/min: 1, [0, 2] 40 L/min: 2, [1, 4] 60 L/min: 3, (1, 4) P=.03	Comfort (VAS scale) (median, [IQR]) Assessed after 15 min 9 [8, 9] Dyspnea (modified Borg scale) (median, [IQR]): 2 [1, 3]

Doshi, 2018 (32) Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV	NR	NR	NR	NR	NR	NR	Comfort (VAS 0 to 5; 5=extreme discomfort) (median (min, max)) Baseline (n=103) 4.0 (0, 5) 30 Min (n=95) 3.0 (0, 5) 240 Min (n=72) 2.0 (0, 4) Dyspnea (modified Borg scale 1-10; higher=greater exertion) Baseline (n=102) 6.3 (3.0) Mean difference -0.2 (95%CI -1.0, 0.6) 30 Min (n=94) 4.4 (2.3) Mean difference 0.1 (95%CI -0.6, 0.8) 240 Min (n=71 2.6 (2.0) Mean difference 0.4 (95%CI -0.2, 1.0) **Dyspnea--ADHF Subgroup** (modified Borg score) (median) Baseline (n=22): 6 30 Min (n=21): 4 240 Min (n=21): 2 **Dyspnea—AECOPD/hypercapnic ARF Subgroup**	Comfort (median (min, max)) Baseline (n=92) 4.0 (0, 5) 30 Min (n=85) 3.0 (0, 5) 240 Min (n=69) 2.0 (0, 5) Dyspnea (modified Borg scale 1-10; higher=greater exertion) Baseline (n=93) 6.5 (2.6) 30 Min (n=86) 4.3 (2.7) 240 Min (n=72) 2.2 (1.8) **Dyspnea--ADHF Subgroup** (modified Borg score) (median) Baseline (n=20): 7 30 min (n=20): 4 240 min (n=17): 2 **Dyspnea—AECOPD/hypercapnic ARF Subgroup**

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
							(modified Borg score) (median) Baseline (n=33): 7 30 Min (n=33): 4 240 Min (n=28): 2	(modified Borg score) (median) Baseline (n=29): 7 30 Min (n=29): 4 240 Min (n=24): 3

Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	NR	NR	NR	NR	NR	NR	Patient discomfort (VAS 1-100 mm; “no discomfort” to “maximal discomfort”) (n=106) Baseline 38 (31) At 1 hour 29 (26), Overall P<.01 Dyspnea (grade at 1 hour) Marked improvement 22.1% (19/86) Slight Improvement 53.5% (46/86) No Change 20.9% (18/86) Slight deterioration 3.5% (3/86) Marked deterioration 0% (0/86) Overall P<.001	Patient discomfort ***COT*** (n=94) Baseline 44 (29) At 1 hour 40 (29) ***NIV*** **(**n=110) Baseline 46 (30) At 1 hour 43 (29) Dyspnea (grade at 1 hour) ***COT*** Marked improvement 6.8% (5/74) Slight Improvement 35.1% (26/74) No Change 44.6% (33/74) Slight deterioration 12.2% (9/74) Marked deterioration 1.3% (1/74) ***NIV*** Marked improvement 14.3% (13/91) Slight Improvement 44.0% (40/91) No Change 25.3% (23/91) Slight deterioration 8.8% (8/91) Marked deterioration 7.7% (7/91)

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Grieco, 2020 (35) ICU 1 hour NIV (helmet)	NR	NR	NR	NR	NR	NR	Device-related discomfort (VAS; 0=no discomfort, 10=extreme discomfort) (median, [IQR]) 5 [3,7], P=0.5 Dyspnea (VAS; 0=no shortness of breath, 10= extreme shortness of breath) (median, [IQR]) 8 [6,9], P=.002	Device-related discomfort (VAS; 0=no discomfort, 10=extreme discomfort) (median, [IQR]) 5 [2,6] Dyspnea (VAS; 0=no shortness of breath, 10= extreme shortness of breath) (median, [IQR]) 3 [2,5]
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	NR	NR	NR	NR	NR	NR	Comfort Score (1-10; 1=very comfortable, 10=very uncomfortable) 3.6 (1.9), t=2.345, P=.02 Time assessed: NR	Comfort Score (1-10; 1=very comfortable, 10=very uncomfortable) 5.2 (2.3) Time assessed: NR
Jones, 2016 (40) ED NR COT	NR	NR	NR	NR	NR	NR	Patient satisfaction survey (6 questions, Likert scale; 1=Strongly Disagree, 5=Strongly Agree; % with Agree or Strongly Agree) 1.O_2 delivery method was comfortable 74.2% (69/94), P=.08 2.Breathing did not improve	Patient satisfaction survey (6 questions, Likert scale; 1=Strongly Disagree, 5=Strongly Agree; % with Agree or Strongly Agree) 1.O_2 delivery method was comfortable 85.9% (55/64) 2.Breathing did not improve

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
							20.4% (19/93), P=.24 3. O_2 dried out nose or mouth 29.8% (28/94), P=.046 4. Breathing got easier 81.7% (76/93), P=.15 5. If needed O_2 again, I would be happy with this method 76.3% (71/93), P=.044 6.O_2 delivery was worse than what had before 20% (17/85), P=.01 Survey response rate: 52%	28.6% (18/63) 3. O_2 dried out nose or mouth 45.3% (29/64) 4. Breathing got easier 71.9% (46/64) 5. If needed O_2 again, I would be happy with this method 89.1% (57/64) 6.O_2 delivery was worse than what had before 5.3% (3/57)
Lemiale, 2015 (41) ICU 2 hours COT	NR	NR	NR	NR	NR	NR	Discomfort (VAS score at 120 min) (median, [IQR]) 3 [1, 5], P=.88 Dyspnea (VAS score at 120 min) (median, [IQR]) 3 [2,6], P=.87	Discomfort (VAS score at 120 min) (median, [IQR]) 3 [0, 5] Dyspnea (VAS score at 120 min) (median, [IQR]) 3, [1,6]

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Maggiore, 2014 (42) ICU 48 hours COT	NR	NR	NR	NR	NR	NR	Discomfort related to interface (0=no discomfort, 10=maximum discomfort) Assessed at 24 hours 2.6 (2.2), P=.006 Discomfort related to airway dryness (0=no discomfort, 10=maximum discomfort) Assessed at 24 hours 2.2 (1.8), P=.002 Other symptoms during 48 hour study Mouth dryness: 3.6 (2.5), P=.016 Throat dryness: 2.7 (2.4), P=.002 Difficulty swallowing: 2.5 (2.6), P=.007 Throat pain: 1.7 (2.1), P=.008	Discomfort related to interface (0=no discomfort, 10=maximum discomfort) Assessed at 24 hours 5.1 (3.3) Discomfort related to airway dryness (0=no discomfort, 10=maximum discomfort) Assessed at 24 hours 3.7 (2.4) Other symptoms during 48 hour study Mouth dryness: 5.0 (3.1) Throat dryness: 4.5 (3.3) Difficulty swallowing: 4.1 (3.4) Throat pain: 3.1 (3.4)

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Makdee, 2017 (43) ED 24 hours to 7 days COT	Discharged from ED 28.6% (18/63) Admitted to hospital 31.7% (20/63) Observation room 41.3% (26/63) Transfer to different hospital 4.8% (3/63)	Discharged from ED 29.2% (19/65) Admitted to hospital 38.5% (25/65) Observation room 38.5% (25/65) Transfer to different hospital 3.1% (2/65)	NR	NR	NR	NR	Comfort score (VAS 0-10; higher=more discomfort) 8.1 (2.0) Mean difference -1.8 (95%CI -2.4, -1.1) Dyspnea (VAS 0-10; higher=more dyspnea; at 60 min) 3.1 (2) Mean difference 0.5 (95%CI -0.3, 1.2)	VAS comfort score (0-10; higher=more discomfort) 6.4 (1.9) Dyspnea (VAS 0-10; higher=more dyspnea; at 60 min) 3.6 (2.2)
Matsuda, 2020 (58) ICU 1, 6, 24, and 48 hours; 5 and 7 days COT (heated, humidified	NR	NR	NR	NR	NR	NR	Discomfort (numeric rating scale or faces pain scale, 0-10); median [IQR] Nasal 60 min 0 [0-4.5], P=.78 360 min 0 [0-2], P=.92 Oral 60 min 0 [0-3], P=.94 360 min 0 [0-2], P=.82 Pharynx 60 min 1 [0-4], P=.44 360 min 0 [0-3.5], P=.87	Discomfort (numeric rating scale or faces pain scale, 0-10); median [IQR] Nasal 60 min 0 [0-2.5] 360 min 0 [0-3] Oral 60 min 0 [0-3] 360 min 0 [0-3] Pharynx 60 min 2 [0-4.5] 360 min 1.5 [0-4]

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Pilcher, 2017 (45) Hospital End of 2nd treatment phase (~90 min) COT	NR	NR	NR	NR	NR	NR	Comfort wearing nasal interface (1=very comfortable, 5=very uncomfortable) 2.4 (1.3), P=.92 Mean difference 0.92 (95%CI -0.8, 0.9) Breathing through nose (1=easy, 5=very difficult) 2.3 (1.2), P=.18 Mean difference 0.5 (95%CI -0.2, 1.1) Nasal passages (1=comfortable, 5=dry) 1.9 (1.2), P=.051 Mean difference -1.0 (-2.1, 0.0)	Comfort wearing nasal interface (1=very comfortable, 5=very uncomfortable) 2.4 (1.1) Breathing through nose (1=easy, 5=very difficult) 1.8 (1.0) Nasal passages (1=comfortable, 5=dry) 3.0 (1.7)
Rittayamai, 2015 (46) ED 1 hour COT	Hospitaliza-tion 50.0% (10/20), P=.34	Hospitaliza-tion 65.0% (13/20)	NR	NR	NR	NR	Comfort scale score Assessed at 1 hour 1.6 (1.7), P=.01 Dyspnea scale score 2.0 (1.8), P=.01 2.5% (1/20) withdrew immediately due to intolerance	Comfort scale score Assessed at 1 hour 3.7 (2.4), P=.01 Dyspnea scale score 3.8 (2.3)
Ruangsomboon, 2019 (47) ED	NR	NR	NR	NR	NR	NR	First study period (n=22)	First study period (n=21)

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
1 hour COT							Dyspnea – Modified Borg (0 [none] to 10 [severe]) Baseline: 6.1 (2.4) 60 min: 3.3 (2.0) Difference between groups at 60 min: 2.3 (95%CI 1.1, 3.5) Dyspnea – Numeric Rating Scale (0 [no shortness of breath] to 10 [worst shortness of breath]) Baseline: 6.1 (2.4) 60 min: 3.5 (2.1) Difference between groups at 60 min 2.5 (95%CI 1.3, 3.5)	Dyspnea – Modified Borg (0 [none] to 10 [severe]) Baseline: 6.8 (2.4) 60 min: 5.6 (1.8) Dyspnea – Numeric Rating Scale (0 [no shortness of breath] to 10 [worst shortness of breath]) Baseline: 6.6 (2.2) 60 min: 5.9 (1.5)
Saksitthichok, 2019 (48) General ward or intermediate care unit 30 min NIV	NR	NR	NR	NR	NR	NR	Dyspnea (10 cm; 0=no dyspnea; 10=extreme dyspnea) Dyspnea at baseline 4.3 (3.1) Mean change from baseline to after HFNC initiation -0.1 (0.7), P=.07	Dyspnea (10 cm; 0=no dyspnea; 10=extreme dyspnea) Dyspnea at baseline 5.2 (2.6) Mean change from baseline to after NIV initiation -0.9 (2.1)
Schwabbauer, 2014 (49) ICU 30 min COT & NIV	NR	NR	NR	NR	NR	NR	Comfort scale (10-point numeric rating scale; low numbers indicate low discomfort) Baseline: 2.5 (1.6) After 30 min	Comfort scale (10-point numeric rating scale; low numbers indicate low discomfort) Baseline: 2.5 (1.6) After 30 min

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
							2.7 (1.8) HFNC-NIV, P<.05 HFNC-COT, NS Dyspnea (Borg category ratio 10 scale; low numbers indicate little dyspnea, high numbers severe dyspnea) Baseline: 3.6 (2.5) After 30 min: 2.9 (2.1) HFNC-NIV, P<.05 HFNC-COT, NS Global rating scale (6 points; 1=very good, 6=failed) 2.3 (1.3) HFNC-NIV, P<.01 HFNC-COT, NS	NIV: 5.4 (3.1) COT: 3.1 (2.8) Dyspnea (Borg category ratio 10 scale; low numbers indicate little dyspnea, high numbers severe dyspnea) Baseline: 3.6 (2.5) After 30 min: NIV: 5.0 (3.3) COT: 3.3 (2.3) Global rating scale (6 points; 1=very good, 6=failed) NIV: 4.5 (1.7) COT: 3.1 (1.7)
Sklar, 2018 (50) Hospital ward End of 2nd treatment phase (~80 min) NIV	NR	NR	NR	NR	NR	NR	Comfort (0=maximal discomfort, 10=very comfortable) (median [IQR]) Baseline 9 [8-10] Post-treatment 6 [5-8], P=.99 Comfort scores were significantly reduced with both NIV and HFNT	Comfort (0=maximal discomfort, 10=very comfortable) (median [IQR]) Baseline 9 [8-10] Post-treatment 7 [6-9]

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
							Dyspnea (0=no dyspnea, 10=maximal dyspnea) (median [IQR]) Baseline 1 [0-3] Post-treatment 1 [0-3], P=.99	Dyspnea (0=no dyspnea, 10=maximal dyspnea) (median [IQR]) Baseline 1 [0-3] Post-treatment 1 [0-2]
Song, 2017 (51) ICU 24 hours COT	NR	NR	NR	NR	NR	NR	Comfort (VAS at 24 hours; 0=no discomfort to 10=maximum discomfort), (median (range)) Related to Interface 3 (3-4.5) Related to dryness 3 (2-3.5), Both P<.001	Comfort (VAS at 24 hours; 0=no discomfort to 10=maximum discomfort), (median (range)) Related to Interface 7 (6-8) Related to dryness 5 (4.7-6)
Spoletini, 2018 (52) ICUs (5) or Intermediate Care Units (2) Through 6 breaks or until off NIV COT	NR	NR	NR	NR	NR	NR	Comfort (VAS 10 cm, higher=more comfortable) (n=23) Baseline 6.2 (3.3) Breaks 8.3 (2.7), P<.05 Dyspnea (Borg) (n=23) Baseline 2.1 (2.7) Breaks 2.1 (2.8),	Comfort (VAS 10 cm, higher=more comfortable) (n=24) Baseline 6.0 (3.3) Breaks 6.9 (2.3) Dyspnea (Borg) (n=23) Baseline 2.5 (2.7) Breaks 2.4 (2.2)

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
							P=NS Dryness of nose & mouth 48% P=NS Eye irritation 8% P=.05 Nasal discomfort 2% P=NS Difficulty in eating 13.3% P≤.05	Dryness of nose & mouth 47% Eye irritation 22% Nasal discomfort 8% Difficulty in eating 36.2%
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	NR	NR	NR	NR	NR	NR	Comfort score of "Good" 1 hour 58.2% (234/402) [95%CI 53.2, 63.1] 6-12 hours 51.0% (101/372) [95%CI 46.1, 56.5] Dyspnea score Improvement 1 hour 58.6% (236/403) [95%CI 53.6, 63.4] 6-12 hours 58.2% (217/373) [95%CI 52.9, 63.2] Data for entire study population	Comfort score of "Good" 1 hour 55.0% (218/397) [95% CI 49.9, 60.1] 6-12 hours 53.0% (199/376) [95% CI 47.7, 58.1] Dyspnea score Improvement 1 hour 65.8% (266/404) [95%CI 61.0, 70.7] 6-12 hours 60.4% (229/379) [95% CI 55.3, 65.4]

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Vargas, 2015 (54) ICU 20 min COT & NIV (CPAP)	NR	NR	NR	NR	NR	NR	Comfort Scale (1=severe discomfort, 5=very good comfort) Assessed at 20 min (median, [IQR]) **HFNC** 4 [4, 4] Dyspnea (VAS scale) (median, [IQR]) **HFNC** 14 [8, 28] Patient Preference HFNC 58.3% (7/12) COT 16.7% (2/12) NIV 8.3% (1/12) No difference 17% (2/12)	Comfort Scale (1=severe discomfort, 5=very good comfort) Assessed at 20 min (median, [IQR]) **COT (first treatment)** 3.5 [3, 4] **COT (last treatment)** 3.4 [3, 4] **NIV (CPAP_** 3 [3,4] Dyspnea (VAS scale) (median, [IQR]) **COT (first treatment)** 35 [16, 50] **COT (last treatment)** NR **NIV (CPAP)** 25 [12, 55] (not significant improvement from HFNC) Patient Preference HFNC 58.3% (7/12) COT 16.7% (2/12) NIV 8.3% (1/12) No difference 17% (2/12)

Author, Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)		Patient Comfort (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	NR	NR	NR	NR	NR	NR	Tolerance Mucus dryness 38.3% (18/47), P=.003 Mean Difference -31.1 (95%CI -51.0, -12.0) Nasal Bleeding 8.5% (4/47) P=.36 Mean Difference 7 (95%CI -3.0, 16.0) Satisfaction (1=very dissatisfied, 5-very satisfied) (median [IQR]) 4.0 [3.0, 4.0], P=.0002	Tolerance Mucus dryness 69.8% (30/43) Nasal Bleeding 2.3% (1/43) Satisfaction (1=very dissatisfied, 5-very satisfied) (median [IQR]) 3.0 [2.0, 3.0]

ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; CI=confidence interval; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=Emergency Department; HFFM=high-flow face mask; HFNC=high flow nasal cannulae; HFNT=high flow nasal oxygen therapy; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not significant; O_2=oxygen; SD=standard deviation; VAS=visual analog scale

Supplementary Table 7. Patient-Centered Outcomes, Part 4

Author, Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	NR	NR	NR	NR	NR	NR	Acute colonic pseudo-obstruction 2.2% (9/414), P=.86 Data for entire study population	Acute colonic pseudo-obstruction 1.9% (8/416)

ADHF=acute decompensated heart failure; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=emergency department; HFFM=high-flow face mask; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported

Supplementary Table 8. Patient-Centered Outcomes, Part 5

Author, Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	During ICU stay 3.8% (4/106) Overall P=.32 PaO_2/FiO_2 ratio ≤200 subgroup 3.6% (3/83) Overall P=.81	During ICU stay ***COT*** 8.5% (8/94) ***NIV*** 8.2% (9/110) PaO_2/FiO_2 ratio ≤200 subgroup ***COT:*** 5.4% (4/74) ***NIV:*** 8.6% (7/81)	NR	NR	NR	NR	NR	NR
Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	Ventilator-associated 1.1% (3/264), P=.31 Difference 1.2 (95%CI -1.3, 3.9)	Ventilator-associated 2.3% (6/263)	NR	NR	Skin trauma 0% (0/264)	N/A (per study authors)	NR	NR
Hernandez, 2016 (37) (high risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes NIV	Ventilator-associated 4.1% (12/290) Difference 1.3 (95%CI -2.3, 4.8)	Ventilator-associated 5.4% (17/314)	NR	NR	Nasal septum and skin trauma 0% (0/290), P<.001	Nasal septum and skin trauma 42.9% (135/314)	NR	NR

Author, Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	NR	NR	NR	NR	Pressure sore 0% (0/22), P=.04 Time assessed: NR	Pressure sore 20.0% (4/20) Time assessed: NR	NR	NR
Jones, 2016 (40) ED NR COT	NR	NR	Pneumothorax 0% (0/165)	Pneumothorax 0% (0/138)	Pressure sore 0% (0/165)	Pressure sore 0% (0/138)	NR	NR
Makdee, 2017 (43) ED 24 hours to 7 days COT	NR	NR	NR	NR	Nasal ulceration 0% (0/63)	NR	NR	NR
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	20.0% (83/414), P=.57 Data for entire study population	21.6% (90/416)	1.9% (8/414), P=.86 Data for entire study population	1.7% (7/416)	Day 1 3.2% (13/405), P<.001 Day 2 7.9% (20/252), P=.05 Day 3 12.2% (18/147), P>.99 Data for entire study population	Day 1 9.9% (40/403) Day 2 14.2% (38/267) Day 3 17.9% (26/145)	NR	NR
Vargas, 2015 (54) ICU 20 min COT & NIV (CPAP)	NR	NR	NR	NR	NR	NR	0% (0/12)	

ADHF=acute decompensated heart failure; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure; ED=emergency department; HFFM=high-flow face mask; ICU=intensive care unit; NA=not applicable; NIV=non-invasive ventilation; NR=not reported

Supplementary Table 9. Intermediate Outcomes, Part 1

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Azoulay, 2018 (27) ICU 28 days COT	6 hours after randomization Per min (median [IQR]) 25 [20-30]	6 hours after randomization Per min (median [IQR]) 26 [21-31]	6 hours after randomization Per min (median [IQR]) 150 [104-230]	6 hours after randomization Per min (median [IQR]) 119 [86-165]	NR	NR
Bell, 2015 (28) ED 2 hours COT	Reduction in respiratory rate >20% from baseline within 2 hours 66.7% (32/48), P=.005	Reduction in respiratory rate>20% from baseline within 2 hours 38.5% (20/52)	NR	NR	NR	NR
Cho, 2020 (56) ICU Not specified COT	Before extubation 19.7 (4.8), P=.71) 30 minutes after extubation 21.7 (5.4), P=.71 24 hours after extubation 22.8 (5.9), P=.12	Before extubation 20.1 (4.9) 30 minutes after extubation 21.1 (5.9) 24 hours after extubation 20.7 (4.5)	Before extubation 271.5 (99.0), P=.36 30 min after extubation 262.8 (114.6), P=.10 24 hours after extubation 277.1 (102.5), P=.17	Before extubation 297.2 (118.9) 30 min after extubation 311.3 (112.9) 24 hours after extubation 314.2 (102.1)	NR	NR
Cong, 2019 (29) Hospital 12 hours & 5 days NIV	NR	NR	NR	NR	Before therapy 77.5 (14.1) 12 hours 87.8 (8.2) 5 days 91.9 (4.4) P>.05 between groups	Before therapy 77.5 (14.2) 12 hours 88.7 (7.2) 5 days 92.8 (4.1)

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Corley, 2015 (30) ICU 1 & 5 days COT	0-8 hours 16.0 >16-24 hours 18.3	0-8 hours 16.0 >16-24 hours 17.9	0-8 hours (n=81) 203.5 >16-24 hours (n=33) 175.8	0-8 hours (n=74) 281.4 >16-24 hours (n=19) 159.3	NR	NR
Delorme, 2017 (31) Hospital (Mixed) Every 15 min for four periods COT	Breaths/min (median, [IQR]) 20 L/min: 20 [16, 24] 40 L/min: 23 [16, 26] 60 L/min: 19 [15, 24], P=.43 Assessed after 15 min	Breaths/min (median, [IQR]) 20 [18, 25] Assessed after 15 min	NR	NR	Median, [IQR] 20 L/min 92 [89, 92] 40 L/min 92 [90, 92] 60 L/min 92 [90, 93] P=.02 Assessed after 15 min	Median, [IQR] 93 [89, 94] Assessed after 15 min

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Doshi, 2018 (32) Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV	Breaths/min Baseline (n=104) 31.3 (8.0) Mean difference 2.0 (95%CI -0.2, 4.2) 240 min (n=73) 22.2 (4.7) Mean difference 0.1 (95%CI -1.4, 1.6) **ADHF subgroup** (median) Baseline (n=22) 33 30 min (n=21) 27 240 min (n=21) 20 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=34) 32 30 min (n=34) 27.5 240 min (n=29) 21	Breaths/min Baseline (n=100) 29.3 (8.2) 240 min (n=76) 22.1 (4.8) **ADHF subgroup** (median) Baseline (n=20) 34 30 min (n=21) 27 240 min (n=19) 20 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=31) 28 30 min (n=31) 21 240 min (n=26) 22	**ADHF subgroup** (median) Baseline (n=15) 118 240 min (n=15) 200	**ADHF subgroup** (median) Baseline (n=16) 154 240 min (n=16) 203	Baseline (n=104) 93.2 (7.0) Mean difference -0.3 (95%CI -2.5, 1.9) 240 min (n=73) 96.8 (2.8) Mean difference -0.4 (95%CI -1.2, 0.4) **ADHF subgroup** (median) Baseline (n=22) 96 30 min (n=21) 99 240 min (n=21) 99 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=34) 96.5 30 min (n=34) 99 240 min (n=29) 97	Baseline (n=100) 93.5 (8.9) 240 min (n=75) 97.2 (2.3) **ADHF subgroup** (median) Baseline (n=20) 99 30 min (n=20) 100 240 min (n=19) 98 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=31) 98 30 min (n=31) 99 240 min (n=26) 96

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	Breaths/min (n=106) Baseline 33 (6) At 1 hour 28 (7), Overall P<.01 At 6 hours 27 (7), Overall P=.13 **Immuno-compromised subgroup** (n=26) Baseline 32 (5) At 1 hour 26 (8), Overall P=.003	Breaths/min ***COT (***n=94) Baseline 32 (6) At 1 hour 31 (7) At 6 hours 29 (8) ***NIV*** (n=110) Baseline 33 (7) At 1 hour 31 (8) At 6 hours 29 (7) **Immuno-compromised subgroup** ***COT*** (n=30) Baseline 32 (6) At 1 hour 31 (6) ***NIV*** (n=26) Baseline 33 (8) At 1 hour 32 (9)	Baseline (n=106) 157 (89) At 1 hour 133 (73), Overall P<.001 At 6 hours 130 (60), Overall P<.001	***COT*** (n=94) Baseline 161 (73) At 1 hour 146 (69) At 6 hours 161 (77) ***NIV*** (n=110) Baseline 149 (72) At 1 hour 183 (83) At 6 hours 186 (85)	NR	NR
Grieco, 2020 (35) ICU 1 hour NIV (helmet)	1 hour (median, [IQR] 29 [26,32], P=.027	1 hour (median, [IQR] 24 [23,31]	1 hour (median, [IQR] 138 [101,172], P=.001	1 hour (median, [IQR] 255 [140,299]	1 hour (median, [IQR] 92 [90,94] P=.002	1 hour (median, [IQR] 98 [82,99]

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	NR	NR	Baseline prior to extubation 227 (25) 12 hours after extubation 105 (32), P=.57 Difference -3 (95%CI -9, 3)	Baseline prior to extubation 237 (34) 12 hours after extubation 108 (34)	NR	NR
Hernandez, 2016 (37) (high risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes NIV	NR	NR	Baseline prior to extubation 191 (34) 12 hours after extubation 99 (2), P=.83	Baseline prior to extubation 194 (37) 12 hours after extubation 104 (32)	NR	NR
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	Baseline 18.7 (3.7) bpm 48 hours 22.4 (4.4) bpm	Baseline 19.0 (4.1) bpm 48 hours 21.0 (4.5) bpm	Baseline 235.8 (77) 48 hours 201.2 (92.4)	Baseline 250.8 (75.8) 48 hours 257.5 (130.7)	NR	NR
Jones, 2016 (40) ED NR COT	T0 (immediately prior to study treatment) (n=154) 29.9 Mean Difference 1.2 (95%CI -0.5, 2.9), P=.16	T0 (immediately prior to study treatment) (n=119) 28.7 T6 (3 hours post treatment initiation) (n=41) 24	NR	NR	T0 (immediately prior to study treatment) 91.4 (n=156) Mean Difference -0.5 (95%CI -1.9, 0.73), P=.39	T0 (immediately prior to study treatment) 91.9 (n=131)

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
	T6 (3 hours post treatment initiation) (n=58) 23.9 Mean Difference -0.1 (95%CI -2.5, 1.2), P=.93				T6 (3 hours post treatment initiation) 92.9 (n=64) Mean Difference -0.8 (95%CI -2.1, 0.6), P=.29	T6 (3 hours post treatment initiation) 93.7 (n=45)
Lemiale, 2015 (41) ICU 2 hours COT	Baseline (median, [IQR]) 26 [22, 31] 120 min (median, [IQR]) 25 [22, 29]	Baseline (median, [IQR]) 27 [22, 32] 120 min (median, [IQR]) 25 [21, 31]	NR	NR	NR	NR
Maggiore, 2014 (42) ICU 48 hours COT	Respiratory rate did not differ significantly between groups at baseline; over 48 hours, respiratory rate was always significantly lower with nasal high flow (mean difference 4 (SD 1) breaths per min)		Baseline prior to extubation 239.4 (42.4) 48 hours 313.3 (83.8), P=.01	Baseline prior to extubation 241.7 (51.1) 48 hours 250.2 (110.1)	SaO_2 did not differ significantly between groups at baseline; over 48 hours, SaO_2 was always significantly greater with nasal high flow at all time points	
Makdee, 2017 (43) ED 24 hours to 7 days COT	Breaths/min Baseline 30.8 (3.7) 60 min 21.8 (4.1) Mean difference 3.3 (95%CI 1.9, 4.6)	Breaths/min Baseline 31.2 (3.9) 60 min 25.1 (3.6)	NR	NR	Baseline 89.3 (5.5) 1 hour 99.2 (1.2) Mean difference -0.5 (95%CI -1.0, -0.02)	Baseline 88.2 (9.8) 1 hour 98.7 (1.5)
Matsuda, 2020 (58) ICU 1, 6, 24, and 48 hours; 5 and 7 days COT (heated, humidified	NR	NR	Data from graph 24 hours 264 (105), P=.07	Data from graph 24 hours 224 (53)	NR	NR

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Parke, 2011 (44) ICU 30 min, 1 hour, 2 hours, and 4 hours COT (HFFM)	"No effect"		Did not differ significantly between groups, P=.08 Note: Only included patients who had complete data available for first 4 hours NHF (n=28) COT (HFFM) (n=22)		"No effect"	
Pilcher, 2017 (45) Hospital End of 2nd treatment phase (~90 min) COT	Breaths/min Baseline (n=12) 22.3 (4.6) 30 min (n=12) 20.1 (6.0), P=.10	Breaths/min Baseline (n=12) 21.3 (5.3) 30 min (n=11) 21.4 (4.7)	NR	NR	Baseline (n=12) 93.5 (2.7) 30 min (n=12) 93.7 (2.9), P=.96	Baseline (n=12) 93.5 (2.8) 30 min (n=11) 93.9 (2.9)
Rittayamai, 2015 (46) ED 1 hour COT	Breaths/min Baseline 31.7 (5.5), P=.81 1 hour 26.0 (6.2), P=.82	Breaths/min Baseline 32.1 (5.0) 1 hour 27.5 (4.9)	NR	NR	Baseline 85.9 (9.0), P=.23 1 hour 96.8 (2.5), P=.13	Baseline 88.7 (4.5) 1 hour 97.6 (2.0)
Ruangsomboon, 2019 (47) ED 1 hour COT	Baseline: 29.6 (5.1) 60 min: 26.0 (3.7) Difference between groups at 60 min: 2.5 (95%CI 1.6, 10.0)	Baseline: 33.9 (9.2) 60 min: 31.9 (9.3)	NR	NR	60 min: 98.1 (2.1) Difference between groups at 60 min: -0.7 (95%CI -2.5, 1.1)	60 min: 97.4 (3.7)
Saksitthichok, 2019 (48) General ward or intermediate care unit 30 min NIV	Baseline 23.6 (6.2), P=0.16 Mean difference from baseline to after HFNC initiation	Baseline 28.1 (14.4) Mean difference from baseline to after NIV initiation -4.0 (13.5)	NR	NR	SaO_2 Mean difference from baseline to after HFNC initiation 9.2 (5.2), P=.33	SaO_2 Mean difference from baseline to after NIV initiation 11.3 (9.3)

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
	-2.5 (3.8), P=.57					
Schwabbauer, 2014 (49) ICU 30 min COT & NIV	Baseline 28 (9) 30 min 26 (7)	Baseline 28 (9) 30 min COT: 28 (8) NIV: 24 (9) COT-NIV, P<.01	NR	NR	Baseline 93 (3) 30 min 96 (3), NS	Baseline 93 (3) 30 min COT: 95 (4) NIV: 98 (3)
Sklar, 2018 (50) Hospital ward End of 2nd treatment phase (~80 min) NIV	Breaths/min (median [IQR]) Baseline 21 [17-26] Post-treatment 18 [13-20], P=.13	Breaths/min (median [IQR]) Baseline 21 [17-26] Post-treatment 19 [18-26]	NR	NR	Median [IQR] Baseline 93 [90-94] Post-treatment 94 [93-95], P=.51	Median [IQR] Baseline 93 [90-94] Post-treatment 93 [92-94]
Song, 2017 (51) ICU 24 hours COT	24 hours (n=27) 22 (4), P=.003	24 hours (n=19) 26 (4)	NR	NR	Baseline (n=30) 96.2 (2.3) 24 hours (n=27) 98.0 (1.3), P=.011	Baseline (n=30) 95.1 (2.9) 24 hours (n=19) 96.9 (1.4)
Spoletini, 2018 (52) ICUs (5) or Intermediate Care Units (2) Through 6 breaks or until off NIV COT	Breaths/min Baseline (n=23) 27.2 (5.6) Breaks 23.8 (6.8), P=NS	Breaths/min Baseline (n=24) 25.6 (7.3) Breaks 21.8 (5.2)	NR	NR	Baseline (n=23) 96.5 (2.7) Breaks 94.1 (3.2), P=NS	Baseline (n=24) 95.4 (3.3) Breaks 94.7 (2.1)
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	Breaths/min Mean (95% CI) Baseline 22.8 (22.1, 23.5) 1 hour 21.0 (20.4, 21.7), P<.001 6-12 hours 21.6 (20.9, 22.2),	Breaths/min Mean (95% CI) Baseline 23.3 (22.6, 24.0) 1 hour 23.0 (22.3, 23.7) 6-12 hours 22.5 (21.9, 23.1)	Mean (95%CI) Baseline 196 (187, 204) 1 hour 184 (177, 192), P<.001 6-12 hours 198 (187, 208), P<.001	Mean (95%CI) Baseline 203 (195, 212) 1 hour 221 (213, 230) 6-12 hours 261 (248, 274)	NR	NR

Author, Year Setting Follow-up Comparator	**Respiratory Rate (mean, SD)**		**PaO_2/FiO_2 ratio (mean, SD)**		**SpO_2 (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
	P=.16 Data for entire study population		Data for entire study population			
Vargas, 2015 (54) ICU 20 min COT & NIV (CPAP)	NR	NR	Baseline Mean: 180.2 Median [IQR]: 178 [157-199] **HFNC** (median, [IQR]) 167 [157, 184], P <.01 vs first COT treatment; NS vs **NIV (CPAP)**	Baseline Mean: 180.2 Median [IQR]: 178 [157-199] **COT (first treatment)** (median, [IQR]) 156 [110, 171] **COT (last treatment)** (median, [IQR]) NR **NIV (CPAP)** (median, [IQR]) 228 [205, 269], NS vs HFNC	NR	NR
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	Breaths/min Baseline 21.0 (5.0) 1 hour 18.3 (4.9), P=.08 Mean Difference -1.7 (95%CI -3.5, 0.2) 48 hours 19.2 (4.0), P=.16 Mean Difference -1.4 (95%CI -3.4, 0.6)	Breaths/min Baseline 22.0 (4.0) 1 hour 20.0 (4.3) 48 hours 20.6 (4.1)	Baseline 147.7 (30.7) 1 hour 137.8 (57.0), P=.026 Mean Difference 24.4 (95%CI 2.9, 45.9) 24 hours 129.9 (54.0), P=.04 Mean Difference 23.0 (95%CI 1.5, 44.6)	Baseline 131.5 (27.7) 1 hour 113.4 (50.2) 24 hours 106.9 (62.6)	NR	NR

ADHF=acute decompensated heart failure: AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; CI=confidence interval; COT=conventional oxygen therapy; CPAP=continuous positive airway pressure ED=emergency department; HFFM=high-flow face mask; HFNC=high flow nasal cannula; ICU=intensive care unit; IQR=interquartile range; NHF=nasal high flow; NIV=non-invasive ventilation; NR=not reported; NS=not significant; SD=standard deviation

Supplementary Table 10. Intermediate Outcomes, Part 2

Author, Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Cho, 2020 (56) ICU Not specified COT	Before extubation 7.42 (0.08), P=.11 30 minutes after extubation 7.43 (0.07), P=.13 24 hours after extubation 7.45 (0.05), P=.86	Before extubation 7.45 (0.05) 30 minutes after extubation 7.45 (0.05) 24 hours after extubation 7.46 (0.04)	NR	NR	Before extubation 38.5 (7.5), P=.05 30 minutes after extubation 38.2 (8.6), P=,14 24 hours after extubation 35.9 (7.0), P=.54	Before extubation 35.2 (5.4) 30 minutes after extubation 35.3 (5.8) 24 hours after extubation 37.1 (8.8)
Cong, 2019 (29) Hospital 12 hours & 5 days NIV	Before therapy 7.3 (0.1) 12 hours 7.3 (0.1) 5 days 7.4 (0.1)	Before therapy 7.32 (0.09) 12 hours 7.36 (0.06) 5 days 7.36 (0.07)	Before therapy 53.9 (15.2) 12 hours 72.2 (17.5) 5 days 81.9 (15.3)	Before therapy 54.1 (16.2) 12 hours 72.0 (17.5) 5 days 82.2 (15.6)	Before therapy 72.5 (16.4) 12 hours 63.2 (15.9) 5 days 58.9 (14.4)	Before therapy 72.2 (17.0) 12 hours 63.1 (16.0) 5 days 60.0 (13.6)
Delorme, 2017 (31) Hospital (Mixed) Every 15 min for four periods COT	Median, [IQR] 20 L/min 7.4 [7.4, 7.4] 40 L/min 7.4 [7.4, 7.5] 60 L/min 7.2 [7.4, 7.5] P=.11 Assessed after 15 min	Median, [IQR] 7.4 [7.4, 7.4] Assessed after 15 min	NR	NR	$PaCO_2$ Median, [IQR] 20 L/min 47.2 [40.6, 62.7] 40 L/min 43.9 [38.9, 59.6] 60 L/min 43.9 [39.2, 61.4] P=.31 Assessed after 15 min	$PaCO_2$ Median, [IQR] 52.1 [40.8, 61.3] Assessed after 15 min

Author, Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Doshi, 2018 (32) Haywood, 2019 (36) (ADHF subgroup) Doshi 2020 (57) (AECOPD/hyper-capnic ARF subgroup) ED 72 hours NIV	Baseline (n=104) 7.4 (0.1) Mean difference 0.02 (95%CI 0.00, 0.04) 240 min (n=74) 7.4 (0.1) Mean difference 0.02 (95%CI 0.00, 0.04) **ADHF subgroup** (median) Baseline (n=22) 7.4 240 min (n=21) 7.4 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=34) 7.33 240 min (n=27) 7.38	Baseline (n=99) 7.3 (0.1) 240 min (n=72) 7.4 (0.1) **ADHF subgroup** (median) Baseline (n=19) 7.3 240 min (n=19) 7.4 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=31) 7.32 240 min (n=25) 7.35	**ADHF subgroup** (median) Baseline (n=15) 82 240 min (n=15) 98 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=34) 98.5 240 min (n=27) 83	**ADHF subgroup** (median) Baseline (n=16) 116.5 240 min (n=16) 79 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=31) 98 240 min (n=25) 88	$PaCO_2$ Baseline (n=104) 53.4 (20.6) Mean difference -5.3 (95%CI -11.6, 1.0) 240 min (n=74) 46.3 (12.7) Mean difference -6.2 (95%CI -11.2, -1.2) **ADHF subgroup** (median) Baseline (n=22) 42.5 240 min (n=21) 43 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=34) 56 240 min (n=27) 50	$PaCO_2$ Baseline (n=99) 58.7 (25.0) 240 min (n=72) 52.5 (17.8) **ADHF subgroup** (median) Baseline (n=19) 42 240 min (n=19) 39 AECOPD/hyper-capnic ARF subgroup (median) Baseline (n=31) 64.6 240 min (n=25) 57

Author, Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Frat, 2015 (34) Frat, 2016 (33) (immuno-compromised subgroup) ICU 28 days COT & NIV	Baseline (n=106) 7.4 (0.1) At 1 hour 7.5 (0.1), Overall P<.05 At 6 hours 7.4 (0.1), Overall P=.33	***COT*** (n=94) Baseline 7.4 (0.1) At 1 hour 7.4 (0.1) At 6 hours 7.4 (0.1) ***NIV*** (n=110) Baseline 7.4 (0.1) At 1 hour 7.4 (0.1) At 6 hours 7.4 (0.1)	Baseline (n=106) 85 (31) At 1 hour 106 (66), Overall P<.05 At 6 hours 90 (35), Overall P<.01	***COT*** (n=94) Baseline 92 (32) At 1 hour 91 (32) At 6 hours 93 (36) ***NIV*** (n=110) Baseline 90 (36) At 1 hour 118 (72) At 6 hours 111 (59)	Baseline (n=106) 36 (6) At 1 hour 35 (7), Overall P=.84 At 6 hours 36 (7), Overall P=.69	***COT*** (n=94) Baseline 35 (5) At 1 hour 35 (6) At 6 hours 36 (6) ***NIV*** (n=110) Baseline 34 (6) At 1 hour 35 (7) At 6 hours 35 (6)
Grieco, 2020 (35) ICU 1 hour NIV (helmet)	NR	NR	1 hour (median, [IQR] 69 [61,90], P=.001	1 hour (median, [IQR] 108 [70,135]	1 hour (median, [IQR] 33 [29,35], P=.80	1 hour (median, [IQR] 31 [28,36]
Hernandez, 2016 (38) (low risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes COT	Baseline prior to extubation 7.4 (0.3) 12 hours after extubation 7.4 (0.3), P=.49 Difference -0.3 (95%CI -0.09, 0.03)	Baseline prior to extubation 7.4 (0.2) 12 hours after extubation 7.4 (0.4)	NR	NR	Baseline prior to extubation 39 (2.4) 12 hours after extubation 37 (8), P=.84 Difference 1 (95%CI -0.2, 2.2)	Baseline prior to extubation 38 (2.9) 12 hours after extubation 36 (6)

Author, Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
Hernandez, 2016 (37) (high risk patients) ICU 72 hours for reintubation; to hospital discharge for other outcomes NIV	Baseline prior to extubation 7.4 (0.3) 12 hours after extubation 7.4 (0.05), P=.57	Baseline prior to extubation 7.4 (0.2) 12 hours after extubation 7.4 (0.1)	NR	NR	Baseline prior to extubation 41 (2.2) 12 hours after extubation 46 (3.1), P=.67	Baseline prior to extubation 39 (3.2) 12 hours after extubation 47 (2.8)
Jing, 2019 (39) ICU 3, 24, and 48 hours post-extubation NIV	Baseline: 7.5 (0.1) 48 hours: 7.4 (0.1)	Baseline: 7.4 (0.1) 48 hours: 7.41 (0.1)	NR	NR	Baseline 52.4 (6.4) 48 hours 56.9 (10)	Baseline 53.7 (8.6) 48 hours 61.5 (16.3)
Maggiore, 2014 (42) ICU 48 hours COT	NR	NR	NR	NR	$PaCO_2$ did not differ significantly between groups at baseline; over 48 hours, $PaCO_2$ was always lower with nasal high flow with a statistically significant difference at 3 hours (32.3 (7.1) vs 36.2 (11) mmHg; P=.04)	
Pilcher, 2017 (45) Hospital End of 2nd treatment phase (~90 min) COT	NR	NR	NR	NR	$PtCO_2$ Baseline (n=12) 49.0 (10.3) 30 min (n=12) 47.4 (10.1), P=.001	$PtCO_2$ Baseline (n=12) 48.9 (10.4) 30 min (n=11) 48.5 (10.1)
Saksitthichok, 2019 (48) General ward or intermediate care unit 30 min NIV	Baseline 7.5 (0.04), P=0.74 Mean difference from baseline to	Baseline 7.46 (0.04) Mean difference from baseline to after NIV initiation	Baseline 56.6 (10.6), P=0.07 Mean difference from baseline to after HFNC initiation	Baseline 51.3 (9.4) Mean difference from baseline to after NIV initiation 99.8 (64.7)	Baseline 32.8 (4.9), P=0.89 Mean difference from baseline to after HFNC initiation	Baseline 33.0 (6.8) Mean difference from baseline to after NIV initiation 2.5 (6.0)

Author, Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
	after HFNC initiation -0.004 (0.037), P=.66	0.001 (0.039)	100.9 (62.9), P=.95		1.0 (5.0), P=.35	
Schwabbauer, 2014 (49) ICU 30 min COT & NIV	Baseline 7.5 (0.01) 30 min 7.5 (0.1), NS	Baseline 7.5 (0.01) 30 min COT: 7.5 (0.1) NIV: 7.4 (0.1)	Baseline 67 (15) 30 min 101 (34), HFNC-COT, P<.01; HFNC-NIV, P<.01	Baseline 67 (15) 30 min COT: 85 (22) NIV: 129 (38), COT-NIV, P<.001	NR	NR
Sklar, 2018 (50) Hospital ward End of 2nd treatment phase (~80 min) NIV	NR	NR	NR	NR	$PtCO_2$ (median [IQR]) Baseline 53 [42-60] Post-treatment 54 [41-60], P=.99	$PtCO_2$ (median [IQR]) Baseline 53 [42-60] Post-treatment 53 [41-60]
Song, 2017 (51) Setting: ICU 24 hours COT	NR	NR	Baseline (n=30) 82.8 (11.0) 24 hours (n=27) 83.2 (10.5), P=.016	Baseline (n=30) 81.7 (11.6) 24 hours (n=19) 74.5 (13.1)	Baseline (n=30) 41.5 (6.7) 24 hours (n=27) 41.4 (6.5), P=.591	Baseline (n=30) 42.3 (7.1) 24 hours (n=19) 42.2 (13.1)
Stéphan, 2015 (53) ICU Duration of ICU stay NIV	Mean (95% CI) Baseline 7.4 (7-39, 7.40) 1 hour 7.4 (7.39, 7.40), P=.75 6-12 hours 7.4 (7.40, 7.42), P=.99	Mean (95% CI) Baseline 7.4 (7.39, 7.40) 1 hour 7.4 (7.39, 7.40) 6-12 hours 7.4 (7.40, 7.41)	NR	NR	Mean (95% CI) Baseline 38.7 (38.1, 39.4) 1 hour 37.9 (37.2, 38.5), P=.09 6-12 hours 38.2 (37.6, 38.9), P=.19	Mean (95% CI) Baseline 39.1 (38.4, 39.8) 1 hour 39.0 (38.4, 39.7) 6-12 hours 39.3 (38.6, 40.4)

Author, Year Setting Follow-up Comparator	**pH (mean, SD)**		**PaO_2 (mean, SD)**		**$PaCO_2$ (mean, SD)**	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
	Data for entire study population				Data for entire study population	
Vargas, 2015 (54) ICU 20 min COT & NIV (CPAP)	**HFNC** (median, [IQR]) 7.4 [7.4, 7.5]	**COT (first treatment)** (median, [IQR]) 7.5 [7.4, 7.5] **COT (last treatment)** (median, [IQR]) NR **NIV (CPAP)** (median, [IQR]) 7.4 [7.4, 7.5]	**HFNC** (median, [IQR]) 101 [85, 127], P<.01 vs first COT treatment, NS vs NIV	**COT (first treatment)** (median, [IQR]) 90 [76, 114] **COT (last treatment)** (median, [IQR]) NR **NIV (CPAP)** (median, [IQR]) 134 [119, 161], NS vs HFNC	**HFNC** (median, [IQR]) 37 [33,41]	**COT (first treatment)** (median, [IQR]) 35 [32,39] **COT (last treatment)** (median, [IQR]) NR **NIV (CPAP)** (median, [IQR]) 35 [33, 41]
Vourc'h, 2019 (55) ICU Duration of ICU stay (24 hours for primary outcome) COT (HFFM)	NR	NR	NR	NR	Baseline 40.5 (3.8) Mean from hour 1 to hour 48 39.8 (3.0) Mean difference 0.8 (95%CI 3.0, 3.8)	Baseline 39.8 (4.5) Mean from hour 1 to hour 48 39.0 (3.8)

ADHF=acute decompensated heart failure; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; ARF=acute respiratory failure; CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HFFM=high-flow face mask; HFNC=high flow nasal cannula; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not significant; $PtCO_2$=transcutaneous carbon dioxide tension; SD=standard deviation

Supplementary Table 11. HFNO vs NIV—Initial Management

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Intubation			
Primary analysis	**2 (420)**	**RR 0.71 [0.53 to 0.95]**	**0%**
HFNO event rate *	2 (210)	20.1% [14.9 to 25.8]	
NIV event rate *	2 (210)	30.7% [24.6 to 37.2]	
Setting			
ICU	1 (216)	RR 0.75 [0.55 to 1.03]	-
ED	1 (204)	RR 0.52 [0.22 to 1.24]	-
Disease indication – both mixed diseases			
Acute respiratory failure			
Hypoxic	1 (216)	RR 0.75 [0.55 to 1.03]	-
Hypoxic and/or hypercapnic	1 (204)	RR 0.52 [0.22 to 1.24]	-
Treatment duration – both ≥6 hours			
All-cause Mortality			
Primary analysis	**1 (216)**	**RR 0.44 [0.24 to 0.79]**	**-**
HFNO event rate *	1 (106)	12.3% [6.6 to 19.3]	-
NIV event rate *	1 (110)	28.2% [20.1 to 37.0]	-
Setting – ICU			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
Follow-up duration (the trial reported data at both time points)			
Short-term, ≤7 days, ICU, or hospital	1 (216)	RR 0.40 [0.22 to 0.74]	-
Long-term, >7 days	1 (216)	RR 0.44 [0.24 to 0.79]	-
Hospital-acquired Pneumonia			
Primary analysis	**1 (216)**	**RR 0.46 [0.15 to 1.45]**	**-**
HFNO event rate *	1 (106)	3.8% [0.8 to 8.4]	-
NIV event rate *	1 (110)	8.2% [3.7 to 14.1]	-
Setting – ICU			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
ICU Admissions (yes/no)			
Primary analysis	**1 (204)**	**RR 0.98 [0.73 to 1.32]**	**-**
HFNO event rate *	1 (104)	46.2% [36.6 to 55.8]	-
NIV event rate *	1 (100)	47.0% [37.3 to 56.9]	-
Setting – ED			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic and/or hypercapnic			
Treatment duration – ≥6 hours			
ICU Length of Stay			

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Primary analysis	**2 (420)**	**MD -0.64 days [-1.67 to 0.39]**	**0%**
Setting			
ICU	1 (216)	MD -1.10 days [-4.83 to 2.63]	-
ED	1 (204)	MD -0.60 days [-1.67 to 0.47]	-
Disease indication – both mixed diseases			
Acute respiratory failure			
Hypoxic	1 (216)	MD -1.10 days [-4.83 to 2.63]	-
Hypoxic and/or hypercapnic	1 (204)	MD -0.60 days [-1.67 to 0.47]	-
Treatment duration – both ≥6 hours			
Hospital Length of Stay			
Primary analysis	**2 (372)**	**MD 0.45 days [-0.69 to 1.59]**	**0%**
Setting			
Hospital	1 (168)	MD -0.27 days [-2.26 to 1.72]	-
ED	1 (204)	MD 0.80 days [-0.59 to 2.19]	-
Disease indication			
COPD	1 (168)	MD -0.27 days [-2.26 to 1.72]	-
Mixed diseases	1 (204)	MD 0.80 days [-0.59 to 2.19]	-
Acute respiratory failure – both hypoxic and/or hypercapnic			
Treatment Duration – both ≥6 hours			
Comfort (7 trials reported a measure of comfort, 1 provided data suitable to calculate a SMD and 1 provided data suitable to calculate an ARD, see Table 1 for more details)			
Primary analysis (SMD)	**1 (216)**	**SMD -0.51 [-0.78 to -0.24]**	**-**
Setting – ICU			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
Follow-up duration – <6 hours			
Primary analysis (ARD)	**1 (168)**	**ARD 21.4% [9.4 to 33.4]**	**-**
Setting – Hospital			
Disease indication – COPD			
Acute respiratory failure – hypoxic and/or hypercapnic			
Treatment duration – ≥6 hours			
Follow-up duration – not reported			
Dyspnea (7 trials reported a measure of dyspnea, 1 provided data at two time points suitable to calculate a SMD and 1 provided data suitable to calculate an ARD, see Table 1 for more details)			
Primary analysis – 30 min	**1 (180)**	**SMD 0.04 [-0.25 to 0.33]**	-
Primary analysis – 240 min	**1 (142)**	**SMD 0.21 [-0.12 to 0.54]**	**-**
Setting – ED			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic and/or hypercapnic			
Treatment duration – ≥6 hours			
Follow-up duration – ≥6 hours			
Primary analysis (ARD)	**1 (177)**	**ARD 17.3% [3.7 to 30.9]**	**-**

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Setting – ICU			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
Follow-up duration – <6 hours			
Skin breakdown NOT REPORTED			
Treatment escalation			
Primary analysis	**1 (44)**	**RR 2.41 [1.24 to 4.68]**	**-**
HFNO event rate *	1 (27)	85.2% [68.9 to 96.5]	
NIV event rate *	1 (17)	35.3% [14.0 to 59.8%]	
Setting – ED			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic and/or hypercapnic			
Treatment duration – ≥6 hours			

ARD=absolute risk difference; CI=confidence interval; COPD=chronic obstructive pulmonary disease; ED=emergency department; HFNO=high flow nasal oxygen; ICU=intensive care unit; MD=mean difference; NIV=non-invasive ventilation; RR=relative risk; SMD=standardized mean difference

* Absolute event rates with Freeman-Tukey double arcsine variance-stabilizing transformation

Supplementary Table 12. HFNO vs NIV—Post- extubation

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Intubation			
Primary analysis	**3 (1476)**	**RR 1.13 [0.90 to 1.43]**	**0%**
HFNO event rate *	3 (726)	16.6% [13.9 to 19.4]	
NIV event rate *	3 (750)	14.7% [12.2 to 17.4]	
Setting – all ICU			
Post-extubation type			
Medical	2 (646)	RR 1.20 [0.88 to 1.64]	0%
Post-surgery	1 (830)	RR 1.06 [0.75 to 1.50]	-
Acute respiratory failure			
Hypoxic	2 (1434)	RR 1.13 [0.89 to 1.42]	0%
hypoxic, non-hypercapnic	*1 (604)*	*RR 1.19 [0.87 to 1.63]*	-
Hypercapnic	1 (42)	RR 1.82 [0.18 to 18.55]	-
Treatment duration – all ≥6 hours			
All-cause Mortality			
Primary analysis	**3 (1476)**	**RR 1.15 [0.88 to 1.51]**	**0%**
HFNO event rate *	3 (726)	11.4% [9.1 to 13.9]	-
NIV event rate *	3 (750)	9.8% [7.7 to 12.2]	-
Setting – all ICU			
Post-extubation type			
Medical	2 (646)	RR 1.12 [0.82 to 1.53]	0%

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Post-surgery	1 (830)	RR 1.22 [0.72 to 2.09]	-
Acute respiratory failure			
Hypoxic	2 (1434)	RR 1.17 [0.88 to 1.54]	0%
hypoxic, non-hypercapnic	*1 (604)*	*RR 1.14 [0.82 to 1.59]*	-
Hypercapnic	1 (42)	RR 0.91 [0.31 to 2.68]	-
Treatment duration – all ≥6 hours			
Follow-up duration			
Short-term, ≤7 days, ICU, or hospital	2 (1434)	RR 1.17 [0.88 to 1.54]	0%
Long-term, >7 days	1 (42)	RR 0.91 [0.31 to 2.68]	-
Hospital-acquired Pneumonia			
Primary analysis	**2 (1434)**	**RR 0.90 [0.70 to 1.16]**	**0%**
HFNO event rate *	2 (704)	12.3% [9.9 to 14.8]	-
NIV event rate *	2 (730)	13.6% [11.2 to 16.1]	-
Setting –both ICU			
Post-extubation type			
Medical	1 (604)	RR 0.76 [0.37 to 1.57]	-
Post-surgery	1 (830)	RR 0.93 [0.71 to 1.21]	-
Acute respiratory failure – both hypoxic			
hypoxic, non-hypercapnic	*1 (604)*	*RR 0.76 [0.37 to 1.57]*	-
Treatment duration – both ≥6 hours			
ICU Admissions (yes/no) NOT REPORTED			
ICU Length of Stay (3 trials reported, 2 provided data suitable to calculate a MD)			
Primary analysis	**2 (646)**	**MD -0.98 days [-1.99 to 0.03]**	**0%**
Setting – both ICU			
Post-extubation type – both medical			
Acute respiratory failure			
Hypoxic	1 (604)	MD -1.00 days [-2.10 to 0.10]	-
hypoxic, non-hypercapnic	*1 (604)*	*MD -1.00 days [-2.10 to 0.10]*	-
Hypercapnic	1 (42)	MD -0.90 days [-3.46 to 1.66]	-
Treatment duration –both ≥6 hours			
Hospital Length of Stay (2 trials reported, 1 provided data suitable to calculate a MD)			
Primary analysis	**1 (604)**	**MD -3.00 days [-6.80 to -0.80]**	**-**
Setting – ICU			
Post-extubation type – medical			
Acute respiratory failure – hypoxic, non-hypercapnic			
Treatment duration – ≥6 hours			
Comfort (2 trials reported, 1 provided data suitable to calculate a SMD and 1 provided data suitable to calculate an ARD, see Table 1 for more details)			
Primary analysis (SMD)	**1 (42)**	**SMD -0.75 [-1.38 to -0.12]**	**-**
Setting – ICU			
Post-extubation type – medical			
Acute respiratory failure – hypercapnic			

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Treatment duration – ≥6 hours			
Follow-up duration – ≥6 hours			
Primary analysis (ARD)	**1 (748)**	**ARD -1.6% [-8.7 to 5.6]**	**-**
Setting – ICU			
Post-extubation type – post-surgery			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
Follow-up duration – ≥6 hours			
Dyspnea			
Primary analysis (ARD)	**1 (752)**	**ARD -2.4% [-8.5 to 4.8]**	**-**
Setting – ICU			
Post-extubation type – post-surgery			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
Follow-up duration – ≥6 hours			
Skin breakdown			
Primary analysis	**3 (1454)**	**Peto OR 0.15 [0.02 to 1.13]**	**88%**
HFNO event rate *	3 (717)	0.7% [0.09 to 1.7]	
NIV event rate *	3 (737)	22.0% [19.0 to 25.1]	
Setting – all ICU			
Post-extubation type			
Medical	2 (646)	Peto OR 0.08 [0.06 to 0.12]	0%
Post-surgery	1 (808)	Peto OR 0.33 [0.19 to 0.58]	-
Acute respiratory failure			
Hypoxic	2 (1412)	Peto OR 0.17 [0.00 to >1000]	94%
hypoxic, non-hypercapnic	*1 (604)*	*Peto OR 0.08 [0.06 to 0.12]*	-
Hypercapnic	1 (42)	Peto OR 0.10 [0.01 to 0.80]	-
Treatment duration – all ≥6 hours			
Treatment Escalation (3 trials reported, data not suitable to calculate an effect size)			

CI=confidence interval; ED=emergency department; HFNO=high flow nasal oxygen; ICU=intensive care unit; MD=mean difference; NIV=non-invasive ventilation; OR=odds ratio; RR=relative risk; SMD=standardized mean difference

* Absolute event rates with Freeman-Tukey double arcsine variance-stabilizing transformation

Supplementary Table 13. HFNO vs COT—Initial Management

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Intubation			
Primary analysis	**8* (1694)**	**Peto OR 0.98 [0.34 to 2.82]**	**12%**
HFNO event rate †	8 (865)	8.1% [0.2 to 23.5]	-
COT event rate †	8 (829)	7.6% [0.0 to 25.4]	-
Setting			
ICU	4 (1123)	Peto OR 0.81 [0.63 to 1.05]	23%
ED	4* (571)	Peto OR 0.46 [0.09 to 2.30]	19%
Disease indication			
Mixed diseases	5* (690)	Peto OR 0.69 [0.41 to 1.17]	29%
Immunocompromised	2 (876)	Peto OR 0.83 [0.63 to 1.10]	0%
Immunocompromised + Frat 2016‡	*3 (932)*	*Peto OR 0.81 [0.62 to 1.06]*	*0%*
Cardiogenic pulmonary edema	1 (128)	Peto OR 7.63 [0.15 to >100]	-
Acute respiratory failure			
Hypoxic	7* (1647)	Peto OR 0.79 [0.61 to 1.01]	0%
hypoxic, non-hypercapnic	*3 (503)*	*Peto OR 0.75 [0.22 to 2.48]*	*25%*
Hypoxic and/or hypercapnic	1 (47)	Peto OR 8.1 [0.49 to >100]	-
Treatment duration			
≥6 hours	3 (1023)	Peto OR 0.80 [0.62 to 1.03]	31%
<6 hours	5* (671)	Peto OR 0.91 [0.29 to 2.88]	23%
All-cause Mortality			
Primary analysis	**4 (1407)**	**RR 0.97 [0.82 to 1.14]**	**42%**
HFNO event rate †	4 (722)	24.5% [21.4 to 27.7]	-
COT event rate †	4 (685)	25.1% [21.9 to 28.5]	-
Setting			
ICU	2 (976)	RR 0.78 [0.02 to 37.83]	72%
ED	2 (431)	RR 1.25 [0.79 to 1.99]	0%
Disease indication			
Mixed diseases	2 (503)	RR 0.82 [0.00 to >100]	78%
Immunocompromised	1 (776)	RR 0.99 [0.82 to 1.19]	-
Immunocompromised + Frat 2016‡	*2 (832)*	*RR 0.97 [0.80 to 1.16]*	*0%*
Cardiogenic pulmonary edema	1 (128)	RR 3.03 [0.13 to 71.85]	-
Acute respiratory failure – all hypoxic			
hypoxic, non-hypercapnic	*1 (303)*	*RR 1.22 [0.76 to 1.95]*	-
Treatment duration			
≥6 hours	2 (976)	RR 0.78 [0.02 to 37.8]	72%
<6 hours	2 (431)	RR 1.25 [0.79 to 1.99]	0%
Follow-up duration (2 trials reported data at both time points)			
Short-term, ≤7 days, ICU, or hospital	3 (631)	RR 0.79 [0.49 to 1.27]	33%
Long-term, >7 days	3 (1279)	RR 0.90 [0.33 to 2.42]	57%
Hospital-acquired Pneumonia			

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Primary analysis	**1 (200)**	**RR 0.44 [0.14 to 1.43]**	**-**
HFNO event rate †	1 (106)	3.8% [0.8 to 8.4]	-
COT event rate †	1 (94)	8.5% [3.6 to 15.1]	-
Setting – ICU			
Indication – mixed diseases			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
ICU Admissions (yes/no)			
Primary analysis	**2 (403)**	**RR 1.11 [0.58 to 2.12]**	**0%**
HFNO event rate †	2 (213)	7.1% [3.9 to 11.0]	-
COT event rate †	2 (190)	6.7% [3.4 to 10.8]	-
Setting – both ED			
Disease indication – both mixed diseases			
Acute respiratory failure – both hypoxic			
Treatment duration – both <6 hours			
ICU Length of Stay (3 trials reported, 2 reported data suitable to calculate a MD)			
Primary analysis	**2 (976)**	**MD 0.41 days [-1.08 to 1.90]**	**0%**
Setting – both ICU			
Disease indication			
Mixed diseases	1 (200)	MD -0.80 days [-4.83 to 3.23]	-
Immunocompromised	1 (776)	MD 0.60 days [-1.00 to 2.20]	-
Acute respiratory failure – both hypoxic			
Treatment duration – both ≥6 hours			
Hospital Length of Stay (4 trials reported, data not suitable to calculate a MD)			
Comfort (12 trials reported measure of comfort, 4 provided data suitable to calculate a SMD and 1 provided data suitable to calculate an ARD, see Table 2 for more details)			
Primary analysis (SMD)	**4 (415)**	**SMD -0.61 [-0.81 to -0.41]**	**44%**
Setting			
ICU	2 (247)	SMD -0.43 [-0.68 to -0.17]	0%
ED	2 (168)	SMD -0.90 [-1.21 to -0.58]	0%
Disease indication			
Mixed diseases	3 (287)	SMD -0.50 [-0.74 to -0.26]	24%
Cardiogenic pulmonary edema	1 (128)	SMD -0.87 [-1.23 to -0.50]	-
Acute respiratory failure			
Hypoxic	3 (368)	SMD -0.69 [-1.47 to 0.09]	63%
Hypoxic and/or hypercapnic	1 (47)	SMD -0.55 [-1.13 to 0.03]	-
Treatment duration			
≥6 hours	2 (247)	SMD -0.43 [-0.68 to -0.17]	0%
<6 hours	2 (168)	SMD -0.90 [-1.21 to -0.58]	0%
Follow-up duration			
≥6 hours	1 (47)	SMD -0.55 [-1.13 to 0.03]	-
<6 hours	3 (368)	SMD -0.69 [-1.47 to 0.09]	63%

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Primary analysis (ARD)	**1 (158)**	**ARD -15.5% [-30.8 to -0.2]**	**-**
Setting – ED			
Disease indication – mixed diseases			
Acute respiratory failure – hypoxic, non-hypercapnic			
Treatment duration – <6 hours			
Follow-up duration – <6 hours			
Dyspnea (13 trials reported measure of dyspnea, 4 provided data suitable to calculate a SMD and 3 provided data suitable to calculate an ARD, see Table 2 for more details)			
Primary analysis (SMD)	**4 (258)**	**SMD -0.56 [-1.35 to 0.24]**	**67%**
Setting			
ICU	1 (47)	SMD -0.12 [-0.69 to 0.46]	-
ED	3 (211)	SMD -0.70 [-1.93 to 0.54]	74%
Disease indication			
Mixed diseases	2 (87)	SMD -0.47 [-5.14 to 4.21]	64%
Cardiogenic pulmonary edema	1 (128)	SMD -0.24 [-0.58 to 0.11]	-
Palliative care	1 (43)	SMD -1.19 [-1.84 to -0.53]	
Acute respiratory failure			
Hypoxic	3 (211)	SMD -0.70 [-1.93 to 0.54]	74%
Hypoxic and/or hypercapnic	1 (47)	SMD -0.12 [-0.69 to 0.46]	-
Treatment duration			
≥6 hours	1 (47)	SMD -0.12 [-0.69 to 0.46]	-
<6 hours	3 (211)	SMD -0.70 [-1.93 to 0.54]	74%
Follow-up duration			
≥6 hours	1 (47)	SMD -0.12 [-0.69 to 0.46]	-
<6 hours	3 (211)	SMD -0.70 [-1.93 to 0.54]	74%
Primary analysis (ARD)	**3 (417)**	**ARD 22.2% [13.3 to 31.1]**	**65%**
Setting			
ICU	1 (160)	ARD 33.7% [19.2 to 48.1]	-
ED	2 (257)	ARD 14.8% [3.8 to 25.7]	0%
Disease indication – all mixed diseases			
Acute respiratory failure – all hypoxic			
hypoxic, non-hypercapnic	*2 (257)*	*ARD 14.8% [3.8 to 25.7]*	*0%*
Treatment duration			
≥6 hours	1 (160)	ARD 33.7% [19.2 to 48.1]	
<6 hours	2 (257)	ARD 14.8% [3.8 to 25.7]	0%
Follow-up duration			
≥6 hours	1 (160)	ARD 33.7% [19.2 to 48.1]	-
<6 hours	2 (257)	ARD 14.8% [3.8 to 25.7]	0%
Skin Breakdown (2 trials reported, data not suitable to calculate an effect size)			
Treatment Escalation (excluding intubation) (7 trials reported, 6 provided data suitable to calculate an OR)			
Primary analysis	**6* (727)**	**RR 0.46 [0.16 to 1.34]**	**38%**
HFNO event rate †	6 (377)	4.6% [1.0 to 9.9]	-

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
COT event rate †	6 (350)	10.8% [0.7 to 28.3]	-
Setting			
ICU	2 (156)	RR 0.64 [0.00 to >1000]	81%
ED	4* (571)	RR 0.40 [0.20 to 0.81]	0%
Disease indication			
Mixed diseases	4* (499)	RR 0.35 [0.19 to 0.64]	0%
Immunocompromised	1 (100)	RR 1.85 [0.49 to 6.97]	-
Cardiogenic pulmonary edema	1 (128)	RR 0.34 [0.04 to 3.22]	-
Acute respiratory failure – all hypoxic			
hypoxic, non-hypercapnic	*3 (503)*	*RR 0.62 [0.06 to 6.93]*	*54%*
Treatment duration – all <6 hours			

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HFNO=high flow nasal oxygen; ICU=intensive care unit; MD=mean difference; OR=odds ratio; RR=relative risk; SMD=standardized mean difference

* One trial reported no events occurred over the study duration (did not contribute to the pooled analysis)
† Absolute event rates with Freeman-Tukey double arcsine variance-stabilizing transformation
‡ Subgroup of immunocompromised patients

Supplementary Table 14. HFNO vs COT – Post-extubation Management

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Intubation			
Primary analysis	**7 (1,065)**	**Peto OR 0.60 [0.23 to 1.61]**	**40%**
HFNO event rate †	7 (536)	4.7% [0.9 to 10.7]	-
COT event rate †	7 (529)	8.3% [2.6 to 16.4]	-
Setting – all ICU			
Post-extubation type			
Post-surgery	2 (244)	Peto OR 1.35 [0.23 to 8.01]	45%
Medical	5 (821)	Peto OR 0.53 [0.17 to 1.69]	42%
Acute respiratory failure			
Hypoxic	5 (936)	Peto OR 0.59 [0.12 to 2.88]	51%
hypoxic, non-hypercapnic	*4 (847)*	*Peto OR 0.43 [0.07 to 2.67]*	*41%*
Hypoxic and/or hypercapnic	2 (129)	Peto OR 0.79 [0.27 to 2.33]	0%
Treatment duration – all ≥6 hours			
All-cause Mortality			
Primary analysis	**4* (782)**	**RR 1.01 [0.60 to 1.72]**	**0%**
HFNO event rate †	4 (395)	4.6% [2.6 to 7.1]	-
COT event rate †	4 (387)	5.0% [2.9 to 7.6]	-
Setting – all ICU			
Post-extubation type			
Medical	3 (692)	RR 1.01 [0.60 to 1.72]	0%
Post-surgery	1 (90)	No events	-
Acute respiratory failure – all hypoxic			
hypoxic, non-hypercapnic	*3 (692)*	*RR 1.01 [0.60 to 1.72]*	*0%*
Treatment duration – all ≥6 hours			
Follow-up duration – all short-term (≤7 days, ICU, or hospital)			
Hospital-acquired Pneumonia			
Primary analysis	**1 (527)**	**RR 0.50 [0.13 to 1.97]**	**-**
HFNO event rate †	1 (264)	1.1% [0.1 to 2.9]	-
COT event rate †	1 (263)	2.3% [0.8 to 4.5]	-
Setting – ICU			
Post-extubation type – medical			
Acute respiratory failure – hypoxic, non-hypercapnic			
Treatment duration – ≥6 hours			
ICU Admissions (yes/no) NOT REPORTED			
ICU Length of Stay (6 trials reported, 5 provided data suitable to calculate a MD)			
Primary analysis	**5 (479)**	**MD 0.19 days [-0.19 to 0.57]**	**0%**
Setting – all trials ICU			
Post-extubation type			
Post-surgery	2 (245)	MD 0.04 days [-0.32 to 0.40]	0%
Medical	3 (234)	MD 0.64 days [-0.19 to 1.47]	0%
Acute respiratory failure – all hypoxic			

Outcomes and subgroups	Number of trials (n)	Relative effect, MD, SMD, or event rates [95% CI]	I^2
Hypoxic	4 (410)	MD 0.05 days [-0.31 to 0.41]	0%
hypoxic, non-hypercapnic	*3 (320)*	*MD 0.02 days [-0.38 to 0.42]*	*0%*
Hypoxic and/or hypercapnic	1 (69)	MD 0.60 days [-0.26 to 1.46]	-
Treatment duration – all ≥6 hours			
Hospital Length of Stay (2 trials reported, 1 provided data suitable to calculate a MD)			
Primary analysis	1 (60)	MD 12.00 days [0.15 to 23.85]	**-**
Setting – ICU			
Post-extubation type – medical			
Acute respiratory failure – hypoxic, non-hypercapnic			
Treatment duration – ≥6 hours			
Comfort (4 trials reported, 2 provided data suitable to calculate a SMD or ARD, see Table 2 for more details)			
Primary analysis (SMD)	**1 (105)**	**SMD -0.70 [-1.10 to -0.31]**	**-**
Setting – ICU			
Post-extubation type – medical			
Acute respiratory failure – hypoxic, non-hypercapnic			
Treatment duration – ≥6 hours			
Follow-up duration – ≥6 hours			
Primary analysis (ARD)	**1 (90)**	**ARD -31.5% [-51.0 to -11.9]**	**-**
Setting – ICU			
Post-extubation type – post-surgery			
Acute respiratory failure – hypoxic			
Treatment duration – ≥6 hours			
Follow-up duration – ≥6 hours			
Dyspnea (1 trial reported, data not suitable to calculate a SMD or ARD (reported as medians). See Table 2 for more details)			
Skin Breakdown (1 trial reported, data not suitable to calculate an effect size)			
Treatment Escalation (excluding intubation)			
Primary analysis	**5 (479)**	**RR 0.43 [0.27 to 0.70]**	**0%**
HFNO event rate †	5 (241)	6.3% [0.0 to 21.6]	-
COT event rate †	5 (238)	18.5% [1.6 to 45.9]	-
Setting – all ICU			
Post-extubation type			
Post-surgery	2 (245)	RR 0.52 [0.32 to 0.87]	0%
Medical	3 (234)	RR 0.26 [0.09 to 0.72]	0%
Acute respiratory failure			
Hypoxic	3 (350)	RR 0.46 [0.29 to 0.75]	0%
hypoxic, non-hypercapnic	*2 (260)*	*RR 0.40 [0.14 to 1.10]*	*0%*
Hypoxic and/or hypercapnic	2 (129)	RR 0.27 [0.07 to 1.08]	0%
Treatment duration – all ≥6 hours			

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HFNO=high flow nasal oxygen; ICU=intensive care unit; MD=mean difference; OR=odds ratio; RR=relative risk; SMD=standardized mean difference

* One trial reported no events occurred over the study duration (did not contribute to the pooled analysis)
† Absolute event rates with Freeman-Tukey double arcsine variance-stabilizing transformation

Supplementary Table 15. Physiologic Outcomes HFNO vs NIV – Initial Management: Between Group Differences at Follow-up

Study Time measured	PaO_2/FiO_2 ratio Direction and Mean*	SpO_2 Direction and Mean*	PaO_2 Direction and Mean*	$PaCO_2$ Direction and Mean*
Cong, 2019 (29) 5 days†	NR	↔ 91.9 HFNO 92.8 NIV	↔ 81.9 HFNO 82.2 NIV	↔ 58.9 HFNO 60.0 NIV
Doshi, 2018 (32) 4 hours	NR	↔ 96.8 HFNO 97.2 NIV	NR	↑ 46.3 HFNO 52.5 NIV
Frat, 2015 (34) 6 hours‡	↓ 130 HFNO 186 NIV	NR	↓ 90 HFNO 111 NIV	↔ 36 HFNO 35 NIV
Saksitthichok, 2019 (48) 30 min	NR	↔ Change from baseline	↔ Change from baseline	↔ Change from baseline

*means unless noted; ↔ No difference between groups; ↑ Favors HFNO; ↓ Poorer outcome with HFNO
†also reported at 12 hours
‡also reported at 1 hour

Supplementary Table 16. Physiologic Outcomes HFNO vs NIV – Post-extubation Management: Between Group Differences at Follow-up

Study Time measured	PaO_2/FiO_2 ratio Direction and Mean*	SpO_2 Direction and Mean*	PaO_2 Direction and Mean*	$PaCO_2$ Direction and Mean*
Hernandez, 2016 (37) (high risk) 12 hours	↔ 99 HFNO 104 NIV	NR	NR	↔ 46 HFNO 47 NIV
Jing, 2019 (39) 48 hours	↓ 201.2 HFNO 257.5 NIV	NR	NR	↑ 56.9 HFNO 61.5 NIV
Stéphan, 2015 (53) 6-12 hours†	↓ 198 HFNO 261 NIV	NR	NR	↔ 38.2 HFNO 39.3 NIV

*means unless noted; ↔ No difference between groups; ↑ Favors HFNO; ↓ Poorer outcome with HFNO
†also reported at 1 hour

Supplementary Table 17. Physiologic Outcomes HFNO vs COT – Initial Management: Between Group Differences at Follow-up

Study Time measured	PaO_2/FiO_2 ratio Direction and Mean*	SpO_2 Direction and Mean*	PaO_2 Direction and Mean*	$PaCO_2$ Direction and Mean*
Azoulay, 2018 (27) 6 hours	↑ Medians 150 HFNO 119 COT	NR	NR	NR
Bell, 2015 (28) 2 hours	NR	NR	NR	NR
Frat, 2015 (34) 6 hours†	↓ 130 HFNO 161 COT	NR	↔ 90 HFNO 93 COT	↔ 36 HFNO 36 COT
Jones, 2016 (40) 3 hours	NR	↔ 92.9 HFNO 93.7 COT	NR	NR
Lemiale, 2015 (41) 2 hours	NR	NR	NR	NR
Makdee, 2017 (43) 1 hour	NR	↑ 99.2 HFNO 98.7 COT	NR	NR
Parke, 2011 (44) 30 min; 1, 2, 4 hours	↔ Data not reported	↔ Data not reported	NR	NR
Rittayamai, 2015 (46) 1 hour	NR	↔ 96.8 HFNO 97.6 CIT	NR	NR
Spoletini, 2018 (52) during “breaks”	NR	↔ 94.1 HFNO 94.7 COT	NR	NR

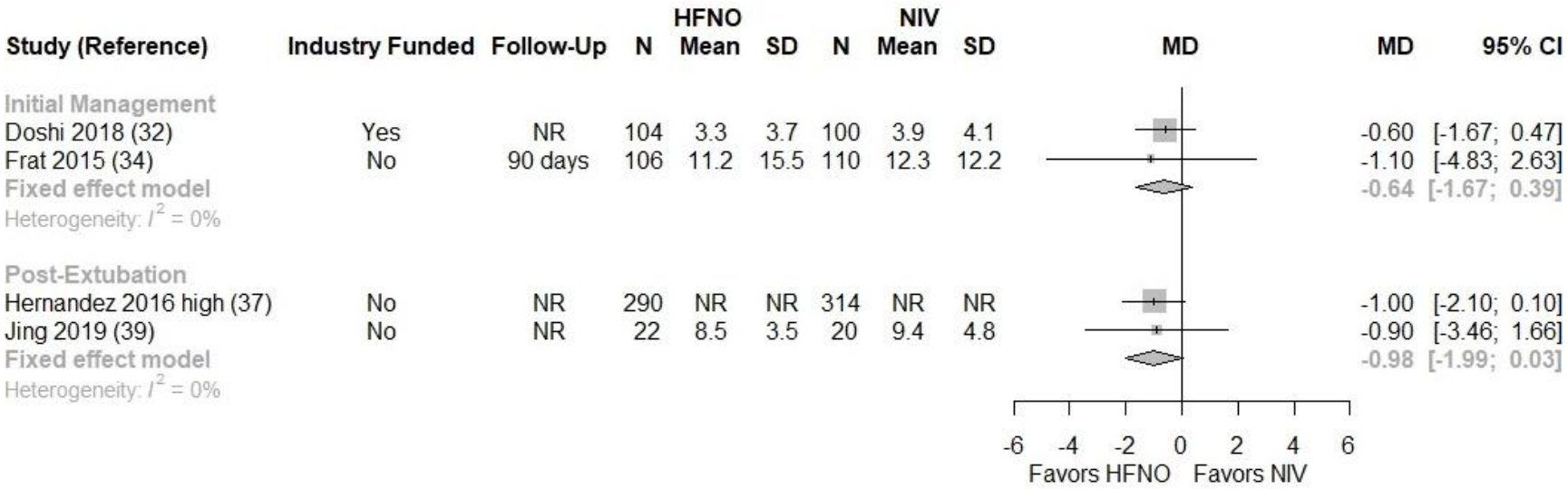
*means unless noted; ↔ No difference between groups; ↑ Favors HFNO; ↓ Poorer outcome with HFNO
†also reported at 1 hour

Supplementary Table 18. Physiologic Outcomes HFNO vs COT – Post extubation: Between Group Differences at Follow-up

Study Time measured	PaO_2/FiO_2 ratio Direction and Mean*	SpO_2 Direction and Mean*	PaO_2 Direction and Mean*	$PaCO_2$ Direction and Mean*
Cho, 2020 (56) 24 hours	↔ 277 HFNO 314 COT	NR	NR	↔ 36 HFNO 37 COT
Corley, 2015 (30) >16-24 hours†	↑ 175.8 HFNO 159.3 COT	NR	NR	NR
Hernandez, 2016 (38) (low risk) 12 hours	↔ 105 HFNO 108 COT	NR	NR	↔ 37 HFNO 36 COT
Maggiore, 2014 (42) 48 hours	↑ 313.3 HFNO 250.2 COT	↑ Data not reported	NR	↑ Data not reported
Matsuda, 2020 (58) 24 hours	↔ 264 HFNO 224 COT	NR	NR	NR
Song, 2017 (51) 24 hours	NR	↑ 98.0 HFNO 96.9 COT	↑ 83.2 HFNO 74.5 COT	↔ 41.4 HFNO 42.2 COT
Vourc'h, 2019 (55) 24 hours‡	↑ 129.9 HFNO 106.9 COT	NR	NR	↔ 39.8 HFNO 39.0 COT

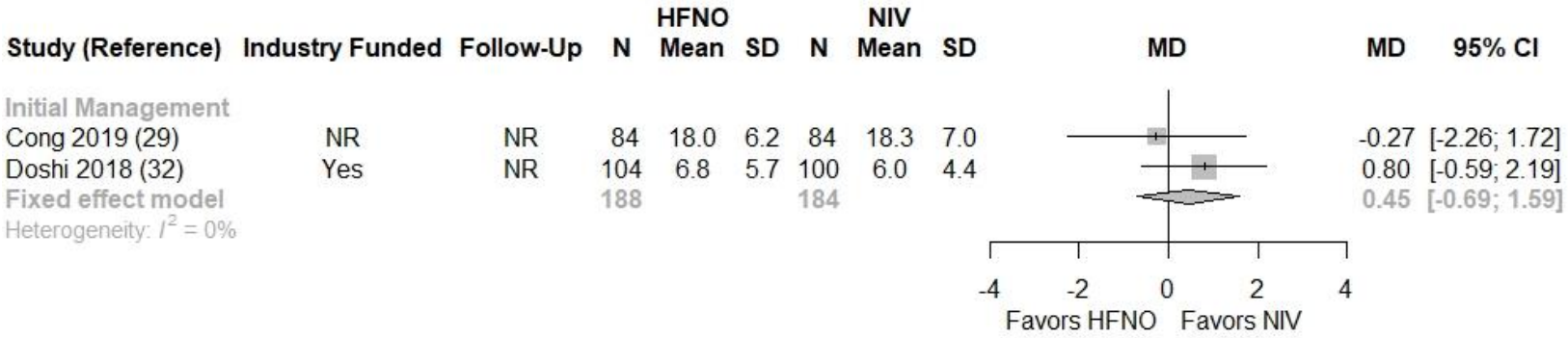
*means unless noted; ↔ No difference between groups; ↑ Favors HFNO; ↓ Poorer outcome with HFNO
†also reported at 0-8 hours
‡also reported at 1 hour

Supplementary Figure 1. HFNO vs NIV – ICU Length of Stay (MD unit: days)



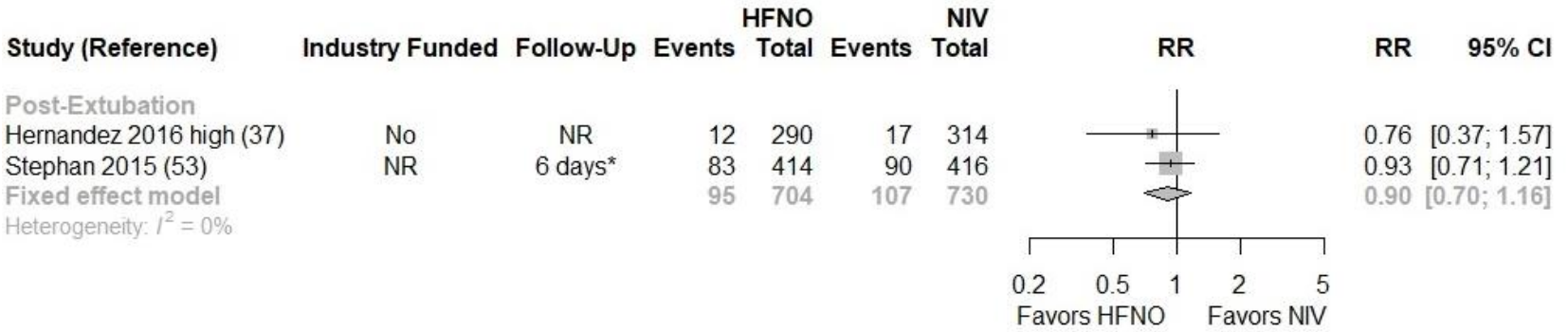
CI=confidence interval; HFNO=high-flow nasal oxygen; ICU=intensive care unit; MD=mean difference; NIV=non-invasive ventilation; NR=not reported

Supplementary Figure 2. HFNO vs NIV – Hospital Length of Stay (MD unit: days)



CI=confidence interval; HFNO=high-flow nasal oxygen; MD=mean difference; NIV=non-invasive ventilation; NR=not reported; SD=standard deviation

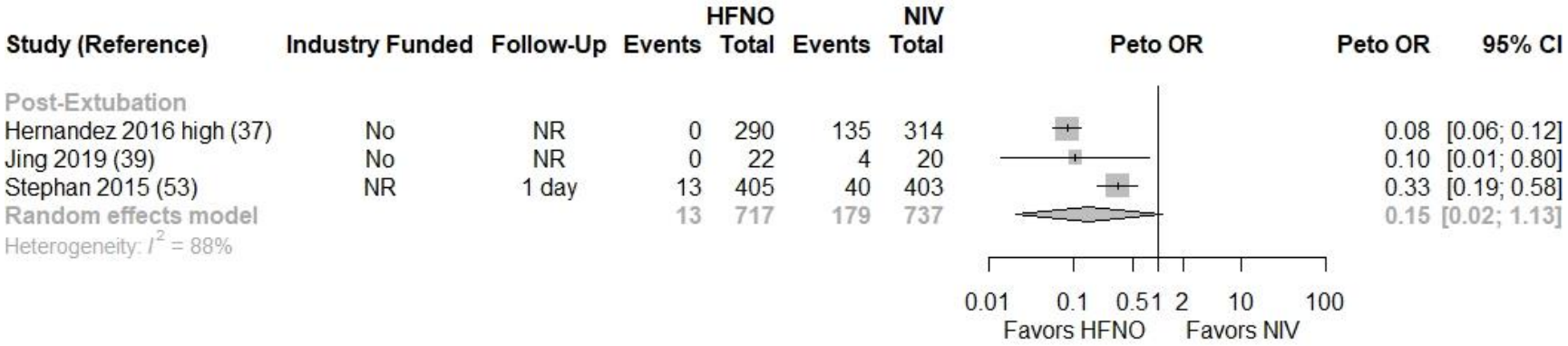
Supplementary Figure 3. HFNO vs NIV – Hospital-acquired Pneumonia



CI=confidence interval; HFNO=high-flow nasal oxygen; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported; RR=risk ratio

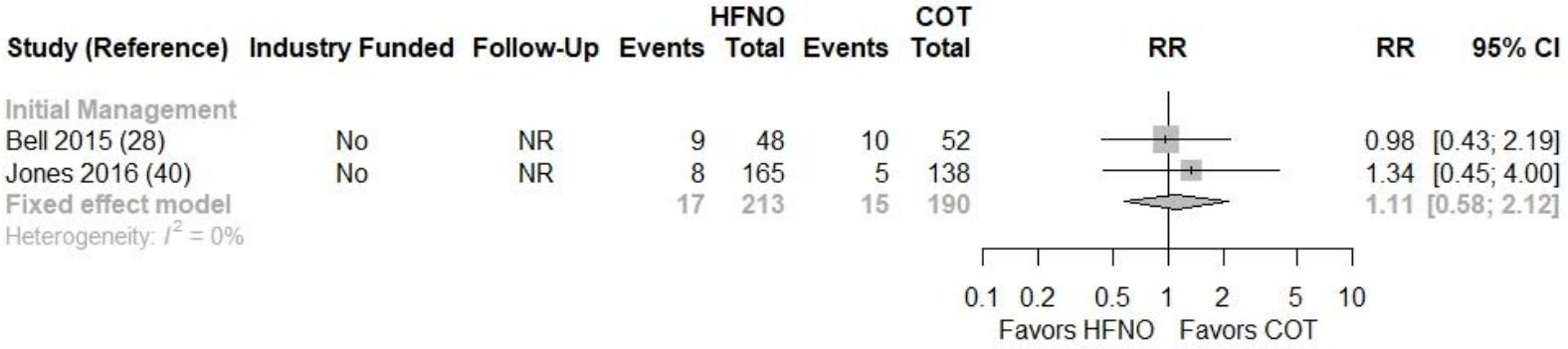
*Patients were monitored for pneumonia while they were in the ICU. This is an estimated follow-up time based on the reported median ICU length of stay.

Supplementary Figure 4. HFNO vs NIV – Skin breakdown



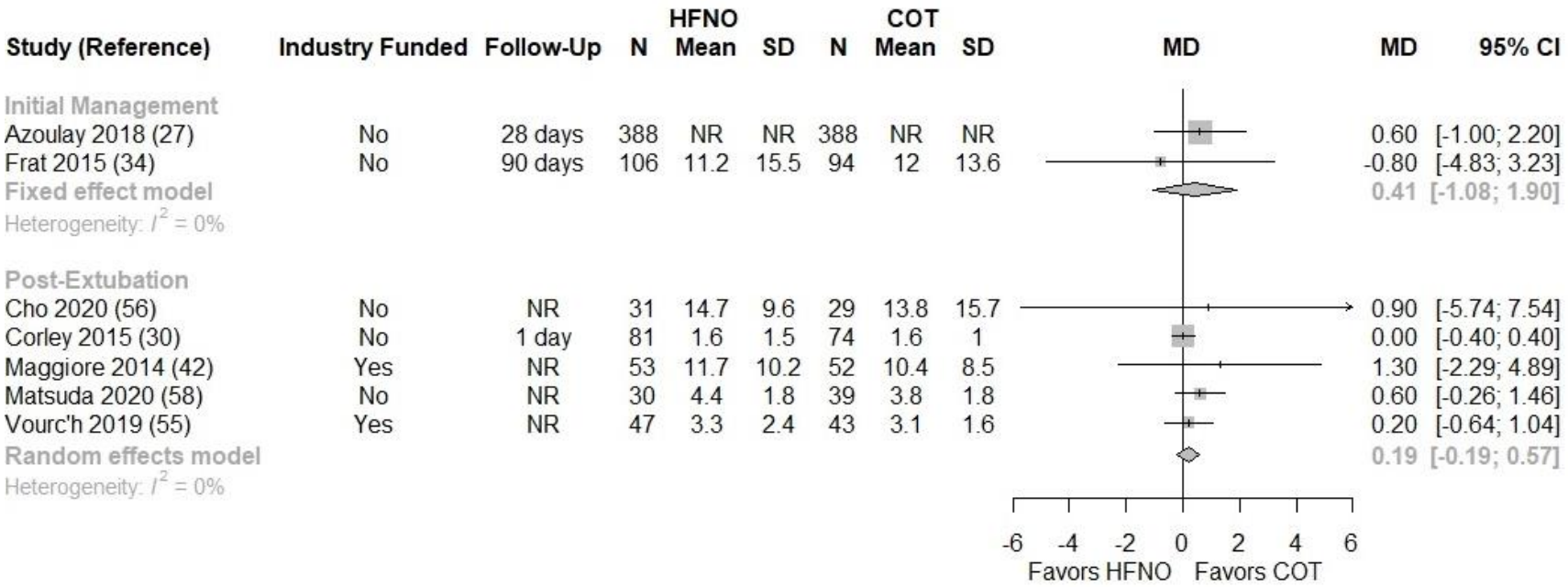
CI=confidence interval; HFNO=high-flow nasal oxygen; OR=odds ratio; NIV=non-invasive ventilation; NR=not reported

Supplementary Figure 5. HFNO vs COT – ICU Admissions (yes or no)



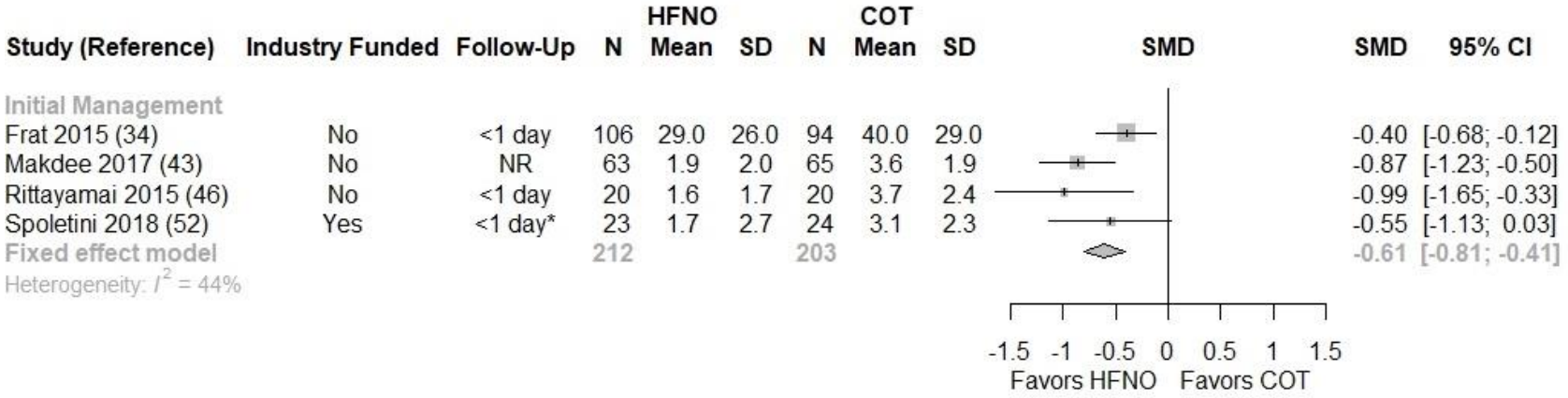
CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; ICU=intensive care unit; RR=risk ratio; NR=not reported

Supplementary Figure 6. HFNO vs COT – ICU Length of Stay (MD unit: days)



CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; ICU=intensive care unit; MD=mean difference; NR=not reported

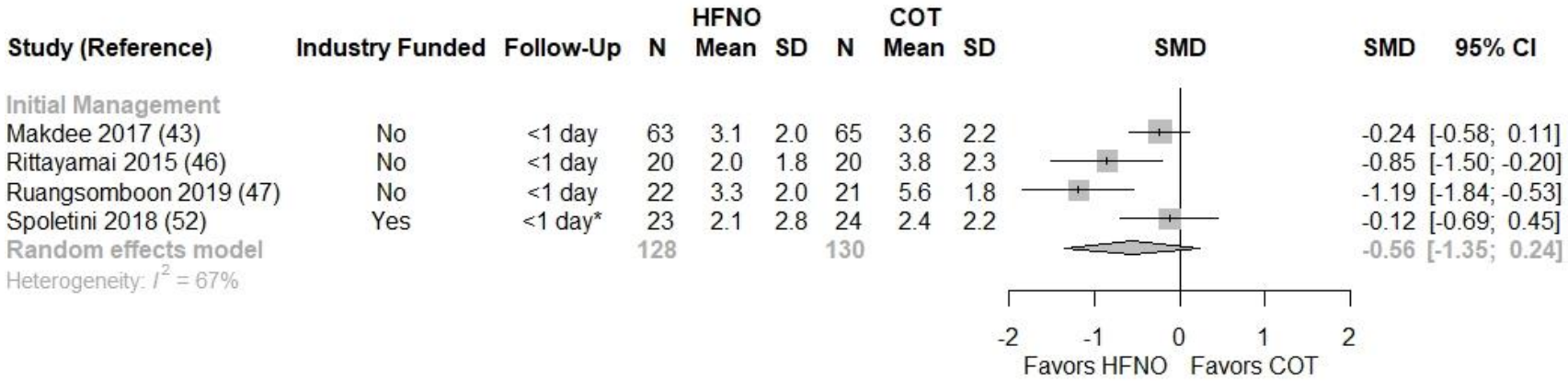
Supplementary Figure 7. HFNO vs COT – Patient Comfort



CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; SD=standard deviation; SMD=standardized mean difference

*In the Spoletini, 2018 (52) trial, all patients were on NIV and were randomized to HFNO or COT during breaks off NIV. In their respective treatment groups, patients were on HFNO for a mean duration of 520 minutes and COT for 370 minutes.

Supplementary Figure 8. HFNO vs COT – Dyspnea

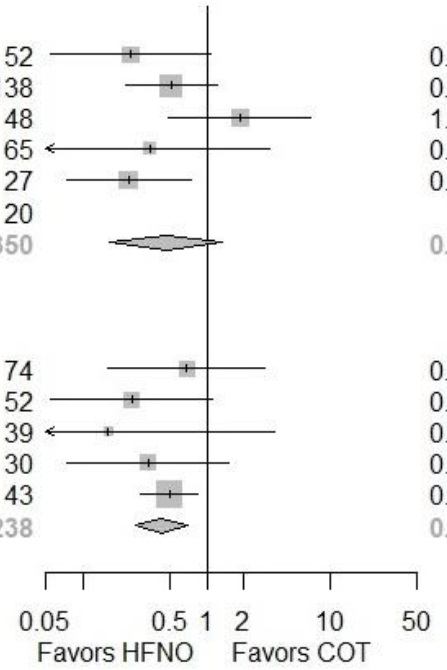


CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; SD=standard deviation; SMD=standardized mean difference

*In the Spoletini, 2018 (52) trial, all patients were on NIV and were randomized to HFNO or COT during breaks off NIV. In their respective treatment groups, patients were on HFNO for a mean duration of 520 minutes and COT for 370 minutes.

Supplementary Figure 9. HFNO vs COT – Treatment Escalation (excluding intubation)*

Study (Reference)	Industry Funded	Follow-Up	HFNO Events	HFNO Total	COT Events	COT Total	RR	95% CI
Initial Management								
Bell 2015 (28)†	No	<1 day	2	48	9	52	0.24	[0.05; 1.06]
Jones 2016 (40)	No	1 day	8	165	13	138	0.51	[0.22; 1.21]
Lemiale 2015 (41)	Yes	<1 day	6	52	3	48	1.85	[0.49; 6.97]
Makdee 2017 (43)	No	1 day	1	63	3	65	0.34	[0.04; 3.22]
Parke 2011 (44)†	Yes	1 day	3	29	12	27	0.23	[0.07; 0.74]
Rittayamai 2015 (46)	No	<1 day	0	20	0	20		
Random effects model			20	377	40	350	0.46	[0.16; 1.34]
Heterogeneity: I^2 = 38%								
Post-Extubation								
Corley 2015 (30)†	No	1 day	3	81	4	74	0.69	[0.16; 2.96]
Maggiore 2014 (42)	Yes	2 days	2	53	8	52	0.25	[0.05; 1.10]
Matsuda 2020 (58)	No	2 days	0	30	3	39	0.16	[0.01; 3.56]
Song 2017 (51)†	No	1 day	2	30	6	30	0.33	[0.07; 1.52]
Vourc'h 2019 (55)	Yes	NR	13	47	24	43	0.50	[0.29; 0.84]
Random effects model			20	241	45	238	0.43	[0.27; 0.70]
Heterogeneity: I^2 = 0%								



* Defined as switching of the assigned treatment to a higher level of oxygen therapy (excluding intubation). All events are escalations to NIV unless noted otherwise.
† COT events include escalations to NIV or HFNO.

CI=confidence interval; COT=conventional oxygen therapy; HFNO=high-flow nasal oxygen; NR=not reported; RR=risk ratio

Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: An Updated Systematic Review and Network Meta-Analysis

I. Introduction

Osteoporosis is a condition characterized by reduced bone density or mass resulting in bone weakness and increased susceptibility to fractures.[1,2] Low bone density is sometimes referred to as osteopenia. Bone mineral density (BMD) assessment is used to diagnose osteoporosis and osteopenia. The World Health Organization (WHO) defines osteoporosis as a BMD of greater than -2.5 standard deviations (SD) below the average for young healthy women, referred to as the T-score. Osteopenia is defined as having a T-score between -1 and -2.5.[2] New criteria have expanded the definition of osteoporosis to include history of fractures from low-level trauma (such as a fall from standing height) in the absence of a BMD score, and the FRAX algorithm is widely recognized as another valid tool.[3] When these definitions are incorporated, it is estimated that in the United States (US) about 16% of men and 30% of women over 50 years of age have osteoporosis. The aging population is projected to further increase these figures. Given the increasing prevalence of osteoporosis and its cost and impact on patients, there is great interest in understanding the best and most cost-effective treatments to prevent fractures in those with low bone density.

The first comparative effectiveness/efficacy review of interventions to prevent osteoporosis-related fractures was published in 2007.[4] Subsequently, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers program commissioned a follow-up review which was published in 2012,[5] and was further updated for pharmacological treatments in an Annals of Internal Medicine journal publication in 2014.[6] The review found good quality evidence supporting a number of medications, including bisphosphonates, denosumab, and teriparatide to reduce fractures when compared to placebo. It also found a previously synthesized harm of bisphosphonate use (i.e., atypical subtrochanteric femur fracture). There was little comparative effectiveness evidence, and no evidence on costs. In the intervening years, some new medications have been approved (e.g., abaloparatide, romosozumab), and there may be new data on harms and costs. In light of this we will be updating some of the key questions of the prior reviews. To address the lack of data on comparative effectiveness, we also plan to conduct a network meta-analysis.

II. Key Questions

KQ 1. What are the effects of pharmacologic interventions on fracture-related outcomes in women with osteopenia?

KQ 2. What are the effects of pharmacologic interventions on fracture-related outcomes in men with osteopenia?

KQ 3. What are the comparative effects of pharmacologic treatments on fracture related outcomes in women with osteoporosis?

KQ 4. What are the comparative effects of pharmacologic treatments on fracture related outcomes in men with osteoporosis?

KQ 5. What are the harms of pharmacologic therapy used to treat osteopenia or osteoporosis?

KQ 6. What are the effects of pharmacologic therapy compared to non-pharmacologic therapy (such as exercise) on fracture related outcomes in patients with osteopenia or osteoporosis?

KQ 7. What are patients' values and preferences on osteoporosis prevention and treatment? How do patients with osteopenia or osteoporosis weigh the benefits and harms of pharmacologic and non-pharmacological interventions for fracture prevention? How do patients use this valuation in their decision-making regarding treatment?

KQ 8. What are the costs and cost-effectiveness of pharmacologic interventions used to reduce fracture-related outcomes in men and women with osteopenia or osteoporosis?

III. Inclusion Criteria (PICOTS)

Table 1. Key Questions and Proposed PICOTS for ACP Osteoporosis Review

Key Questions	**KQ 1.** What are the effects of pharmacologic interventions on fracture-related outcomes in women with osteopenia?	**KQ 2.** What are the effects of pharmacologic interventions on fracture-related outcomes in men with osteopenia?	**KQ 3.** What are the comparative effects of pharmacologic treatments on fracture related outcomes in women with osteoporosis?	**KQ 4.** What are the comparative effects of pharmacologic treatments on fracture related outcomes in men with osteoporosis?	**KQ 5.** What are the harms of pharmacologic therapy used to treat osteopenia or osteoporosis?	**KQ 6.** What are the effects of pharmacologic therapy compared to non-pharmacologic therapy (such as exercise) on fracture related outcomes in patients with osteopenia or osteoporosis?	**KQ 7.** What are patients' values and preferences on osteoporosis prevention and treatment? How do patients with osteopenia or osteoporosis weigh the benefits and harms of pharmacologic and non-pharmacological interventions for fracture prevention? How do patients use this valuation in their decision-making regarding treatment?	**KQ 8.** What are the costs and cost-effectiveness of pharmacologic interventions used to reduce fracture-related outcomes in men and women with osteopenia or osteoporosis?
Populations[a]	Adult women with low bone density (osteopenia) as defined by each included study	Adult men with low bone density (osteopenia) as defined by each included study	Adult women with osteoporosis as defined by each included study (not due to a secondary cause)	Adult men with osteoporosis as defined by each included study (not due to a secondary cause)	Adult men or women with osteopenia or osteoporosis as defined by each included study (not due to a secondary cause)			
Interventions	Pharmacologic treatment (see Table 2, below)					Pharmacologic treatments (Table 2), vitamin D, or calcium compared to non-pharmacologic treatments (i.e., exercise)	Pharmacologic treatments (Table 2), vitamin D, or calcium and non-pharmacologic interventions (i.e., exercise)	Pharmacologic treatments (Table 2), vitamin D, or calcium
Comparators	Pharmacologic treatment (Table 2), vitamin D, or calcium compared to other pharmacologic treatment, vitamin D, or calcium (including combination and sequential use), or placebo.					Non-pharmacologic treatments (i.e.,		

Key Questions	**KQ 1.** What are the effects of pharmacologic interventions on fracture-related outcomes in women with osteopenia?	**KQ 2.** What are the effects of pharmacologic interventions on fracture-related outcomes in men with osteopenia?	**KQ 3.** What are the comparative effects of pharmacologic treatments on fracture related outcomes in women with osteoporosis?	**KQ 4.** What are the comparative effects of pharmacologic treatments on fracture related outcomes in men with osteoporosis?	**KQ 5.** What are the harms of pharmacologic therapy used to treat osteopenia or osteoporosis?	**KQ 6.** What are the effects of pharmacologic therapy compared to non-pharmacologic therapy (such as exercise) on fracture related outcomes in patients with osteopenia or osteoporosis?	**KQ 7.** What are patients' values and preferences on osteoporosis prevention and treatment? How do patients with osteopenia or osteoporosis weigh the benefits and harms of pharmacologic and non-pharmacological interventions for fracture prevention? How do patients use this valuation in their decision-making regarding treatment?	**KQ 8.** What are the costs and cost-effectiveness of pharmacologic interventions used to reduce fracture-related outcomes in men and women with osteopenia or osteoporosis?
						exercise) only if compared to pharmacologic treatment		

Outcomes	• Reduction in fractures, including
	  ○ Vertebral fracture: clinical
	  ○ Vertebral fracture: radiologic
	  ○ Hip fracture
	  ○ Nonvertebral (composite outcome including wrist and other nonvertebral fractures)
	  ○ Clinical fractures (composite outcome of clinically apparent/symptomatic fractures)
	• Quality of life
	• Functional status (e.g., fracture-related disability, fracture-related healthcare use)
					Serious adverse events (AEs) as defined by study authors, withdrawal due to AEs, with specific reporting of osteonecrosis of the jaw, atypical/ subtrochanteric fractures, and cardiac atrial fibrillation.	Same outcomes as for KQs 1-4	Patient values and preferences (from shared decisionmaking tools)	Cost and cost-effectiveness

Timing	Minimum follow-up of 12 months							
Setting	No limitations							

Key Questions	**KQ 1.** What are the effects of pharmacologic interventions on fracture-related outcomes in women with osteopenia?	**KQ 2.** What are the effects of pharmacologic interventions on fracture-related outcomes in men with osteopenia?	**KQ 3.** What are the comparative effects of pharmacologic treatments on fracture related outcomes in women with osteoporosis?	**KQ 4.** What are the comparative effects of pharmacologic treatments on fracture related outcomes in men with osteoporosis?	**KQ 5.** What are the harms of pharmacologic therapy used to treat osteopenia or osteoporosis?	**KQ 6.** What are the effects of pharmacologic therapy compared to non-pharmacologic therapy (such as exercise) on fracture related outcomes in patients with osteopenia or osteoporosis?	**KQ 7.** What are patients' values and preferences on osteoporosis prevention and treatment? How do patients with osteopenia or osteoporosis weigh the benefits and harms of pharmacologic and non-pharmacological interventions for fracture prevention? How do patients use this valuation in their decision-making regarding treatment?	**KQ 8.** What are the costs and cost-effectiveness of pharmacologic interventions used to reduce fracture-related outcomes in men and women with osteopenia or osteoporosis?
Study design	Randomized controlled trials (RCTs)				• RCTs • Case-control and cohort studies (N > 1,000)	RCTs	Systematic reviews	Systematic reviews of cost-effectiveness analyses

Notes. [a] We will include evidence for the following subgroups (as available): risk of fractures (defined by BMD, FRAX or other risk assessment score, or prior fractures), demographic characteristics (e.g., age, race, ethnicity), and other factors (e.g., whether the individuals were community dwelling vs. institutionalized, vitamin D deficient vs. not).

Table 2. Proposed Pharmacologic Interventions to Include

Generic name	Brand name and approval year	Category
Abaloparatide	Tymlos (2017)	PTHrP analog
Alendronate	Fosamax (1995, 2005), Binosto (2012)	Bisphosphonate
Denosumab	Prolia (2010), Xgeva (2010)	RANKL Inhibitor
Estradiol	generic tablets, Climara (1994), Menostar (1994), Minivelle (2012)	HRT
Estradiol-Norgestimate	Ortho-Prefest (1999)	HRT
Estradiol/norethindrone acetate tablets	Activella (2000), Femhrt (1999)	HRT
Estrogen	Estratab (1998), Prempro/Premphase (1995), Vivelle (2000), Premarin (2009)	HRT
Estrogen tablets	Menest (1977), Premarin (1942)	HRT
Estrogen + bazedoxifene	Duavee (2013)	HRT
Estrogen patch	Alora (2002)	HRT
Ibandronate	Boniva (2003, 2006)	Bisphosphonate
Parathyroid hormone	Natpara (2015)	Peptide hormone
Pamidronate	Aredia (1998)	Bisphosphonate
Raloxifene	Evista (1997, 1999, 2007)	SERM
Risedronate	Actonel (1998), Atelvia (2010)	Bisphosphonate
Romosozumab	Evenity (2019)	Sclerostin inhibitor
Teriparatide	Forteo (2002), Bonsity (2019)	Peptide hormone
Zoledronic acid	Reclast (2007), Zometa (2001, 2002)	Bisphosphonate

Abbreviations. HRT: hormone replacement therapy; PTHrP: parathyroid hormone-related peptide; RANKL: receptor activator of nuclear factor kappa beta (NFkB ligand); SERM: selective estrogen receptor modulator
Note: Inclusion of estrogen-containing treatments only when the population was selected for osteoporosis. Osteoporosis treatment is an off-label use.

IV. Literature Search Strategies

We will conduct a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the key questions. Search strategies will be developed in consultation with a research librarian and peer reviewed by a second research librarian using the Peer Review of Electronic Search Strategies (PRESS) guidelines.[7] To identify relevant articles, we will search Ovid Medline ALL, Ovid EBM Reviews Cochrane Central Register of Controlled Trials (CCRCT) and Cochrane Database of Systematic Reviews, and lastly ClinicalTrials.gov. See Appendix A for sample search strategy. Only English-language publications since the last systematic review (2014 to 2021) will be included. We will also conduct a bridge search for trials and observational studies on calcium and vitamin D (and its analogues) for osteoporosis or osteopenia in Medline ALL, CCRCT, and ClinicalTrials.gov. Only English-language studies published since the Yao systematic review search (2019-2021) will be included.[8] We will further consult experts and review the bibliographies of relevant articles to identify additional studies.

V. Study Selection

KQs 1 through 4 and KQ 6 pertaining to effectiveness and efficacy
Randomized controlled trials that report fracture outcomes for one or more of the pharmacologic treatments of interest, including vitamin D and calcium, or a non-pharmacologic intervention (i.e., exercise) will be accepted for the efficacy analyses. We will also include reports of post hoc analyses and open-label extensions of trials.

KQ 5 pertaining to harms
For publications obtained from the search for adverse events by intervention of interest, documents will be accepted if they suggest that the manuscript includes information on the relationship between the adverse event and the eligible intervention. We will include randomized controlled trials, as well as large case-control or cohort studies ($n \geq 1{,}000$) that report fracture and specific outcomes of interest (i.e., osteonecrosis of the jaw, atypical subtrochanteric fractures, and atrial fibrillation) in our adverse event analyses. All other harms for analysis will be identified through randomized controlled trials and only captured if they are statistically significantly different or $\geq 10\%$ difference between groups. Although we will not systematically contact researchers for additional data, we might, for newly released drugs, contact FDA and the manufacturers for unpublished data.

KQs 7 and 8 pertaining to patient values and preferences and cost-effectiveness
We will include systematic reviews pertaining to patient values and preferences (KQ 7) and cost-effectiveness (KQ 8) of interventions to prevent fractures in men and women with osteopenia and osteoporosis.

Pertaining to all KQs
We will limit our inclusion of studies to those published in English. The full criteria for patient populations, interventions, comparators, outcomes, timing, settings, and study designs (PICOTS) are specified in Table 1.

Using these pre-specified inclusion and exclusion criteria (PICOTS), all citations will be reviewed for potential relevance using DistillerSR. Two reviewers will independently screen

the title and abstract of each citation for exclusion, and inclusion by one of those reviewers will progress the citation to full-text review. An initial calibration round will be held in which 100 titles and abstracts will be screened by four members of the review team, and concordance will be discussed. At the full-text screening stage, two independent reviewers must agree on a final inclusion or exclusion decision for all articles. Any disagreements will be resolved through consensus or consultation with a third reviewer. Articles meeting eligibility criteria will be included for data abstraction and evidence synthesis.

VI. Data Abstraction

Data from published reports will be abstracted into a customized database by one reviewer and confirmed by a second reviewer. From each study, we will abstract the following where available: study design, objectives, setting, population characteristics, subject inclusion and exclusion criteria, number of participants, duration of follow-up, the study and comparator interventions (including formulation, strength, etc.), important co-interventions, efficacy and effectiveness outcomes, healthcare utilization, and harms.

VII. Assessment of Methodological Quality of Individual Studies

Two reviewers will independently assess the risk of bias of each included study using the Cochrane ROB 2.0 for randomized controlled trials,[9] the SIGN Checklist 3 for cohort studies and Checklist 4 for case-control studies,[10] and AMSTAR for systematic reviews (for KQs 6 and 7 only).[11] Disagreements will be resolved through discussion. Each trial will be given an overall summary assessment of low, moderate, or high risk of bias.

VIII. Data Synthesis

We will summarize the primary literature by abstracting relevant data and qualitatively synthesizing the literature for each key question. If data are determined to be sufficient (e.g., data are not statistically or clinically heterogeneous, transitivity assumption can be met), we will also conduct quantitative syntheses in the forms of pairwise meta-analysis and network meta-analysis. Outcomes for which three or more publications have been identified will be included in a network meta-analysis. For meta-analysis, we will calculate pooled effect sizes by critical outcome. For outcomes that are binary (yes or no), we will calculate risk ratios and 95% confidence intervals. For continuous outcomes that are consistently measured across studies, we will estimate mean differences and 95% confidence intervals. If outcomes are captured in different ways using different scales, we will consider using standardized mean differences or Cohen's D. We will use random effects models for all meta-analyses, which is a conservative approach to estimating pooled effects and assumes there are differences in participant characteristics between studies. To assess statistical heterogeneity in our meta-analysis, we will evaluate Chi-square results and the I^2 statistic. If the Chi-square result is statistically significantly different ($P < .05$) and the I^2 statistic is >90%, we will not report results from the analysis if we are unable to explain the variation by subgroups, study risk of bias, or other factors. Wherever possible, data will be presented separately for postmenopausal women versus younger women, individuals with prior fractures versus those with first fracture, and those with a relevant comorbidity (e.g. transplant patients, corticosteroid recipients) versus those without comorbidities. We will also conduct other relevant subgroup and sensitivity analyses to further our understanding of relationships between our listed interventions and outcomes. For network meta-analysis, we will abstract data from studies with comparable

comparators (placebo) and estimate indirect comparisons (i.e., comparing findings across studies with common comparators). When possible, we will also add head-to-head data into our network in order to estimate direct relationships. We will use RevMan 5.3 for all meta-analyses and Stata (version 16) for all network meta-analyses. The data relevant to each outcome will be presented in individual evidence tables.

IX. Assessment of the Overall Quality of Evidence

We will assign select clinically- and patient-important outcomes a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[12,13] Two independent experienced researchers will assign ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High**: Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
- **Very low**: Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable**: Researchers did not identify any eligible articles.

X. References

1. Viswanathan M, Reddy S, Berkman N, et al. Screening to Prevent Osteoporotic Fractures: An Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 162. AHRQ Publication No. 15-05226-EF-1. Rockville, MD: Agency for Healthcare Research and Quality. 2018.

2. World Health Organization. WHO scientific group on the assessment of osteoporosis at primary health care level. 2004; https://www.who.int/chp/topics/Osteoporosis.pdf.

3. Wright NC, Saag KG, Dawson-Hughes B, Khosla S, Siris ES. The impact of the new National Bone Health Alliance (NBHA) diagnostic criteria on the prevalence of osteoporosis in the USA. *Osteoporos Int*. 2017;28(4):1225-1232. doi: 10.1007/s00198-016-3865-3.

4. MacLean C, Alexander A, J C. Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis. Comparative Effectiveness Review No. 12. (Prepared by Southern California/RAND Evidence-based Practice Center under Contract No. 290-02-0003). Rockville, MD: Agency for Healthcare Research and Quality. 2007.

5. Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, MJ S. Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: An Update of a 2007 Report. Comparative Effectiveness Review no. 53. (Prepared by Southern California Evidence-based Practice Center under contract HHSA-290-2007-10062-I.) Rockville, MD: Agency for Healthcare Research and Quality. 2012.

6. Crandall CJ, Newberry SJ, Diamant A, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. *Ann Intern Med*. 2014;161(10):711-723. doi: 10.7326/m14-0317.

7. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol*. 2016;75:40-46. doi: 10.1016/j.jclinepi.2016.01.021.

8. Yao P, Bennett D, Mafham M, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. *JAMA Network Open*. 2019;2(12):e1917789-e1917789. doi: 10.1001/jamanetworkopen.2019.17789 Accessed 1/6/2021.

9. Cochrane. RoB 2 tool: a revised Cochrane risk of bias tool for randomized trials. 2019; https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0.

10. Scottish Intercollegiate Guidelines Network. Checklists. 2020; https://www.sign.ac.uk/what-we-do/methodology/checklists/.

11. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj*. 2017;358:j4008. doi: 10.1136/bmj.j4008.

12. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj*. 2008;336(7650):924-926. doi: 10.1136/bmj.39489.470347.AD.

13. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE Handbook. 2013; https://gdt.gradepro.org/app/handbook/handbook.html.

Appendix A. Example search strategy

Ovid MEDLINE ALL 1946 to December 31, 2020
Date searched: January 4, 2021
1 Osteoporosis/ or Osteoporosis, Postmenopausal/ or Osteoporotic Fractures/ (59611)
2 (osteopen* or osteopaen* or osteoporosis or osteoporotic or (fragility adj3 fracture*) or (bone adj3 (dense* or density)) or LBD or BMD or FRAX).ti,ab,kf. or osteoporo*.jw. (125218)
3 or/1-2 (136006)
4 Bone Density Conservation Agents/ or Alendronate/ or Anabolic Agents/ or Denosumab/ or Diphosphonates/ or Estradiol/ or Estrogen Replacement Therapy/ or Estrogens/ or Estrogens, Conjugated/ or Hormone Replacement Therapy/ or Ibandronic Acid/ or Pamidronate/ or Parathyroid Hormone/ or Raloxifene Hydrochloride/ or Risedronic Acid/ or Selective Estrogen Receptor Modulators/ or Teriparatide/ or Zoledronic Acid/ (211441)
5 (abaloparatide or alendron* or denosumab or diphosphonate* or bisphosphonate* or estradiol or (estrogen adj2 (bazedoxifene or patch or patches or pill or pills or tablet or tablets)) or "hormone replacement" or HRT or ibandron* or pamidron* or parathormone or "parathyroid hormone" or PTHrP or "peptide hormone" or raloxifene or risedron* or ((RANKL or sclerostin) adj2 inhibit*) or romosozumab or zoledron*).ti,ab,kf,nm,rn. (230382)
6 (Activella$3 or Actonel$3 or Alora$3 or Aredia$3 or Atelvia$3 or Binosto$3 or Boniva$3 or Bonsity$3 or Climara$3 or Duavee$3 or Estratab$3 or Evenity$3 or Evista$3 or Femhrt$3 or Forteo$3 or Fosamax$3 or Menest$3 or Menostar$3 or Minivelle$3 or Natpara$3 or Ortho-Prefest$3 or Premarin$3 or Prempro$3 or Premphase$3 or Prolia$3 or Reclast$3 or Tymlos$3 or Vivelle$3 or Xgeva$3 or Zometa$3).ti,ab. (1171)
7 (anabolic or antifracture or anti-fracture or antiosteoporo* or anti-osteoporo* or antiresorptive* or antiresorption or anti-resorptive* or anti-resorption or antisclerostin or anti-sclerostin or bone-forming or monoclonal or "selective estrogen receptor" or SERM or "selective tissue estrogenic activity regulator" or STEAR or "tissue selective estrogen" or TSEC or FREEDOM or SHOTZ).ti,ab,kf. (306956)
8 or/4-7 (581395)
9 Aged/ or "Aged, 80 and over"/ or Frail Elderly/ or Middle Aged/ or Menopause/ or Postmenopause/ (5171818)
10 ("adult females" or "adult males" or age-related or aged or ageing or aging or climacteric or elderly or elders or fragility or frail or frailty or geriatr* or geront* or men or menopause or menopausal or middle-aged or older or "oldest old" or perimenopause or perimenopausal or peri-menopause or peri-menopausal or postmenopause or post-menopause or postmenopausal or post-menopausal or seniors or women).ti,ab,kf. (2391855)
11 or/9-10 (6494164)
12 and/3,8,11 (23660)
13 12 not ((exp Animals/ not Humans/) or (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti.) (22077)
14 13 not (adolescence or adolescent or adolescents or child or childhood or children or juvenile or juveniles or pediat* or paediat* or "school age" or teen or teens or teenager or teenagers or youth or youths).ti. (21804)
15 14 not (addresses or autobiography or bibliography or biography or case reports or comment or dataset or dictionary or directory or editorial or guideline or interactive tutorial or interview or legal cases or legislation or letter or news or newspaper article or patient education handout or

periodical index or personal narratives or portraits or practice guideline or validation studies or video-audio media or webcasts).pt. (19773)
16 limit 15 to yr="2014 -Current" (5166)
17 limit 16 to english language (4930)
18 Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or Controlled Clinical Trials as Topic/ or Randomized Controlled Trials as Topic/ or (clinical trial, phase III or clinical trial, phase IV or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial).pt. or (((single* or doubl* or trebl* or tripl*) adj2 (blind* or mask*)) or control or controls or controlled or placebo* or random* or trial*).ti,ab. (5041660)
19 and/17-18 (1979)
20 Cohort Studies/ or Follow-Up Studies/ or Longitudinal Studies/ or Prospective Studies/ or Retrospective Studies/ or (case-control studies or observational study).pt. or (case-control or cohort or cohorts or follow-up or longitudinal or observational or postmarketing or post-marketing or prospective or retrospective or surveillance).ti,ab,kf. (3502343)
21 and/17,20 (2104)
22 or/19,21 (3253)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials November 2020
Date searched: January 4, 2021
1 Osteoporosis/ or Osteoporosis, Postmenopausal/ or Osteoporotic Fractures/ (4259)
2 (osteopen* or osteopaen* or osteoporosis or osteoporotic or (fragility adj3 fracture*) or (bone adj3 (dense* or density)) or LBD or BMD or FRAX).ti,ab. (16405)
3 or/1-2 (16846)
4 Bone Density Conservation Agents/ or Alendronate/ or Anabolic Agents/ or Denosumab/ or Diphosphonates/ or Estradiol/ or Estrogen Replacement Therapy/ or Estrogens/ or Estrogens, Conjugated/ or Hormone Replacement Therapy/ or Ibandronic Acid/ or Pamidronate/ or Parathyroid Hormone/ or Raloxifene Hydrochloride/ or Risedronic Acid/ or Selective Estrogen Receptor Modulators/ or Teriparatide/ or Zoledronic Acid/ (11834)
5 (abaloparatide or alendron* or denosumab or diphosphonate* or bisphosphonate* or estradiol or (estrogen adj2 (bazedoxifene or patch or patches or pill or pills or tablet or tablets)) or "hormone replacement" or HRT or ibandron* or pamidron* or parathormone or "parathyroid hormone" or PTHrP or "peptide hormone" or raloxifene or risedron* or ((RANKL or sclerostin) adj2 inhibit*) or romosozumab or zoledron*).ti,ab. (20703)
6 (Activella$3 or Actonel$3 or Alora$3 or Aredia$3 or Atelvia$3 or Binosto$3 or Boniva$3 or Bonsity$3 or Climara$3 or Duavee$3 or Estratab$3 or Evenity$3 or Evista$3 or Femhrt$3 or Forteo$3 or Fosamax$3 or Menest$3 or Menostar$3 or Minivelle$3 or Natpara$3 or Ortho-Prefest$3 or Premarin$3 or Prempro$3 or Premphase$3 or Prolia$3 or Reclast$3 or Tymlos$3 or Vivelle$3 or Xgeva$3 or Zometa$3).ti,ab. (708)
7 (anabolic or antifracture or anti-fracture or antiosteoporo* or anti-osteoporo* or antiresorptive* or antiresorption or anti-resorptive* or anti-resorption or antisclerostin or anti-sclerostin or bone-forming or monoclonal or "selective estrogen receptor" or SERM or "selective tissue estrogenic activity regulator" or STEAR or "tissue selective estrogen" or TSEC or FREEDOM or SHOTZ).ti,ab. (18012)
8 or/4-7 (41348)
9 Aged/ or "Aged, 80 and over"/ or Frail Elderly/ or Middle Aged/ or Menopause/ or Postmenopause/ (346785)

10 ("adult females" or "adult males" or age-related or aged or ageing or aging or climacteric or elderly or elders or fragility or frail or frailty or geriatr* or geront* or men or menopause or menopausal or middle-aged or older or "oldest old" or perimenopause or perimenopausal or peri-menopause or peri-menopausal or postmenopause or post-menopause or postmenopausal or post-menopausal or seniors or women).ti,ab. (360608)
11 or/9-10 (629087)
12 and/3,8,11 (5702)
13 12 not ((exp Animals/ not Humans/) or (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti.) (5694)
14 13 not (adolescence or adolescent or adolescents or child or childhood or children or juvenile or juveniles or pediat* or paediat* or "school age" or teen or teens or teenager or teenagers or youth or youths).ti. (5639)
15 limit 14 to yr="2014 -Current" (1685)
16 limit 15 to medline records (692)
17 15 not 16 (993)

Ovid EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 25, 2020
Date searched: January 4, 2021
1 (osteopen* or osteopaen* or osteoporosis or osteoporotic or (fragility adj3 fracture*) or (bone adj3 (dense* or density)) or LBD or BMD or FRAX).ti,ab. (102)
2 (abaloparatide or alendron* or denosumab or diphosphonate* or bisphosphonate* or estradiol or (estrogen adj2 (bazedoxifene or patch or patches or pill or pills or tablet or tablets)) or "hormone replacement" or HRT or ibandron* or pamidron* or parathormone or "parathyroid hormone" or PTHrP or "peptide hormone" or raloxifene or risedron* or ((RANKL or sclerostin) adj2 inhibit*) or romosozumab or zoledron*).ti,ab. (88)
3 (Activella$3 or Actonel$3 or Alora$3 or Aredia$3 or Atelvia$3 or Binosto$3 or Boniva$3 or Bonsity$3 or Climara$3 or Duavee$3 or Estratab$3 or Evenity$3 or Evista$3 or Femhrt$3 or Forteo$3 or Fosamax$3 or Menest$3 or Menostar$3 or Minivelle$3 or Natpara$3 or Ortho-Prefest$3 or Premarin$3 or Prempro$3 or Premphase$3 or Prolia$3 or Reclast$3 or Tymlos$3 or Vivelle$3 or Xgeva$3 or Zometa$3).ti,ab. (0)
4 (anabolic or antifracture or anti-fracture or antiosteoporo* or anti-osteoporo* or antiresorptive* or antiresorption or anti-resorptive* or anti-resorption or antisclerostin or anti-sclerostin or bone-forming or monoclonal or "selective estrogen receptor" or SERM or "selective tissue estrogenic activity regulator" or STEAR or "tissue selective estrogen" or TSEC or FREEDOM or SHOTZ).ti,ab. (118)
5 or/2-4 (202)
6 ("adult females" or "adult males" or age-related or aged or ageing or aging or climacteric or elderly or elders or fragility or frail or frailty or geriatr* or geront* or men or menopause or menopausal or middle-aged or older or "oldest old" or perimenopause or perimenopausal or peri-menopause or peri-menopausal or postmenopause or post-menopause or postmenopausal or post-menopausal or seniors or women).ti,ab. (2624)
7 and/1,5-6 (23)
8 7 not (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti. (23)

9 8 not (adolescence or adolescent or adolescents or child or childhood or children or juvenile or juveniles or pediat* or paediat* or "school age" or teen or teens or teenager or teenagers or youth or youths).ti. (23)
10 limit 9 to last 7 years (12)

ClinicalTrials.gov
Date searched: January 5, 2021
EXPERT SEARCH: (AREA[ConditionSearch] (osteopenia OR osteopaenia OR osteoporosis OR osteoporotic OR fragility fracture) OR AREA[TitleSearch] (osteopenia OR osteopaenia OR osteoporosis OR osteoporotic OR fragility fracture)) AND (abaloparatide OR alendronate OR calcium OR denosumab OR diphosphonate OR bisphosphonate OR estradiol OR EXPAND[Concept] "estrogen bazedoxifene" OR EXPAND[Concept] "estrogen patch" OR EXPAND[Concept] "estrogen pill" OR EXPAND[Concept] "estrogen tablet" OR EXPAND[Concept] "hormone replacement" OR HRT OR ibandronate OR ibandronic OR pamidronate OR pamidronic OR parathormone OR EXPAND[Concept] "parathyroid hormone" AND or PTHrP OR EXPAND[Concept] "peptide hormone" OR raloxifene OR risedronic OR risedronate OR EXPAND[Concept] "RANKL inhibitor" OR EXPAND[Concept] "sclerostin inhibitor" OR romosozumab OR EXPAND[Concept] "vitamin d" OR zoledronate OR zoledronic OR anabolic OR antifracture OR anti-fracture OR antiosteoporosis OR anti-osteoporosis OR antiresorptive OR antiresorption OR anti-resorptive OR anti-resorption OR antisclerostin OR anti-sclerostin OR bone-forming OR monoclonal OR EXPAND[Concept] "selective estrogen receptor" OR SERM OR EXPAND[Concept] "selective tissue estrogenic activity regulator" OR STEAR OR EXPAND[Concept] "tissue selective estrogen" OR TSEC OR FREEDOM OR SHOTZ OR Activella OR Actonel OR Alora OR Aredia OR Atelvia OR Binosto OR Boniva OR Bonsity OR Climara OR Duavee OR Estratab OR Evenity OR Evista OR Femhrt OR Forteo OR Fosamax OR Menest OR Menostar OR Minivelle OR Natpara OR Ortho-Prefest OR Premarin OR Prempro OR Premphase OR Prolia OR Reclast OR Tymlos OR Vivelle OR Xgeva OR Zometa) | Adult, Older Adult | First posted from 01/01/2014 to 01/05/2021 (334)

Copy and paste following link to reproduce search in ClinicalTrials.gov:
https://clinicaltrials.gov/ct2/results?show_xprt=Y&xprt=%28+AREA%5BConditionSearch%5D+%28+osteopenia+OR+osteopaenia+OR+osteoporosis+OR+osteoporotic+OR+fragility+fracture+%29+OR++AREA%5BTitleSearch%5D+%28+osteopenia+OR+osteopaenia+OR+osteoporosis+OR+osteoporotic+OR+fragility+fracture+%29+%29+AND+%28+abaloparatide+OR+alendronate+OR+calcium+OR+denosumab+OR+diphosphonate+OR+bisphosphonate+OR+estradiol+OR+EXPAND%5BConcept%5D+%22estrogen+bazedoxifene%22+OR+EXPAND%5BConcept%5D+%22estrogen+patch%22+OR+EXPAND%5BConcept%5D+%22estrogen+pill%22+OR+EXPAND%5BConcept%5D+%22estrogen+tablet%22+OR+EXPAND%5BConcept%5D+%22hormone+replacement%22+OR+HRT+OR+ibandronate+OR+ibandronic+OR+pamidronate+OR+pamidronic+OR+parathormone+OR+EXPAND%5BConcept%5D+%22parathyroid+hormone%22+AND+or+PTHrP+OR+EXPAND%5BConcept%5D+%22peptide+hormone%22+OR+raloxifene+OR+risedronic+OR+risedronate+OR+EXPAND%5BConcept%5D+%22RANKL+inhibitor%22+OR+EXPAND%5BConcept%5D+%22sclerostin+inhibitor%22+OR+romosozumab+OR+EXPAND%5BConcept%5D+%22vitamin+d%22+OR+zoledronate+OR+zoledronic+OR+anabolic+OR+antifracture+OR+anti-fracture+OR+antiosteoporosis+OR+anti-osteoporosis+OR+antiresorptive+OR+antiresorption+OR+anti-resorptive+OR+anti-

resorption+OR+antisclerostin+OR+anti-sclerostin+OR+bone-forming+OR+monoclonal+OR+EXPAND%5BConcept%5D+%22selective+estrogen+receptor%22+OR+SERM+OR+EXPAND%5BConcept%5D+%22selective+tissue+estrogenic+activity+regulator%22+OR+STEAR+OR+EXPAND%5BConcept%5D+%22tissue+selective+estrogen%22+OR+TSEC+OR+FREEDOM+OR+SHOTZ+OR+Activella+OR+Actonel+OR+Alora+OR+Aredia+OR+Atelvia+OR+Binosto+OR+Boniva+OR+Bonsity+OR+Climara+OR+Duavee+OR+Estratab+OR+Evenity+OR+Evista+OR+Femhrt+OR+Forteo+OR+Fosamax+OR+Menest+OR+Menostar+OR+Minivelle+OR+Natpara+OR+Ortho-Prefest+OR+Premarin+OR+Prempro+OR+Premphase+OR+Prolia+OR+Reclast+OR+Tymlos+OR+Vivelle+OR+Xgeva+OR+Zometa+%29+AND+AREA%5BStdAge%5D+EXPAND%5BTerm%5D+COVER%5BFullMatch%5D+%28+%22Adult%22+OR+%22Older+Adult%22+%29+AND+AREA%5BStudyFirstPostDate%5D+EXPAND%5BTerm%5D+RANGE%5B01%2F01%2F2014%2C+01%2F05%2F2021%5D

Calcium and Vitamin D Bridge Searches

Ovid MEDLINE ALL 1946 to January 04, 2021

Date searched: January 5, 2021

1 Osteoporosis/ or Osteoporosis, Postmenopausal/ or Osteoporotic Fractures/ (59638)

2 (osteopen* or osteopaen* or osteoporosis or osteoporotic or (fragility adj3 fracture*) or (bone adj3 (dense* or density)) or LBD or BMD or FRAX).ti,ab,kf. or osteoporo*.jw. (125335)

3 or/1-2 (136124)

4 Calcium/ or exp "Vitamin D"/ or Ergocalciferol/ or Cholecalciferol/ (314855)

5 (calcium or "vitamin d" or "25-hydroxyvitamin D").ti,ab,kf,nm,rn. (644342)

6 or/4-5 (652650)

7 Aged/ or "Aged, 80 and over"/ or Frail Elderly/ or Middle Aged/ or Menopause/ or Postmenopause/ (5173043)

8 ("adult females" or "adult males" or age-related or aged or ageing or aging or climacteric or elderly or elders or fragility or frail or frailty or geriatr* or geront* or men or menopause or menopausal or middle-aged or older or "oldest old" or perimenopause or perimenopausal or peri-menopause or peri-menopausal or postmenopause or post-menopause or postmenopausal or post-menopausal or seniors or women).ti,ab,kf. (2393942)

9 or/7-8 (6497111)

10 and/3,6,9 (16734)

11 10 not ((exp Animals/ not Humans/) or (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti.) (15950)

12 11 not (adolescence or adolescent or adolescents or child or childhood or children or juvenile or juveniles or pediat* or paediat* or "school age" or teen or teens or teenager or teenagers or youth or youths).ti. (15431)

13 12 not (addresses or autobiography or bibliography or biography or case reports or comment or dataset or dictionary or directory or editorial or guideline or interactive tutorial or interview or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or validation studies or video-audio media or webcasts).pt. (14508)

14 limit 13 to yr="2019 -Current" (997)

15 limit 14 to english language (964)

16 Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or Controlled Clinical Trials as Topic/ or Randomized Controlled Trials as Topic/ or (clinical trial, phase III or clinical trial, phase IV or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial).pt. or (((single* or doubl* or trebl* or tripl*) adj2 (blind* or mask*)) or control or controls or controlled or placebo* or random* or trial*).ti,ab. (5045729)
17 and/15-16 (346)
18 Cohort Studies/ or Follow-Up Studies/ or Longitudinal Studies/ or Prospective Studies/ or Retrospective Studies/ or (case-control studies or observational study).pt. or (case-control or cohort or cohorts or follow-up or longitudinal or observational or postmarketing or post-marketing or prospective or retrospective or surveillance).ti,ab,kf. (3506002)
19 and/15,18 (379)
20 or/17,19 (590)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials November 2020
Date searched: January 5, 2021
1 Osteoporosis/ or Osteoporosis, Postmenopausal/ or Osteoporotic Fractures/ (4259)
2 (osteopen* or osteopaen* or osteoporosis or osteoporotic or (fragility adj3 fracture*) or (bone adj3 (dense* or density)) or LBD or BMD or FRAX).ti,ab. or osteoporo*.jw. (16872)
3 or/1-2 (17286)
4 Calcium/ or exp "Vitamin D"/ or Ergocalciferol/ or Cholecalciferol/ (7793)
5 (calcium or "vitamin d" or "25-hydroxyvitamin D").ti,ab. (31090)
6 or/4-5 (32384)
7 Aged/ or "Aged, 80 and over"/ or Frail Elderly/ or Middle Aged/ or Menopause/ or Postmenopause/ (346785)
8 ("adult females" or "adult males" or age-related or aged or ageing or aging or climacteric or elderly or elders or fragility or frail or frailty or geriatr* or geront* or men or menopause or menopausal or middle-aged or older or "oldest old" or perimenopause or perimenopausal or peri-menopause or peri-menopausal or postmenopause or post-menopause or postmenopausal or post-menopausal or seniors or women).ti,ab. (360608)
9 or/7-8 (629087)
10 and/3,6,9 (3912)
11 10 not (adolescence or adolescent or adolescents or child or childhood or children or juvenile or juveniles or pediat* or paediat* or "school age" or teen or teens or teenager or teenagers or youth or youths).ti. (3816)
12 limit 11 to yr="2019 -Current" (224)
13 limit 12 to medline records (87)
14 12 not 13 (137)

ClinicalTrials.gov
Date searched: January 5, 2021
(AREA[ConditionSearch] (osteopenia OR osteopaenia OR osteoporosis OR osteoporotic OR fragility fracture) OR AREA[TitleSearch] (osteopenia OR osteopaenia OR osteoporosis OR osteoporotic OR fragility fracture)) AND AREA[InterventionSearch] (calcium OR EXPAND[Concept] "vitamin D" OR EXPAND[Concept] "25-hydroxyvitamin D" OR cholecalciferol OR ergocalciferol) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch]

("Adult" OR "Older Adult") AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[01/01/2019, 01/05/2021] (37)

Copy and paste following link to reproduce search in ClinicalTrials.gov:
https://clinicaltrials.gov/ct2/results?show_xprt=Y&xprt=%28+AREA%5BConditionSearch%5D+%28+osteopenia+OR+osteopaenia+OR+osteoporosis+OR+osteoporotic+OR+fragility+fracture+%29+OR+AREA%5BTitleSearch%5D+%28+osteopenia+OR+osteopaenia+OR+osteoporosis+OR+osteoporotic+OR+fragility+fracture+%29+%29+AND+AREA%5BInterventionSearch%5D+%28+calcium+OR+EXPAND%5BConcept%5D+%22vitamin+D%22+OR+EXPAND%5BConcept%5D+%2225-hydroxyvitamin+D%22+OR+cholecalciferol+OR+ergocalciferol+%29+AND+AREA%5BStdAge%5D+EXPAND%5BTerm%5D+COVER%5BFullMatch%5D+%28+%22Adult%22+OR+%22Older+Adult%22+%29+AND+AREA%5BStudyFirstPostDate%5D+EXPAND%5BTerm%5D+RANGE%5B01%2F01%2F2019%2C+01%2F05%2F2021%5D

Medical Management of Acute Colonic Diverticulitis: A Systematic Review

Ethan M. Balk, MD, MPH[1]; Gaelen P. Adam, MLIS[1]; …

[1] Brown Evidence-based Practice Center, Center for Evidence Synthesis in Health, Brown School of Public Health, Brown University, Providence, RI

Ethan M. Balk, M.D., M.P.H.	All	
Gaelen P. Adam, M.L.I.S., M.P.H.	Elective surgery/All	
Wangnan Cao, Ph.D.	Colonoscopy	
Kristin Danko	Outpatient	
Monika Reddy Bhuma, B.D.S, M.P.H.	Antibiotics	
Shivani Mehta, B.A.	5-ASA	
Ian J. Saldanha, M.B.B.S., M.P.H., Ph.D.	IR	
Michael D. Beland, M.D.	?	
Nishit Shah, M.D.	All?	0

Corresponding Author:
Ethan Balk, MD MPH
Box G-S121-8
Brown School of Public Health
Providence, RI 02912, USA
ethan_balk@brown.edu

Running Title: Medical management of acute diverticulitis systematic review

Word Count:
Total XXXX

Tables: 3
Figures: 4
Supplements: 1 file

Disclaimer: This report is based on research conducted by the Brown Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Acknowledgment: The authors gratefully acknowledge the contribution of Lionel Bañez, MD, our AHRQ Task Order Office….

Conflict of Interest: None of the authors have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this article.

Financial Support: This project was funded under contract No. 290-20-1500002 I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, Rockville, MD 20850, www.ahrq.gov

Key words: acute colonic diverticulitis, outpatient management, antibiotics, interventional radiology, systematic review, meta-analysis

PROSPERO registration number CRD42020151246

Abstract:

Background: The relative effectiveness and harms of various nonsurgical treatment options for acute colonic diverticulitis is unclear.

Purpose: Evaluate hospitalization of patients with uncomplicated diverticulitis, antibiotics for all patients with acute diverticulitis, and interventional radiology procedures for patients with complicated diverticulitis.

Data Sources: MEDLINE, Cochrane Central Trials Registry, Cochrane Database of Systematic Reviews, Embase, CINAHL, and ClinicalTrial.gov from January 1990 through November 16, 2020.

Study Selection: Randomized trials and multivariable-adjusted nonrandomized comparative studies of interventions of interest reporting clinical or patient-centered outcomes.

Data Extraction: Six researchers extracted study data and risk of bias, verified by an independent researcher. The team assessed strength of evidence (SoE) across studies.

Data Synthesis: For patients with uncomplicated acute diverticulitis, six studies provide low SoE that initial outpatient or inpatient management have similar risks of recurrence or elective surgery, but insufficient evidence regarding other outcomes. Also for patients with uncomplicated acute diverticulitis, five studies provide low SoE that antibiotics do not affect pain symptoms, length of hospital stay, quality of life, risk of recurrence, or need for surgery. Evidence is insufficient to determine choice of antibiotic regimen (6 studies) or effect of interventional radiology procedures (2 studies).

Limitations: The evidence base is of, at best, low SoE. Studies did not adequately assess heterogeneity of treatment effect.

Conclusions: For selected patients with uncomplicated diverticulitis, outpatient treatment leads to clinical outcomes no worse than inpatient treatment. Avoidance of antibiotics for patients with uncomplicated acute diverticulitis may be safe for most patients. The evidence is too sparse to guide the decision whether to use percutaneous drainage for patients with acute complicated diverticulitis.

Registration: PROSPERO CRD42020151246

Funding Source: Agency for Healthcare Research and Quality.

Reproducible Research Statement: Data set: Available at https://srdr.ahrq.gov/projects/1520/

Commented [EB1]: Possibly drop (mostly to save space, arguably it's the least important outcome covered; but I'm sure not all would agree). Just a thought.

Abstract: 275 words (275 max)
MSS: 4247 words (4000 max)

Commented [KC2]: Authors seeking input on where to trim. Currently, this manuscript does not cover diagnosis (KQ1 of the AHRQ report).

Acute colonic diverticulitis is common and becoming more so as the population ages and as younger adults are increasingly experiencing episodes (1-3). Traditional management for patients with uncomplicated diverticulitis (with no sequelae of gut perforation) includes bowel rest, antibiotics, and hydration, and may involve hospitalization for intravenous (IV) antibiotics and fluids, and monitoring. However, in recent years emerging concepts have suggested that the pathogenesis of the disease may be related more to alterations in the gut microbiome, gut dysmotility, and inflammatory processes rather than an infectious etiology (4-6). Thus, the traditional management approach has been questioned. Recent narrative reviews have highlighted where current common practices in the management of acute diverticulitis may not be supported by the evidence for all patients, including universal hospitalization, use of IV antibiotics, duration of antibiotic treatment, and need for colectomy and other aggressive surgical procedures, in contrast to interventional radiology procedures, for complicated episodes (7, 8).

To address these controversies, we conducted a systematic review (SR) under the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program in support the American College of Physicians' (ACP) effort to create a new clinical practice guideline on management of acute diverticulitis (9). Here we address the effectiveness, comparative effectiveness, and harms of hospitalization for acute uncomplicated diverticulitis, antibiotics use for acute complicated or uncomplicated diverticulitis, and interventional radiology techniques for acute complicated diverticulitis. In a companion article, we address colonoscopy after an episode of acute diverticulitis and elective, prophylactic surgery (10).

Methods

The Brown EPC used established SR methodologies as outlined in AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (11). The PROSPERO registration number is CRD42020151246. Detailed descriptions of the systematic review and methods can be found in the full report (9) and Supplement A.

Data Sources and Searches

For the AHRQ report (9), we conducted literature searches in Medline (via PubMed), the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, Embase, CINAHL, and ClinicalTrials.gov, restricted to 1990 through June 1, 2020 to capture contemporary evidence. Subsequently, the searches were updated through November 16, 2020. The restriction to recent studies (since 1990) was based on important changes in diagnosis and clinical management of diverticulitis based on increased use of computed tomography (CT) imaging since the 1990s. See Supplement A for search strategies.

All identified citations (abstracts) were independently double-screened using Abstrackr (http://abstrackr.cebm.brown.edu) by a team of 8 researchers after pilot training sessions; conflicts were resolved by group discussion. All potentially relevant studies were rescreened in full text in duplicate.

Study Selection

We included studies of adults with acute complicated or uncomplicated left-sided colonic diverticulitis; the full report (9) summarizes the sparse data for right-sided diverticulitis. We excluded studies of patients with diverticulosis or symptomatic uncomplicated diverticular disease. Studies had to evaluate either hospitalization (vs. no hospitalization) for patients with

uncomplicated diverticulitis, antibiotics (vs. no antibiotics or other antibiotic regimens) for patients with uncomplicated or complicated diverticulitis, or interventional radiology procedures (vs. no procedure, with or without surgery) for complicated diverticulitis. We did not evaluate laparoscopic or other surgical procedures. Studies had to report clinical outcomes (e.g., death, resolution, diverticulitis-related complications, emergent procedures/surgery, recurrent diverticulitis), patient-centered outcomes (e.g., quality of life, pain), resource use (e.g., length of hospital stay, rehospitalization), or harms related to the interventions.

We included randomized controlled trials (RCT) with at least 10 participants per intervention group and nonrandomized comparative studies (NRCS) that used analytic methods to minimize selection bias (e.g., multivariable adjustment, propensity score analysis), although we allowed unadjusted analyses of long-term outcomes under the assumption that characteristics during acute diverticulitis that were associated with treatment choice would not have a major impact on long-term outcomes.

Data Extraction and Quality Assessment

Each study was extracted and assessed for methodological quality, by one of six methodologists, into a customized form in the Systematic Review Data Repository (SRDR; https://srdr.ahrq.gov/projects/1520). Each extraction and quality assessment was reviewed and confirmed by at least one other experienced methodologist. Disagreements were resolved by discussion among the team, as needed. To assess quality, we used the Cochrane risk of bias tool for RCTs (12). For NRCSs, we used elements from the ROBINS-I Tool (13) related to confounding and selection bias, and items from the Cochrane Risk of Bias (12) that were not specific to randomized trials. For all studies we also used items from the National Heart, Lung, and Blood Institute (NHLBI) tool on the adequacy of descriptions of study eligibility criteria, interventions, and outcomes (14).

Data Synthesis and Analysis

When feasible and appropriate, we conducted restricted maximum likelihood random effects model, pairwise, meta-analyses with the metaan package in Stata 14.2 (StataCorp). We evaluated odds ratios (OR) for categorical outcomes and differences or net differences (difference-in-differences) for continuous outcomes, as reported data allowed.

We graded the strength of evidence (SoE) as per the AHRQ Methods Guide (15). For each SoE assessment, we considered the number of studies, their study designs, study limitations/quality, the directness of the comparisons to the research question, consistency of study results, precision of estimates of effect, likelihood of reporting bias, and other limitations. Based on these assessments, we assigned a SoE rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect.

Role of the Funding Source

This topic was nominated by the ACP for systematic review by an Evidence-based Practice Center in partnership with AHRQ. ACP members joined panels of key informants and technical experts, which provided perspectives that led to revisions to the key questions and protocol. AHRQ program officers, ACP members, and other reviewers (both invited and public) provided comments on draft versions of the protocol and full evidence report. ACP and AHRQ did not participate in the literature search, determination of study eligibility criteria, data analysis, or interpretation of findings. After completion of the AHRQ report (9), we discussed draft versions

of the manuscript with ACP members to ensure it met the needs of the guideline development committee and adequately conveyed our conclusions. However, the ACP did not draft any portion of the manuscript or attempt to alter our conclusions.

Results

The literature database searches yielded 17,133 citations (for all topics addressed in the full report (9)). We found 744 citations to retrieve for further screening (Supplement Figure B-1). Ultimately we found six eligible studies addressing hospitalization, 12 eligible studies (in 18 reports) addressing antibiotics, and two eligible studies addressing interventional radiology. The literature search update since the full report (9) did not find additional studies.

Outpatient Management of Acute Diverticulitis

For patients with uncomplicated diverticulitis, the evidence comparing outpatient versus inpatient management is inconclusive (insufficient) about the difference in risk of death, treatment failure, need for emergency surgery, and quality of life (Table 1). With low SoE, the studies suggest there may be no differences in rates of long-term recurrence or elective surgery regardless of outpatient versus inpatient management.

One small RCT (16) and five NRCSs (17-21) evaluated outpatient treatment protocols compared with inpatient care for the management of an episode of acute uncomplicated diverticulitis (details, including risk of bias assessment and study results, are in Supplement Table B-1). The average age was similar across studies, with participants in their mid to late 50s and between 37% and 64% being male. The RCT reported non-industry funding; the five NRCSs did not report funding. The RCT was of overall low risk of bias; the NRCSs had high risk of bias for confounding, but were mostly at low risk of participant selection bias. In brief, the RCT (Biondo 2014 (16)) enrolled 132 participants with uncomplicated diverticulitis who were responsive to initial treatment in the Emergency Department, which included intravenous (IV) antibiotics. The one prospective NRCS (Moya 2012 (17)) studied adults with uncomplicated diverticulitis who could tolerate oral intake; the study used a pre-post interrupted time series design around a hospital policy change. The remaining four adjusted, retrospective NRCSs (Bolkenstein 2018 (18), Joliat 2017 (19), Lorente 2013 (20), and Ünlü 2013 (21)) compared outpatient with inpatient treatment protocols.

Treatment Failure

The RCT (Biondo 2014 (16)) and the adjusted NRCS (Bolkenstein 2018 (18)) reported treatment failure. Biondo 2014 found that treatment failure occurred at similar rates between inpatient- and outpatient-treated groups and was uncommon (~5%). Their findings yielded an imprecise comparison (OR 0.74; 95% CI 0.16, 3.43). In contrast, Bolkenstein 2018 found that patients treated as outpatients had significantly *fewer* treatment failures compared to inpatients (4.5% vs. 11.3%; adjusted OR 0.41; 95% CI 0.20, 0.83).

Recurrence

Four NRCSs reported unadjusted analyses of recurrence across average follow-up ranging from approximately 8 to 55 months (17, 19-21). Recurrence rates across the studies tracked with average follow-up time (from 6.6% at about 8 months (17) to 41% at about 55 months (19)). By meta-analysis (Figure 1), the summary OR showed no evidence of a difference in recurrence rates between outpatient and inpatient management (summary OR 0.85; 95% CI 0.62, 1.17).

Elective Surgical Treatment

Three NRCSs, with an average follow-up ranging from approximately 8 to 55 months, reported no statistically significant differences in elective surgical treatment between outpatient and inpatient management across studies (17, 19, 21). Two studies had elective surgery rates of 4% at about 8 months and 48 months (17, 21); one reported 12% at about 55 months (19). By meta-analysis (Figure 2), the summary OR yielded no evidence of a difference in rates of elective surgery between outpatient and inpatient management (summary OR 0.76; 95% CI 0.42, 1.37).

Other Outcomes

Death was rare. Only two of 1009 (0.2%) died due to acute diverticulitis across three studies (16, 18, 21). Among 208 patients in two studies (16, 17), none required emergency surgery, regardless of treatment assignment. The RCT (Biondo 2014 (16)) reported on quality of life and found no difference in physical (P=0.59) and mental health (P=0.99) scales of Short Form-12 (SF-12) between the outpatient and inpatient arms at 2 months.

Antibiotics

Seven RCTs (22-32) and four adjusted NRCSs (33-36) addressed the use of antibiotics in patients with acute diverticulitis. One RCT (Schug-Pass 2010 (32)) was industry-funded. Four RCTs and one NRCS were funded by non-industry sources, including the AVOD (Antibiotika Vid Okomplicerad Divertikulit) (22, 23), DIABOLO (Diverticulitis: Antibiotics or Close Observation (24-27), and STAND (Selective Treatment with Antibiotics for Non-complicated Diverticulitis) (28) trials, the RCT by Ribas 2010 (31), and the NRCS by Hjern 2007 (34). The other studies did not report industry funding. Study details, including risk of bias assessment and study results, are in Supplement Table B-2.

Overall, for patients with uncomplicated or mild diverticulitis, the evidence does not support that there are differences in most clinically important outcomes with or without use of antibiotics or in choice of antibiotic regimens (Table 2). Specifically, studies found no evidence of differences in pain symptoms, length of hospital stay, risk of recurrence, and quality of life (low SoE). The risk of surgery at 6 to 12 months after the episode of acute diverticulitis may be lower among patients who received antibiotics, but the finding was highly nonsignificant (low SoE). Evidence for comparative rates of death, treatment failure, diverticulitis-related morbidities, rehospitalization, and adverse events is insufficient, largely due to sparse events. Although seven studies have compared antibiotic regimens, each evaluated a different comparison; therefore, the evidence is insufficient. However, in general, no evidence of differences in clinical outcomes were found for different regimens.

Antibiotics Versus No Antibiotics for Uncomplicated Diverticulitis

Three RCTs (22-28) and two NRCSs (33, 34) compared antibiotic treatment with either no antibiotics or placebo in patients with acute, uncomplicated diverticulitis. The numbers of enrolled participants ranged from 125 to 623. The average ages of participants ranged from 37 to 62 years. The RCTs were at generally low risk of bias, except that only STAND blinded participants, providers, and outcome assessors. All RCTs had low levels of loss to follow-up. The NRCSs adjusted for possible confounding and had low risk of bias in selection of participants into the study and low levels of loss to follow-up.

STAND randomized patients to 5 days of oral amoxicillin/clavulanate (but additional IV cefuroxime and oral metronidazole was allowed) or placebo. All patients, at enrollment, had CT-diagnosed Hinchey stage 1a uncomplicated diverticulitis. The other two RCTs (AVOD, DIABOLO) compared various antibiotics to open-label no antibiotics. In AVOD, the treating clinicians were allowed to choose the antibiotics to be administered. Patients had CT-confirmed uncomplicated diverticulitis. The DIABOLO trial compared IV amoxicillin/clavulanate with no antibiotics in patients with a first episode of modified Hinchey stage 1a or 1b acute diverticulitis. The two NRCSs (Hjern 2007 (34) and de Korte 2012 (33)) compared antibiotic treatment with no antibiotics for a minimum of 7 days. Hjern 2007 evaluated a combination of IV cephalosporin and metronidazole, followed by oral quinolone and metronidazole. de Korte 2012 was a multicenter NRCS, in which antibiotic regimens differed across centers. All patients in both NRCSs had acute mild sigmoid diverticulitis.

Mortality

All three trials reported imprecise or near imprecise estimates of effect of antibiotics on mortality. AVOD and STAND reported rare deaths at 30 days (2/791, total). In DIABOLO, diverticulitis-related mortality at 24 months was uncommon (0.8%, total), with a highly imprecise between-groups comparison (OR 0.33; 95% CI 0.03, 3.15). In AVOD, at very long-term follow-up (11 years), about 10% of patients died in both groups (OR 1.06; 95% 0.60, 1.86).

Treatment Failure

An individual-patient data meta-analysis (IPD MA) of DIABOLO and AVOD redefined outcomes in the AVOD trial to analyze "ongoing diverticulitis" within 3 months of treatment (37). The combined rate of ongoing diverticulitis was nonsignificantly lower with antibiotics (5.0%) than no antibiotics (7.2%, P=0.062, where the threshold for statistical significance was set at 0.025 to account for multiple testing).

Length of Hospital Stay

The three RCTs reported somewhat conflicting findings regarding length of hospital stay. AVOD found a mean difference (MD) of 0 days. STAND found a statistically nonsignificant shorter median stay with antibiotics than placebo (−5.9 hours; IQR −15.5, 3.7). DIABOLO found a statistically significantly shorter length of stay in the antibiotics group compared with the no antibiotics group (2 vs. 3 days, P=0.006). Across studies, the summary difference between groups nominally favored antibiotics (−7.7 hours; 95% CI −20.2, 4.8; I^2 =52%). The conclusion of the IPD MA also nominally favored the no antibiotics group: median 3 days (antibiotics) versus 2 days (no antibiotics), P=0.037 (statistically nonsignificant per *a priori* criteria) (37).

Commented [EB3]: Drop?

Rehospitalization

STAND and DIABOLO reported nonsignificant differences in risk of rehospitalization. STAND reported *more* rehospitalizations at 1 week in those treated with antibiotics (6.0% vs. 1.1%, P=0.07), but no significant difference at 1 month (6.0% vs. 10.6%; OR 0.53; 95% CI 0.17, 1.62). DIABOLO reported no statistically significant differences in rate of rehospitalization at 6 and 24 months, although both estimates tended to favor amoxicillin/clavulanate versus placebo (6 month OR 0.64; 95% CI 0.39, 1.05; 24 month OR 0.71; 95% CI 0.44, 1.15).

Surgery for Diverticulitis

Two RCTs reported elective surgeries for diverticulitis (6 to 12 months later). DIABOLO reported an OR for elective surgery at 6 months of 0.36 (95% CI 0.10, 1.38) and AVOD reported an OR for sigmoidectomy at 12 months of 0.33 (95% CI 0.07, 1.63). The IPD MA of the two trials (37), found no statistically significant difference in sigmoid resection rates at 1 month (P=0.82) or approximately 1 year (P=0.21).

Recurrence

The IPD MA of AVOD and DIABOLO found no significant difference in recurrence rates (9.6% [antibiotics] vs. 8.6%, P=0.61) (37). AVOD also reported that long-term recurrence at 11 years was similar between patients with or without antibiotics (OR 1.00 95% CI 0.70, 1.43). In contrast, the four NRCSs reported on recurrence of diverticulitis. Each study had an imprecise comparison, but across studies, the summary OR for recurrence was 1.06 (95% CI 0.70, 1.43; I^2 =0%; Figure 3) . Each of these trials included participants with and without prior episodes of diverticulitis. Of note,

Diverticulitis-Related Morbidities

AVOD and DIABOLO described diverticulitis-related morbidities, such as abscess, fistula, stenosis, and obstruction. Both studies reported that these morbidities occurred in 3% of patients or fewer, regardless of intervention. The IPD MA also found no statistically significant differences in episodes of complicated diverticulitis within 1 month (P=0.20) or approximately 1 year (P=0.079) (37); however, at the approximately 1 year follow-up, the rate of complications were about double in the no antibiotics groups (4.0%) than the antibiotic treatment groups (2.1%).

Pain or Tenderness

Three RCTs reported on pain or tenderness outcomes. Regarding short-term pain, STAND (24 hours) and AVOD (1 to 5 days) both reported no significant differences in acute pain by visual analogue scale (VAS). However, AVOD reported a small, statistically significant *worse* tenderness score with antibiotic treatment (MD 0.2; 95% CI 0.01, 0.39; on a 4-point scale). DIABOLO also found no difference in pain, assessed as experiencing pain of at least 4 on VAS within 10 days (OR 0.99; 95% CI 0.60, 1.46). In the long term, AVOD reported on three types of pain. All effect sizes were imprecise, including likelihood of severe periodic pain at 12 months, and chronic pain at both 12 months and 11 years.

Quality of Life

DIABOLO and AVOD reported on quality of life at various time points. DIABOLO found no differences between groups at 3, 6, 12, and 24 months in three health-related quality of life instruments: the EuroQoL (EQ)-5D, SF-36, and the Gastrointestinal Quality of Life Index (GIQLI). AVOD reported quality of life at 11 years of follow-up. No statistically significant differences were found for the cumulative EQ-5D score or any of its domains (P from 0.34 to 0.84).

Adverse Events

Only AVOD reported on adverse events. They reported an imprecise estimate of differences in “any adverse event,” which actually occurred *more* frequently among those on placebo.

Heterogeneity of Treatment Effects (Subgroup Differences)

Only the IPD MA evaluated potential differences in effectiveness of antibiotic treatment (vs. no antibiotics) across subgroups (37). To increase power, the analysis evaluated the composite outcome "ongoing or complicated diverticulitis or sigmoid resection." However, analyses of interactions between antibiotic treatment and pain scores at presentation, white blood cell count at presentation, and primary (vs. recurrent) diverticulitis were all highly imprecise, with no indication about whether antibiotics or more (or less) effective in any subgroup.

Comparisons of Antibiotics

Four RCTs (Kellum 1992,(29) Ridgway 2009,(30) Ribas 2010,(31) and Schug-Pass 2010(32)) and two NRCSs (Scarpa 2015(35) and Etzioni 2010(36)) compared antibiotic regimens. All RCTs and NRCSs enrolled patients with image-proven acute diverticulitis. Comparisons were either between antibiotics (or combinations of antibiotics), different routes of administration of the same antibiotic(s), or duration of treatment with the same antibiotic(s) as described in Supplement Table B-2. Overall, estimates of outcomes were imprecise or found no evidence of difference between regimens. Among outcomes related to treatment failure, surgery for diverticulitis, length of hospital stay, recurrence of diverticulitis, diverticulitis-related morbidities, pain or tenderness, and antibiotic-related adverse events, the only statistically significant findings was a longer mean hospital stay in patients on than patients on a 7-day course of ertapenem than a 4-day course.

Interventional Radiology

Overall, the evidence is insufficient to make conclusions regarding the potentially beneficial effects of percutaneous drainage for treatment of acute complicated diverticulitis due to sparse and imprecise data (Table 3).

Two retrospective NRCSs, with a total of 483 participants, compared percutaneous drainage with conservative management (no percutaneous drainage) in patients with acute complicated diverticulitis (38, 39). Details, including risk of bias assessment and study results, are in Supplemental Table B-3. Both NRCSs were deemed to be at low risk of confounding bias because they used adequate methods to account for potential confounding. The two studies provided mostly imprecise comparisons of outcomes. One exception is that Lambrichts 2019 reported that patients receiving percutaneous drainage had higher all-cause mortality at 6 years (unadjusted OR 2.30; 95% CI 1.05, 5.02); Mali 2019 provided a highly imprecise estimate of mortality at 30 days. Both studies provided imprecise estimates regarding need for surgery (sigmoid resection) at 30 days or 6 years, treatment failure at 30 days (defined differently in the two studies) and for recurrence of diverticulitis. Mali 2019 provided an imprecise estimate of stoma rates and rehospitalization. Neither NRCS reported on any adverse events that were attributable to percutaneous drainage.

Conclusions

The clinical questions posed by this SR about nonsurgical management of patients with acute colonic diverticulitis remain largely unanswered. Much of the evidence base is sparse and many of the studies, though of at least fair methodological quality, did not address the most pertinent clinical questions or were underpowered to effectively do so.

Very few adequately conducted studies have addressed the question of the need for hospitalization of those patients with relatively mild disease or the value of interventional

radiology procedures for those patients with abscesses. Although the evidence is relatively sparse and of insufficient to low SoE, the evidence suggests that patients with uncomplicated disease may be likely to do as well with outpatient management as hospitalization. Low SoE found no statistical or clinically important differences for most outcomes between use of antibiotic treatment or not for patients with uncomplicated diverticulitis, specifically related to pain symptoms, length of hospital stay, recurrence risk, and quality of life. The likelihood of needing surgery at 6 to 12 months after the episode of acute diverticulitis may be lower among patients who received antibiotics, but the finding was highly nonsignificant. Evidence regarding other outcomes and comparing different antibiotic regimens is insufficient.

The important clinical questions have not been addressed by sufficient numbers of studies that meet basic methodological criteria for comparative studies. In particular, there is very limited evidence regarding which patients might benefit most from (or be most harmed by) the various interventions. It was common that studies were underpowered (too small) to address the most important clinical outcomes, failed to address the clinically important outcomes, or were inadequately analyzed. For many of the questions pertaining to treatment dilemmas, the RCTs tended to be too small (thus, underpowered) to detect differences between treatments in important, but relatively rare, clinical outcomes (such as treatment failure, unplanned emergency surgery, and death). Many of the NRCSs were designed to be large enough to address at least some of the clinically important outcomes, but did not control or adequately control for the inherent differences between groups. Thus, the findings of these NRCSs may have been biased toward findings that more intensive interventions are associated with worse outcomes.

We believe that our literature search was complete and did not systematically miss studies. It appears that the large majority of studies that were unavailable to us were conference abstracts, so we might have missed some cutting-edge studies. We restricted the evidence base to the past 30 years, based on changing diagnostic criteria for acute diverticulitis in the 1990s. We might have, thus, missed some important older studies that might still be pertinent. However, none of the stakeholders we collaborated with knew of such studies or were concerned by the choice of dates. While we restricted some study designs based on sample sizes, we do not believe the smaller studies would have altered conclusions. Our protocol did not cover all management decisions for the care of patients with acute diverticulitis or history of diverticulitis; for example, we did not address questions related to dietary restrictions during episodes of acute diverticulitis.

The evidence base, even where insufficient to make conclusions about intervention effect, appeared to be generally applicable to patients with diagnosed acute diverticulitis. Most studies described their eligibility criteria sufficiently to determine that the included participants are those for whom the intervention is potentially appropriate. However, many studies did not provide sufficient detail to understand the detailed level of severity of disease or of potential risk factors for poor outcomes. However, as described above, studies rarely evaluated subgroups and failed to address heterogeneity of treatment effect. Such analyses could allow a better understanding of whom the findings are most applicable to.

There is a clear need for high-quality research to address all covered issues. Ideally, large-scale, multicenter RCTs should be conducted in unrestricted populations (i.e., without eligibility restrictions that may reduce applicability) with appropriate subgroup analyses. RCTs should be large enough to evaluate potential clinically important differences in rates of the most important outcomes to patients (e.g., death, treatment failure, emergency surgery, and time to recurrence) and important harms, adverse events, and complications.

In addition, large databases should be adequately analyzed to compare interventions. Future analyses need to use best-methods to appropriately adjust for the fundamental differences in patients for whom conservative or more-aggressive therapies are chosen in clinical practice. Ideally, propensity score analysis (or similar techniques) should be used, although, such analyses generally require relatively large numbers of patients for whom there is granular data about their risk factors for outcomes. Furthermore, future studies should emphasize evaluations of heterogeneity of treatment effect, not just subgroup analysis, to better understand which patients may most benefit from (or may be most harmed by) a given intervention.

Many questions remain inadequately answered regarding the best management of patients with acute diverticulitis. With low SoE, for selected patients, outpatient management may be as effective an inpatient care. For patients with acute uncomplicated diverticulitis, it may be safe and appropriate to forgo antibiotics (low SoE). The evidence base is inconclusive, though, about choice of antibiotic regimen for patients with complicated diverticulitis. The evidence is insufficient to assess the clinical value of percutaneous drainage. While findings are likely generalizable to all relevant patients, there is little evidence to guide decisions about which patients may benefit most (or be at highest risk of harm) from the various treatment options. There is a compelling need for future, well-conducted studies that address both effectiveness (and harms) of interventions and heterogeneity of treatment effect.

Table 1. Evidence profile for outpatient versus inpatient management of uncomplicated acute diverticulitis

Outcome	No. Studies (Subjects)	Risk of Bias	Consistency	Precision	Directness	Other	Overall SoE	Conclusion statements
Death	3 (1009)	Low	Consistent	Imprecise	Direct	Sparse	Insufficient	No conclusion Rare event
Treatment failure	2 (697)	Low	Inconsistent	Unclear	Direct	None	Insufficient	No conclusion
Emergency surgery	2 (208)	Low	Consistent	Imprecise	Direct	Sparse	Insufficient	No conclusion Rare event
Recurrence (~8-55 mo)	4 (791)	High	Consistent	Precise	Direct	Unadjusted	Low	No difference found unadj OR 0.85 (0.62, 1.17)
Elective surgery (~8-55 mo)	3 (655)	High	Consistent	Precise	Direct	Unadjusted	Low	No difference found unadj OR 0.76 (0.42, 1.37)
Quality of life	1 (132)	Low	N/A	Precise	Direct	Sparse	Insufficient	No conclusion

Abbreviations: N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence, unadj = unadjusted.

Table 2. Evidence profile for antibiotic treatment for acute diverticulitis [A]

Topic	Outcome	No. Studies (Subjects)	Risk of Bias	Consistency	Precision	Directness	Other	Overall SoE	Conclusion statements
Abx vs. no Abx	Death	3 (1329)	Moderate	Consistent	Imprecise	Direct	Sparse events	Insufficient	No conclusion Rare event.
	Treatment failure [B]	2 (706)	Low	Consistent	Imprecise	Indirect [C]	Sparse	Insufficient	No conclusion
	Length of hospital stay [B]	3 (1329)	Moderate	Inconsistent	Precise	Direct	None	Low	No evidence of a difference Difference −7.7 hr (−20.2, 4.8)
	Rehospitalization	2 (706)	Moderate	Consistent	Precise	Direct	Sparse [D]	Insufficient	No conclusion
	Surgery at 6-12 months	2 (1110)	Moderate	Consistent	Imprecise	Direct	None	Low	No evidence of a difference, but possible trend toward lower risk with antibiotics OR 0.33 (0.07, 1.63) [E]
	Recurrence [F]	4 (1624)	Moderate	Consistent	Precise	Indirect [G]	None	Low	No evidence of a difference Summary OR 1.06 (0.81, 1.39)
	Diverticulitis-related morbidities	2 (1151)	Moderate	Consistent	Imprecise	Direct	Sparse events	Insufficient	No conclusion Rare event.
	Pain/tenderness	3 (1230)	Moderate	Inconsistent	Imprecise	Direct	None	Low	No evidence of clinically significant difference
	Quality of life	2 (732)	Moderate	Consistent	Precise	Direct	Sparse, per analysis	Low	No evidence of a difference
	Adverse events	1 (1197)	Moderate	N/A	Precise	Direct	Sparse	Insufficient	No conclusion
Various Abx regimens	All	7 (1405)	Moderate	N/A	Imprecise	Direct	Sparse, per analysis [H]	Insufficient	No conclusions

Abbreviations: Abx = antibiotics, LOS = length of stay, MD = mean difference, N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

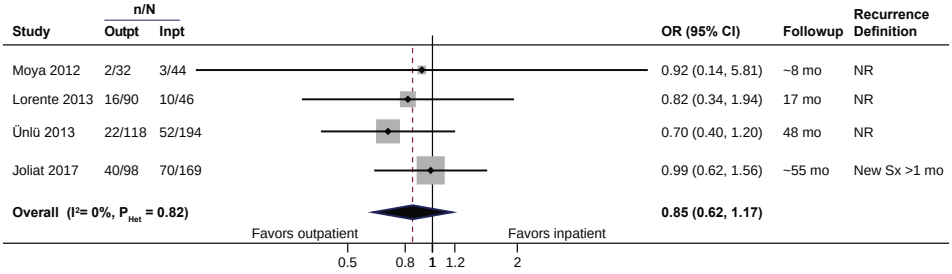
[A] The two trials of right-sided diverticulitis (Kim 2019 and Park 2019) are omitted. Evidence pertaining to right-sided diverticulitis is insufficient due to sparseness of studies. Footnotes indicate which outcomes were reported by the studies of right-sided diverticulitis.
[B] One study provided insufficient evidence about antibiotics vs. placebo in right sided diverticulitis.
[C] The study described treatment failure at 6 months follow-up.
[D] Across 2 trials, only a single estimate at each time point (1 week, 1 month, 6 months, 24 months).
[E] AVOD finding at 12 months. DIABOLO had similar finding at 6 months (OR 0.36; 95% CI 0.10, 1.38).
[F] One study provided insufficient evidence about antibiotics vs. placebo in right sided diverticulitis.
[G] Time points ranged from 12 to 50 months. AVOD also found similar results at 11 years.
[H] Each study evaluated a different comparison of antibiotic regimens.

Table 3. Evidence profile for interventional radiology versus no procedure

Outcome	N Studies (Subjects)	Risk of Bias	Consistency	Precision	Directness	Other	Strength of Evidence	Conclusions
Diverticulitis-related mortality, within 30 days	1 (36)	Low	Not applicable	Imprecise	Direct	Sparse	Insufficient	No conclusion Rare event.
Sigmoid resection at 30 days	2 (483)	Low	Consistent	Imprecise	Direct	None	Insufficient	No conclusion Rare event.
Stoma	1 (24)	Low	Not applicable	Imprecise	Direct	Sparse	Insufficient	No conclusion
Treatment failure at 30 days	2 (483)	Low	Consistent	Precise	Direct	Sparse*	Insufficient	No conclusion
Rehospitalization for diverticulitis or complications	1 (36)	Low	Not applicable	Imprecise	Direct	Sparse	Insufficient	No conclusion
Length of hospital stay	1 (36)	Low	Not applicable	Imprecise	Direct	Sparse	Insufficient	No conclusion
Recurrence of diverticulitis	2 (483)	Low	Consistent	Imprecise	Direct	Sparse*	Insufficient	No conclusion
Adverse event	0							No evidence

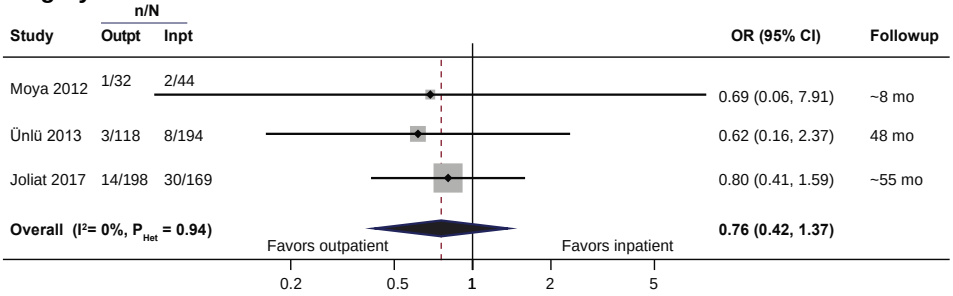
* One study highly imprecise. Therefore, the conclusion is based on only one study.

Figure 1. Meta-analysis of outpatient versus inpatient management: Recurrence of diverticulitis



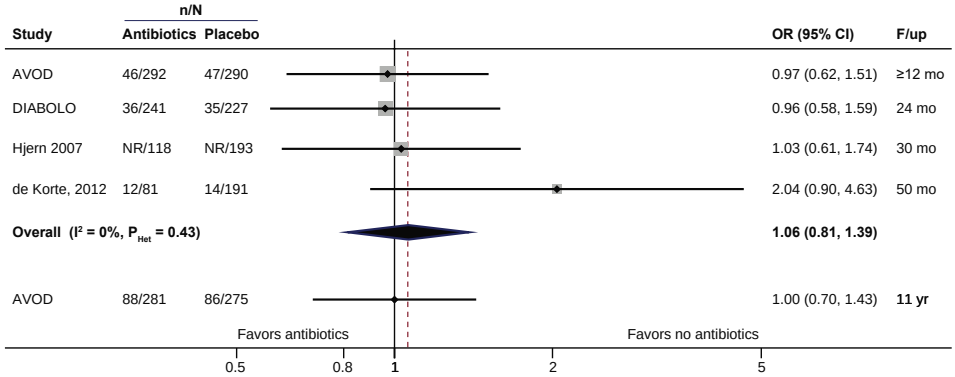
Abbreviations: CI = confidence interval, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), Inpt = inpatient management, mo = months, NR = not reported, OR = odds ratio, Outpt = outpatient management, P_{Het} = statistical heterogeneity P value, Sx = symptoms (of acute diverticulitis).

Figure 2. Meta-analysis of outpatient versus inpatient management: Elective surgery for diverticulitis



Abbreviations: CI = confidence interval, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), Inpt = inpatient management, mo = months, NR = not reported, OR = odds ratio, Outpt = outpatient management, P_{Het} = statistical heterogeneity P value.

Figure 3. Meta-analysis of antibiotics versus no antibiotics/placebo: Long-term recurrence of left-sided diverticulitis



Abbreviations: CI = confidence interval, F/up = Follow up, OR = odds ratio, P_{Het} = P value of test for statistical heterogeneity.

References

1. Wheat CL, Strate LL. Trends in Hospitalization for Diverticulitis and Diverticular Bleeding in the United States From 2000 to 2010. Clin Gastroenterol Hepatol. 2016;14(1):96-103.e1.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. Gastroenterology. 2009;136(3):741-54.
3. Peery AF, Keku TO, Martin CF, Eluri S, Runge T, Galanko JA, et al. Distribution and Characteristics of Colonic Diverticula in a United States Screening Population. Clin Gastroenterol Hepatol. 2016;14(7):980-5.e1.
4. Bassotti G, Battaglia E, De Roberto G, Morelli A, Tonini M, Villanacci V. Alterations in colonic motility and relationship to pain in colonic diverticulosis. Clin Gastroenterol Hepatol. 2005;3(3):248-53.
5. Kvasnovsky CL, Leong LEX, Choo JM, Abell GCJ, Papagrigoriadis S, Bruce KD, et al. Clinical and symptom scores are significantly correlated with fecal microbiota features in patients with symptomatic uncomplicated diverticular disease: a pilot study. Eur J Gastroenterol Hepatol. 2018;30(1):107-12.
6. Barbara G, Scaioli E, Barbaro MR, Biagi E, Laghi L, Cremon C, et al. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. Gut. 2017;66(7):1252-61.
7. Nally DM, Kavanagh DO. Current Controversies in the Management of Diverticulitis: A Review. Dig Surg. 2019;36(3):195-205.
8. Deery SE, Hodin RA. Management of Diverticulitis in 2017. J Gastrointest Surg. 2017;21(10):1732-41.
9. Balk EM, Adam GP, Cao W, Danko K, Bhuma MR, Mehta S, et al. Management of Colonic Diverticulitis. Comparative Effectiveness Review No. 233. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015- 00002-I.) AHRQ Publication No. 20(21)-EHC025. Rockville, MD: Agency for Healthcare Research and Quality; October 2020. DOI: https://doi.org/10.23970/AHRQEPCCER233. Posted final reports are located on the Effective Health Care Program search page.
10. Balk EM, …. Colonoscopy and Elective Surgery After Acute Colonic Diverticulitis: A Systematic Review. submitted. 2021.
11. Agency for Healthcare Research and Quality Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
12. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
13. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
14. National Heart Lung and Blood Institute. Study Quality Assessment Tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed December 3, 2020.
15. Berkman ND, Lohr KN, Ansari MT, Balk EM, Kane R, McDonagh M, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015;68(11):1312-24.

16. Biondo S, Golda T, Kreisler E, Espin E, Vallribera F, Oteiza F, et al. Outpatient versus hospitalization management for uncomplicated diverticulitis: a prospective, multicenter randomized clinical trial (DIVER Trial). Ann Surg. 2014;259(1):38-44.
17. Moya P, Arroyo A, Perez-Legaz J, Serrano P, Candela F, Soriano-Irigaray L, et al. Applicability, safety and efficiency of outpatient treatment in uncomplicated diverticulitis. Tech Coloproctol. 2012;16(4):301-7.
18. Bolkenstein HE, Draaisma WA, van de Wall B, Consten E, Broeders I**.** Treatment of acute uncomplicated diverticulitis without antibiotics: risk factors for treatment failure. Int J Colorectal Dis. 2018;33(7):863-9.
19. Joliat GR, Emery J, Demartines N, Hubner M, Yersin B, Hahnloser D**.** Antibiotic treatment for uncomplicated and mild complicated diverticulitis: outpatient treatment for everyone. Int J Colorectal Dis. 2017;32(9):1313-9.
20. Lorente L, Cots F, Alonso S, Pascual M, Salvans S, Courtier R, et al. [Outpatient treatment of uncomplicated acute diverticulitis: Impact on healthcare costs]. Cir Esp. 2013;91(8):504-9.
21. Ünlü C, Gunadi PM, Gerhards MF, Boermeester MA, Vrouenraets BC**.** Outpatient treatment for acute uncomplicated diverticulitis. Eur J Gastroenterol Hepatol. 2013;25(9):1038-43.
22. Chabok A, Pahlman L, Hjern F, Haapaniemi S, Smedh K**.** Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99(4):532-9.
23. Isacson D, Smedh K, Nikberg M, Chabok A**.** Long-term follow-up of the AVOD randomized trial of antibiotic avoidance in uncomplicated diverticulitis. Br J Surg. 2019;106(11):1542-8.
24. Daniels L, Unlu C, de Korte N, van Dieren S, Stockmann HB, Vrouenraets BC, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017;104(1):52-61.
25. Juncadella AC, Feuerstein JD**.** In uncomplicated, left-sided acute diverticulitis, observation did not differ from antibiotics for recovery. Ann Intern Med. 2017;166(4):JC18.
26. van Dijk ST, Daniels L, de Korte N, Stockmann HB, Vrouenraets BC, EC JC, et al. Quality of Life and Persistent Symptoms After Uncomplicated Acute Diverticulitis. Dis Colon Rectum. 2019;62(5):608-14.
27. van Dijk ST, Daniels L, Unlu C, de Korte N, van Dieren S, Stockmann HB, et al. Long-Term Effects of Omitting Antibiotics in Uncomplicated Acute Diverticulitis. Am J Gastroenterol. 2018;113(7):1045-52.
28. Jaung R, Nisbet S, Gosselink MP, Di Re A, Keane C, Lin A, et al. Antibiotics Do Not Reduce Length of Hospital Stay for Uncomplicated Diverticulitis in a Pragmatic Double-Blind Randomized Trial. Clin Gastroenterol Hepatol. 2020;[Article in press].
29. Kellum JM, Sugerman HJ, Coppa GF, Way LR, Fine R, Herz B, et al. Randomized, prospective comparison of cefoxitin and gentamicin-clindamycin in the treatment of acute colonic diverticulitis. Clin Ther. 1992;14(3):376-84.
30. Ridgway PF, Latif A, Shabbir J, Ofriokuma F, Hurley MJ, Evoy D, et al. Randomized controlled trial of oral vs intravenous therapy for the clinically diagnosed acute uncomplicated diverticulitis. Colorectal Dis. 2009;11(9):941-6.
31. Ribas Y, Bombardo J, Aguilar F, Jovell E, Alcantara-Moral M, Campillo F, et al. Prospective randomized clinical trial assessing the efficacy of a short course of

intravenously administered amoxicillin plus clavulanic acid followed by oral antibiotic in patients with uncomplicated acute diverticulitis. Int J Colorectal Dis. 2010;25(11):1363-70.
32. Schug-Pass C, Geers P, Hugel O, Lippert H, Kockerling F**.** Prospective randomized trial comparing short-term antibiotic therapy versus standard therapy for acute uncomplicated sigmoid diverticulitis. Int J Colorectal Dis. 2010;25(6):751-9.
33. de Korte N, Kuyvenhoven JP, van der Peet DL, Felt-Bersma RJ, Cuesta MA, Stockmann HB**.** Mild colonic diverticulitis can be treated without antibiotics. A case-control study. Colorectal Dis. 2012;14(3):325-30.
34. Hjern F, Josephson T, Altman D, Holmstrom B, Mellgren A, Pollack J, et al. Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory? Scand J Gastroenterol. 2007;42(1):41-7.
35. Scarpa CR, Buchs NC, Poncet A, Konrad-Mugnier B, Gervaz P, Morel P, et al. Short-term Intravenous Antibiotic Treatment in Uncomplicated Diverticulitis Does Not Increase the Risk of Recurrence Compared to Long-term Treatment. Ann Coloproctol. 2015;31(2):52-6.
36. Etzioni DA, Chiu VY, Cannom RR, Burchette RJ, Haigh PI, Abbas MA**.** Outpatient treatment of acute diverticulitis: rates and predictors of failure. Dis Colon Rectum. 2010;53(6):861-5.
37. van Dijk ST, Chabok A, Dijkgraaf MG, Boermeester MA, Smedh K**.** Observational versus antibiotic treatment for uncomplicated diverticulitis: an individual-patient data meta-analysis. Br J Surg. 2020;107(8):1062-9.
38. Lambrichts DPV, Bolkenstein HE, van der Does D, Dieleman D, Crolla R, Dekker JWT, et al. Multicentre study of non-surgical management of diverticulitis with abscess formation. Br J Surg. 2019;106(4):458-66.
39. Mali J, Mentula P, Leppaniemi A, Sallinen V**.** Determinants of treatment and outcomes of diverticular abscesses. World J Emerg Surg. 2019;14:31.

Appendix A. Methods

Literature Search Strategies

Note that the full search strategy included searches for research questions about CT as a diagnostic tool, post-diverticulitis colonoscopy, and elective surgery. These can be found in Appendix A of the full report (see article for reference).

All searches restricted to January 1990 to November 16, 2020 (final search date)

Medline (via PubMed)

(“Diverticulitis”[Mesh] OR "Diverticulosis, Colonic"[Mesh] OR diverticulitis [tiab] OR diverticulosis [tiab] OR diverticular [tiab])
AND
(Hospital OR hospitals OR hospitalization OR "Hospitalization"[Mesh] OR Inpatient* OR discharge* OR outpatient OR "Ambulatory Care"[Mesh] OR antibiotic* OR "Anti-Bacterial Agents"[Mesh] OR medication* OR medical OR "Radiology, Interventional"[Mesh] OR interventional radiology)

NOT
(“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or "comment on" or ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murinae)

Embase
#30 (#6 OR #28) AND ([article]/lim OR [article in press]/lim)
#29 #6 OR #28
#28 #8 AND #27
#27 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#26 'elective surgery'/de
#25 'lactobacillus casei'/de
#24 'balsalazide'/de
#23 'probiotic agent'/de
#22 'rifaximin'/de
#21 'fiber'/de
#20 'diet therapy'/de
#19 'aminosalicylic acid'/de
#18 'mesalazine'/de
#17 'colonography'/de

#16 'colonoscopy'/de
#15 'interventional radiology'/de
#14 'drug therapy'/de
#13 'antibiotic agent'/de
#12 'ambulatory care'/de
#11 'outpatient'/de
#10 'hospital patient'/de
#9 'hospitalization'/de
#8 #1 OR #2Diverticulitis
#7 #4 AND #5 AND ([article]/lim OR [article in press]/lim)
#6 #4 AND #5
#5 #1 OR #2 OR #3
#4 'computer assisted tomography'/de
#3 'acute abdomen'/de
#2 'diverticulosis'/de
#1 'diverticulitis'/de

Cochrane
((Diverticulitis OR diverticulosis OR diverticular OR “acute abdomen” OR ((acute or nonspecific OR non-specific OR emergen*) AND (abdome* OR abdomi*) AND pain) OR peritonitis)
OR
(“CT scan” OR “cat scan” OR tomography)) OR (Diverticulitis OR diverticulosis OR diverticular)

CINAHL
((Diverticulitis OR diverticulosis OR diverticular OR “acute abdomen” OR ((acute or nonspecific OR non-specific OR emergen*) AND (abdome* OR abdomi*) AND pain) OR peritonitis) AND (“CT scan” OR “cat scan” OR tomography))
OR
(Diverticulitis OR diverticulosis OR diverticular)

Inclusion/Exclusion Criteria Details (Treatment of acute diverticulitis)

Population(s):

- Adults with acute complicated or uncomplicated diverticulitis, whether first or recurrent episode
    - KQ 2a: Intervention = hospitalization: uncomplicated diverticulitis
    - KQ 2b: Intervention = antibiotics: uncomplicated or complicated diverticulitis
    - KQ 2c: Intervention = interventional radiology: complicated diverticulitis (e.g., abscess)
- Exclude: Complicated diverticulosis, without diverticulitis (e.g., hemorrhagic diverticulosis)
- Exclude: Symptomatic uncomplicated diverticular disease (SUDD)
- Exclude: Meckel's diverticula (unless concurrent acute diverticulitis)
- Exclude: Non-colonic diverticulitis

Interventions versus Comparators:

- Hospitalization versus No hospitalization (for patients not requiring surgery)
- Antibiotics versus No antibiotics or versus Alternative antibiotic regimen (for any patient)
    - Any class, route, treatment duration, or initiation time, and comparisons among these
    - Use of any antibiotics (e.g., at clinician's discretion) or specific antibiotics
- Interventional radiology procedure versus No procedure (conservative management; for patients with complicated diverticulitis for whom no procedure is an option)
    - Any interventional radiology procedure appropriate for the severity and type of complication
    - Exclude: Comparison of intervention radiology procedures or techniques

Outcomes:

- Short-term (≤30 days)
    - Resolution of diverticulitis
    - Return to normal bowel function
    - Length of hospital (or intensive care unit) stay
- Short- and medium-term (<1 year)
    - Interventional radiology procedure for diverticulitis (avoidance) (exclude for comparisons of interventional radiology procedure with conservative management)
- Medium- to long term (>1 month)
    - Recurrent diverticulitis
    - Opioid misuse
- Any duration (short-, medium-, or long-term)
    - Conversion to complicated diverticulitis
    - Surgery for diverticulitis (avoidance)

        - Including colostomy (avoidance)
    - Rehospitalization for diverticulitis or complications
    - Quality of life/Functional outcomes
    - Resource use
    - Missed work, employment, school outcomes, etc.
    - Diverticulitis-related morbidities
    - Mortality, both diverticulitis-related and all-cause
- All categorical "effectiveness" outcomes include time to outcome
- Harms, adverse events, side effects of interventions (any time frame)
    - Hospitalization comparison:
        - Hospital-based infections and other harms
    - Antibiotics comparisons:
        - Side effects/adverse events attributable to antibiotics
        - Clostridioides difficile (C diff) infection
        - Antibiotic resistance
    - Interventional radiology comparisons:
        - Adverse events related to procedures, including bleeding and catheter infections
        - Need for second procedures or revisions

Modifiers/Subgroups of interest:

- Patient characteristics (e.g., prior history of diverticulitis, age)
- Presentation or course of illness (e.g., specific symptoms)
- Other factors (e.g., complicated or uncomplicated diverticulitis, hospital setting)

Timing:

- Minimum duration of follow-up = treatment duration (hospitalization, antibiotic use)

Setting:

- Inpatient, emergency department (or equivalent), outpatient

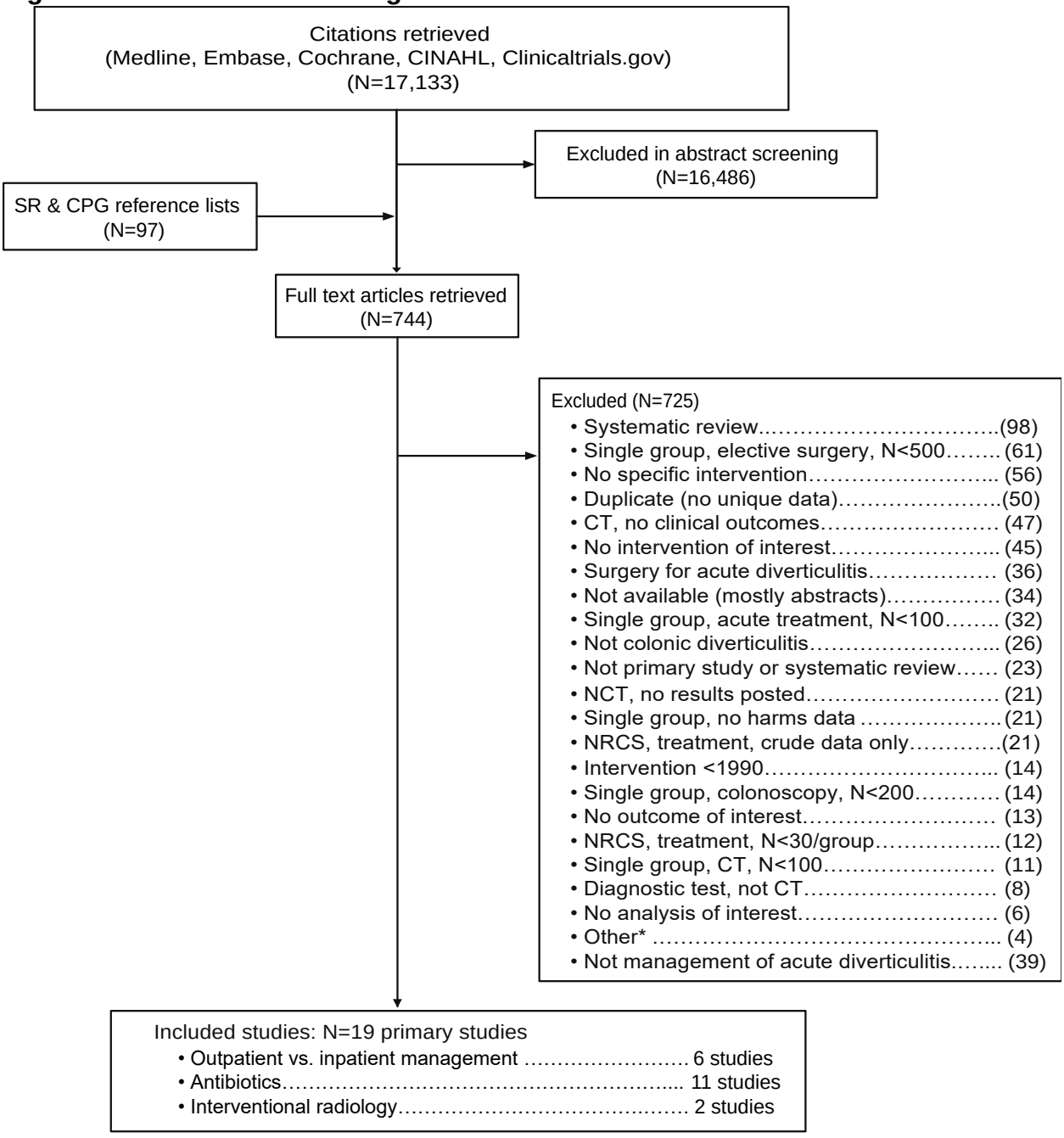
Design:

- Randomized controlled trials (all subquestions)
    - N≥10/arm
- Nonrandomized comparative studies
    - Antibiotics (all outcomes) or hospitalization and IR comparisons (short- to medium-term outcomes; <1 year)
        - Restrict to studies that use modeling or other analytic methods to minimize selection bias (due to inherent differences between people who receive one or the other intervention), or that restrict study eligibility criteria such that comparisons being made are between patients with similar presentations.
    - Long-term outcomes, hospitalization and IR comparisons (long-term outcomes; ≥1 year)
        - Allow crude comparisons of long-term outcomes under the assumption that characteristics during acute diverticulitis that were associated with treatment decision (e.g., older patients being more likely to be hospitalized) would not have a major impact on long-term outcomes.
    - Hospitalization and antibiotics: N≥30/arm; Interventional radiology N≥10/arm
- Single group studies

    - Only for adverse events
    - N>100
- Longitudinal (Exclude: cross-sectional)
- Prospective or retrospective
- Publication since 1990
- Exclude: Case reports (and series of case reports)

Supplement B

Figure B-1. Literature flow diagram



Abbreviations: CPG = clinical practice guideline, CT = computed tomography, NCT = ClinicalTrials.gov record, NRCS = nonrandomized comparative study, SR = systematic review.

* CT of pre-diagnosed groups, not for diagnosis or staging (N=1); randomized controlled trial, N<10/arm (N=1); antibiotics used for both complicated and uncomplicated diverticulitis, not separated (N=1); study design not of interest, focus group (N=1).

Supplemental Table B-1. Outpatient vs. inpatient management

Table B-1-1. Outpatient vs. inpatient: Design Details and Arms

Study Year PMID Country Funding	Design	N	Population, Diverticulitis Details, Setting	Arm	Arm Details	Age Sex	Prior episodes diverticulitis
Biondo, 2014, 23732265, DIVER Trial, Spain, Non-industry	RCT	132	Uncomplicated diverticulitis, tolerate oral intake with good response to first treatment measures in emergency, willing to continue treatment at home under supervision. Tertiary care, academic	Outpatient management	Discharged after 1st dose of IV Abx in the ED	Mean=55.9 (13.4) 52% male	Mean=0.47 (SD=10.9)
				Inpatient management	Admitted	Mean=56.8 (12.8) 58% male	Mean=0.39 (SD=1.0)
Bolkenstein, 2018, 29679152, Netherlands, NR	NRCS (Retrospective)	565	First episode uncomplicated diverticulitis, no Abx treatment 2wks prior or 24hr after presentation to hospital Single center	Outpatient management	Not hospitalized within 24hr of presentation	Mean=57 (SD=12) 39% male	None (by design)
				Inpatient management	Hospitalized within 24hr of presentation	Mean=59 (SD=13) 42% male	None (by design)
Joliat, 2017, 28664347, Switzerland, NR	NRCS (Retrospective)	267	Uncomplicated or mild complicated diverticulitis. Single hospital	Outpatient management	Single dose Abx (IV) in ED followed by Abx (oral) for 10 days	Median=53 (Range=44–64) 64% male	None (72%)
				Inpatient management	Abx and fluids (IV), switched to Abx (oral) when pain was managed by non-opioid analgesics and able to tolerate oral medication (also discharged). No alimentary restrictions in hospital	Median=61 (Range=50–72) 50% male	None (71%)
Lorente, 2013, 23764519, Spain, NR	NRCS (Retrospective)	136	Uncomplicated diverticulitis, tolerate oral intake, absence of comorbidities, adequate family or social support. Single hospital	Outpatient management	Abx for 7 days (oral) and analgesia (oral), liquid diet for 2 days. Follow up assessment between 4-7 days after diagnosis to confirm clinical course	Mean=58.75 (SD=15) 44% male	≥1: 19%
				Inpatient management	Abx (IV) until improvement in symptoms then discharged to continue Abx (oral) at home	Mean=60.52 (SD=19) 43% male	Previous episodes (30%)

Study Year PMID Country Funding	Design	N	Population, Diverticulitis Details, Setting	Arm	Arm Details	Age Sex	Prior episodes diverticulitis
Moya, 2012, 22706731, Spain, NR	NRCS (Prospective)	76	Uncomplicated diverticulitis, tolerate oral intake, adequate family and social support network. Academic	Outpatient management	10 d oral Abx, oral analgesics, and dietary restrictions	Median=56.1 (Range=32–83) 50% male	≥1: 16%
				Inpatient management	5 d IV Abx, IV analgesic, and dietary restrictions	Median=59.7 (Range=36–84) 45% male	≥1: 18%
Ünlü, 2013, 23636075, Netherlands, NR	NRCS (Retrospective)	312	First episode uncomplicated diverticulitis Two hospitals	Outpatient management	IV Abx in ED, 7-10 d oral Abx	Mean=54.5 (SD=11.1) 42% male	None (by design)
				Inpatient management	IV Abx while inpatient, then 7-10 d oral Abx	Mean=59.3 (SD=14.6) 37% male	None (by design)

Abx = antibiotic, ED = emergency department, mos = month, NR = not reported, NRCS = non-randomized controlled study, OR = odds ratio, PMID = Pubmed identifier, RCT = randomized controlled trial, SD = standard deviation, wk = week.

Table B-1-2. Outpatient vs. inpatient: Risk of Bias Assessment for Primary Studies – Randomized Controlled Trials

Study, Year, PMID	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/ care providers	Blinding of outcome assessor (objective outcomes)	Blinding of outcome assessor (subjective outcomes)	Incomplete outcome data	Selective outcome reporting	Other bias	Eligibility criteria prespecified and clearly described	Intervention clearly described and delivered consistently	Outcomes prespecified, clearly defined, valid, reliable, and assessed consistently
Biondo, 2014, 23732265	Low	Low	High	High	Low	Low	Low	Unclear	Low	Yes	Yes	Yes

KQ = Key Question, PMID = PubMed Identifier. Ratings are color coded for emphasis only.

From the Cochrane Risk of Bias Tool (each item rated as Low, High, Unclear, or N/A)

- Random sequence generation (selection bias): Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence;
- Allocation concealment (selection bias): Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment;
- Blinding of participants (performance bias): Performance bias due to knowledge of the allocated interventions by participants during the study;
- Blinding of personnel/care providers (performance bias): Performance bias due to knowledge of the allocated interventions by personnel/care providers during the study;
- Blinding of outcome assessor (detection bias): Detection bias due to knowledge of the allocated interventions by outcome assessors;
- Incomplete outcome data (attrition bias): Attrition bias due to amount, nature or handling of incomplete outcome data;
- Selective outcome reporting (outcome reporting bias): Bias arising from outcomes being selectively reported based on the direction and/or strength of the results;
- Other Bias: Bias due to problems not covered elsewhere in the table.

From the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool (each item rated as Yes, No, or Unclear)

- Eligibility criteria prespecified and clearly described: potentially related to selection bias;
- Intervention clearly described and delivered consistently: potentially related to performance bias;
- Outcomes prespecified, clearly defined, valid, reliable, and assessed consistently: potentially related to detection bias.

Table B-1-3. Outpatient vs. inpatient: Risk of Bias Assessment for Primary Studies – Nonrandomized Comparative Studies – Assessment of Confounding and Selection Bias

Study, Year, PMID	1.1 Potential for any confounding?	1.2 Potential for time-varying confounding?	1.4 Appropriate analysis method for confounding?	1.5 Appropriate confounding variables used?	1.6 Inappropriate control of post-intervention variables?	Judgement – Risk of bias related to confounding	2.1 Participant selection based on post-intervention variables?	2.2 Post-intervention variables associated with intervention?	2.3 Post-intervention variables associated with outcome?	2.4 Start and follow-up (duration) coincide	Start and follow-up calendar years coincide	2.5 Appropriate adjustment for selection bias	Judgement – Risk of bias related to selection bias
Bolkenstein, 2018, 29679152	Yes	No	Yes	Unsure	No	**Serious**	No	N/A	N/A	Yes	No	N/A	**Low**
Joliat, 2017, 28664347	Yes	No	No	N/A	N/A	**Critical**	PY	PY	PY	Yes	No	No	**Critical**
Lorente, 2013, 23764519	Yes	No	No	N/A	N/A	**Critical**	No	N/A	N/A	Yes	No	N/A	**Low**
Moya, 2012, 22706731	Yes	Yes	No	N/A	N/A	**Critical**	No	N/A	N/A	Yes	No	N/A	**Low**
Ünlü, 2013, 23636075	Yes	No	No	N/A	N/A	**Critical**	No	N/A	N/A	Yes	No	N/A	**Low**

KQ = Key Question, PMID = PubMed Identifier, Responses to Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) signaling questions 1.1 to 1.6 and 2.1 to 2.5 are in regular font. Each item rated as Yes, PY (probably yes), NI (no information), PN (probably no), No, or N/A (not applicable).
Judgements about confounding and selection bias are in **bold font**. (each item rated as **Low**, **Moderate**, **Serious**, or **Critical**).

Table B-1-4. Outpatient versus inpatient management: Categorical Outcomes

Study Year PMID, Design	Outcome	Time	Arm	Arm Details	n/N (%)	Effect Size (95% CI), Adjusted	Reported P value
Biondo, 2014, 23732265, RCT	Treatment failure [A]	2 mo	Outpatient management	Discharged after 1st dose of IV Abx in the ED	3/66 (4.5)	0.74 (0.16, 3.43)	0.62
			Inpatient management	Admitted	4/66 (6.1)		
Bolkenstein, 2018, 29679152, NRCS (Retrospective)	Treatment failure [B]	<24 mo	Outpatient management	Not hospitalized within 24hr of presentation	12/264 (5)	0.41 (0.20, 0.83) [C]	0.01
			Inpatient management	Hospitalized within 24hr of presentation	34/301 (11)		
Joliat, 2017, 28664347, NRCS (Retrospective)	Elective surgery	Median=47 mo (29-74)	Outpatient management	Single dose Abx (IV) in ED followed by Abx (oral) for 10 days	14/98 (14)	NR	0.50 [D]
		Median=60 mo (Range=34-82)	Inpatient management	Abx and fluids (IV), switched to Abx (oral) when pain was managed by non-opioid analgesics and able to tolerate oral medication (also discharged). No alimentary restrictions in hospital	30/169 (18)		
	Recurrence [E]	Median=47 mo (Range=29-74)	Outpatient management	Single dose Abx (IV) in ED followed by Abx (oral) for 10 days	40/98 (41)	NR	NR [D]
		Median=60 mo (Range=34-82)	Inpatient management	Abx and fluids (IV), switched to Abx (oral) when pain was managed by non-opioid analgesics and able to tolerate oral medication (also discharged). No alimentary restrictions in hospital	70/169 (41)		
Lorente, 2013, 23764519, NRCS (Retrospective)	Recurrence [F]	Mean=17 mo (SD=5)	Outpatient management	Abx for 7 days (oral) and analgesia (oral), liquid diet for 2 days. Follow up assessment between 4-7 days after diagnosis to confirm clinical course	16/90 (17.8)	NR	0.6 [G]
		Mean=17 mo (SD=5)	Inpatient management	Abx (IV) until improvement in symptoms then discharged to continue Abx (oral) at home	10/46 (21.7)		
Moya, 2012, 22706731, NRCS (Prospective)	Elective surgical treatment	Mean=7 mo (SD=9)	Outpatient management	10 d oral Abx,, oral analgesics, and dietary restrictions	1/32 (3.12)	NR	0.76 [H]
		Mean=9 mo (SD=18)	Inpatient management	5 d IV Abx, IV analgesic, and dietary restrictions	2/44 (4.5)		

Study Year PMID, Design	Outcome	Time	Arm	Arm Details	n/N (%)	Effect Size (95% CI), Adjusted	Reported P value
	Recurrence [F]	Mean=7 mo (SD=9)	Outpatient management	Abx for 10 days (oral), analgesics (oral), and liquid diet. Assessed days 4 and 7; if satisfactory, prescribed low-fiber and fiber-rich diet, respectively	2/32 (6.25)	NR	0.86 [H]
		Mean=9 mo (SD=18)	Inpatient management	Abx for 5 days (IV), analgesics (IV), and liquid diet. Assessed day 3, if satisfactory, started liquid diet. Discharged day 5 and prescribed a fiber-rich diet and Abx for 7 days (oral)	3/44 (6.81)		
Ünlü, 2013, 23636075, NRCS (Retrospective)	Elective surgery	Mean=48 mo (SD=26)	Outpatient management	Hospital admission <24 hr, all managed in the ED; Ab (IV) in hospital and continued Ab (oral) at discharge 7-10 days depending on clinical status	3/118 (3)	NR	NR [I]
		Mean=48 mo (SD=26)	Inpatient management	Treated as inpatients, Abx (IV) in hospital and continued Abx (oral) at discharge 7-10 days depending on clinical status	8/194 (4)	NR	
	Recurrence [F]	Mean=48 mo (SD=26)	Outpatient management	Hospital admission <24 hr, all managed in the ED; Ab (IV) in hospital and continued Ab (oral) at discharge 7-10 days depending on clinical status	22/118 (19)	NR	NR [I]
		Mean=48 mo (SD=26)	Inpatient management	Treated as inpatients, Abx (IV) in hospital and continued Abx (oral) at discharge 7-10 days depending on clinical status	52/194 (27)	NR	

Abx = antibiotic, CI = confidence interval, hr = hour, IV = intravenously, mo = month, NR = not reported, NRCS = non-randomized controlled study, OR = odds ratio, PMID = Pubmed identifier, RCT = randomized controlled trial, SD = standard deviation, wk = week

[A] Defined as persistence, increase, or recurrence of abdominal pain and/or fever, inflammatory bowel obstruction, need for radiological abscess drainage or immediate surgery due to complicated diverticulitis, need for hospital admission, and mortality during the first 60 days after discharge.

[B] Defined as (re)admittance, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia) or need for antibiotics, operative intervention, or percutaneous abscess drainage within 30 days after initial presentation.

[C] Adjusted for female gender, age, ASA score > 2, no rebound tenderness, C-reactive protein (mg/L).

[D] Unadjusted analysis; during their acute attack, patients in the inpatient group had statistically significant higher levels of C-reactive protein and comorbidities (as assessed by the Charlson index), and were more likely to have more severe diverticulitis (according to the Ambrosetti score). Outcomes from this study should be interpreted with caution to the extent these baseline differences may affect long-term outcomes

[E] Defined as new symptoms appearing >1 month after initial treatment.

[F] Not defined.
[G] Unadjusted analyses; during their acute attack, patients in the inpatient group had statistically significant higher rates of fever and pericolonic free fluid. Outcomes in this study should be interpreted with caution to the extent that these baseline may affect long-term outcomes.
[H] Unadjusted analyses; however no observed differences in baseline predictors.
[I] Unadjusted analyses; during their acute attack, patients in the inpatient group had higher levels of inflammatory parameters such as C-reactive protein (CRP) and white blood cells and were more likely to have symptoms of fever, nausea, and vomiting. Outcomes in this study should be interpreted with caution to the extent that these baseline may affect long-term outcomes.

Table B-1-5. Outpatient versus inpatient management: Continuous Outcomes

Study, Year, PMID, Design	Outcome	Time	Arm	Arm Details	N	Mean (SD)	Difference	Reported P value
Biondo, 2014, 23732265, RCT	SF-12 physical	2 mo	Outpatient management	Discharged after 1st dose of Abx (IV) in the ED	66	50.3 (7.2)	NR	0.59
			Inpatient management	Admitted after 1st dose of Abx (IV) in the ED	66	49.6 (8.7)		
	SF-12 mental	2 mo	Outpatient management	Discharged after 1st dose of Abx (IV) in the ED	66	53.0 (8.6)	NR	0.99
			Inpatient management	Admitted after 1st dose of Abx (IV) in the ED	66	52.6 (9.5)		

Abx = antibiotic, CI = confidence interval, ED = emergency department, IV = intravenously, mo = month, NR = not reported, PMID = Pubmed identifier, RCT = randomized controlled trial, SD = standard deviation, wk = week.

Supplemental Table B-2. Antibiotics

Table B-2-1. Antibiotics: Design Details

Author, Year, PMID, Study Name, Country, Funder	Study Design	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
AVOD Trial, Sweden, Non-Industry	RCT	2003, 2009	Age 18-75 years, Has at least 2 of following symptoms: fever, abdominal resistance, leukocyte >10,000/µl, CRP (≥20 and ≥ 2 mg/dl), detection of sigmoid diverticulitis using contrast medium. CT evidence, multicenter	CT or other evidence of complicated diverticulitis or other disease, immunosuppressive Tx, pregnancy, ongoing antibiotics	
de Korte, 2012, 21689302, Netherlands Not Reported	NRCS (Retrospective)	2001, 2007	Image-confirmed acute mild diverticulitis of the sigmoid colon in which the decision (implied based on review of charts) was made to treat conservatively	NR	image confirmed acute mild based on Ambrosetti or Hinchey 1a criteria
DIABOLO Trial, Sweden, Nonindustry	RCT	2010, 2012	Left-sided uncomplicated acute diverticulitis, clinical and diagnostic (ultrasound or CT) proven, modified Hinchey stages 1a-b (abscess size up to 5 cm) and Ambrosetti's 'mild' diverticulitis stage included.	Previous radiologically proven diverticulitis, higher modified Hinchey stages or Ambrosetti's 'severe' diverticulitis stage, sepsis, antibiotic use in the previous 4 weeks.	Patients were eligible if they had a first episode of left-sided, uncomplicated, acute diverticulitis, confirmed within 24 h by CT.
Etzioni, 2010, 20484998, USA Not Reported	NRCS (Retrospective)	2006, 2007	evaluated in Kaiser Permanente ED for a primary assigned diagnosis of acute diverticulitis, continuously enrolled as a member in Kaiser Permanente system before the index treatment episode	admitted for inpatient treatment, prior diagnosis of diverticulitis, colorectal cancer, inflammatory bowel disease, did not have CT within 1 year of ED evaluation	ICD codes
Hjern, 2007, 17190761, Sweden, Nonindustry	NRCS (Prospective)	2000, 2002	Clinical diagnosis of Acute Diverticulitis confirmed by CT	Diagnoses only based on clinical findings, operated immediately following admission because of clinical signs of peritonitis, perforated AD confirmed by CT	Clinical diagnosis of Acute Diverticulitis confirmed by CT

Author, Year, PMID, Study Name, Country, Funder	Study Design	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Jaung, 2019, 32240832, STAND, New Zealand and Australia	RCT	2015-2019	CT-proven Hinchey 1a uncomplicated acute diverticulitis	≥2 criteria for Systemic Inflammatory Response Syndrome (SIRS), temperature <36° or >38° C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or PaCO3 <32mmHg, white cell count <4 or >12 x 10 9/L); were unable to give consent, language barrier or cognitive impairment; previous drug reactions; prior usage of steroids; had been administered regular immunomodulators or biologics within the six months prior to presentation; used regular NSAIDs for greater than a week prior to presentation; had been administered >1 dose of intravenous or >2 doses of oral antibiotics during this illness but prior to enrolment in the study; were pregnant; had an American Society of Anesthesiologists physical status classification (ASA) ≥4; or had CT evidence of complicated acute diverticulitis.	CT
Kellum, 1992, 1638578, USA Not reported	RCT	NR	Acute diverticulitis considered present if there was abdominal tenderness, signs of infection (fever or leukocytosis), and radiological, surgical or pathological evidence.	Creatinine >/= 3mg/dl	Acute diverticulitis considered present if there was abdominal tenderness, signs of infection (fever or leukocytosis), radiological, surgical or pathological evidence.

Author, Year, PMID, Study Name, Country, Funder	Study Design	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Kim, 2019, 31267222, S Korea Not reported	RCT	2014, 2018	(1) age 18–80 years; (2) *right-sided colonic diverticulitis (cecum, ascending colon, or proximal transverse colon)*; and (3) uncomplicated diverticulitis (grade Ia)	(1) age < 18 or > 80 years; (2) distal transverse, left-sided, or sigmoid colonic diverticulitis; (3) complicated colonic diverticulitis (grades Ib, II, III, or IV); (4) sepsis; (5) systemic inflammatory response syndrome (SIRS); (6) immunocompromised patients (taking corticosteroid or immunosuppressive drugs, transplantation, or chronic renal failure with hemodialysis); (7) allergy to quinolone antibiotics; (8) pregnant or lactating patients; (9) American Society of Anesthesiologists (ASA) score > 3; (10) social, psychiatric, or cognitive impairment	Intravenous (IV) contrast–enhanced computed tomography (CT) was performed to confirm the diagnosis. Uncomplicated diverticulitis is defined as grade Ia and complicated diverticulitis includes grades Ib, II, III, and IV.
Park, 2019, 31290747, S Korea, Not Reported	RCT	2011, 2014	*Right colonic diverticulitis* in emergency or hospital setting, CT proven,	Abscess >3 cm in diameter, Hinchey II diseases or worse, ongoing antibiotic therapy from other hospital, pregnancy, or cephalosporin allergy	Inflamed diverticulum, phlegmon formation (Hinchey Ia), and small (≤3 cm) pericolic abscess formation (partial Hinchey Ib) were considered to be consistent with the diagnosis of CT-based uncomplicated diverticulitis
Ribas, 2010, 20526718, Spain, Non-industry	RCT	NR	Clinical diagnosis of uncomplicated acute diverticulitis, CT confirmed within 28-48 h	(1) immunocompromised patients, (2) patients under 18 years of age, (3) pregnant women, (4) clinical suspicion or CT confirmation of complicated acute diverticulitis, (5) Karnofsky performance score less than 50%, or (6) allergy to penicillin	The clinical diagnosis of sigmoid diverticulitis was suggested in patients with abdominal pain localized to the left lower quadrant and tenderness upon physical examination. The presence of fever, change in bowel habits, dysuria, urinary frequency and urgency, as well as leukocytosis was also taken into account to reach the diagnosis of diverticulitis.
Ridgway, 2008, 19016815, Ireland, Not Reported	RCT	2002, 2004	Acute uncomplicated diverticulitis. Hinchey type 1, multicenter	Hinchey types III or IV	Plain radiology and relevant blood investigation
Scarpa, 2015, 25960972, Switzerland Not Reported	NRCS (Prospective)	2007, 2012	1st episode CT-confirmed uncomplicated diverticulitis requiring hospitalization	complicated diverticulitis (Hinchey-Ib class and above), <18 yrs of age, chronic IBD or a tumor	physical examination and laboratory tests revealing an inflammatory syndrome and was confirmed by using an abdominal CT scan

Author, Year, PMID, Study Name, Country, Funder	Study Design	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Schug-Pass, 2010, 20140619, Germany, Industry	RCT	2004, 2008	Sigmoid diverticulitis using contrast medium, CT proven, multi-center	Study Tx or other betalactam. Hypersensitivity to betalactam. Immunosuppressant use. Antibiotic Tx within 2 weeks before enrollment. Incurable hematological/oncological diseases. Pregnancy. Existing sigmoid diverticulitis requiring surgery.	

Table B-2-2. Antibiotics: Arm Details

Author, Year, PMID, Study Name, Country	Arm	Arm Description	Dose	Frequency	Route	Duration of intervention
AVOD Trial, Sweden, Non-Industry	Antibiotics: Multiple (discretionary or undefined)	IV combination of a second- or third-generation cephalosporin (cefuroxime or cefotaxime) and metronidazole, or with carbapenem antibiotics (ertapenem, meropenem or imipenem) or piperacillin – tazobactam. Orally administrated antibiotics such as ciprofloxacin or cefadroxil combined with metronidazole were initiated subsequently on the ward or at discharge.	NR	NR	IV	≥ 7 days
	Placebo	IV fluids only	NR	NR	IV	N/A
de Korte, 2012, 21689302, Netherlands	Antibiotics: Multiple (discretionary or undefined)	Two hospitals, different antibiotic protocols. No formal protocol at H1; antibiotics not routinely given. H2 had protocol for antibiotic treatment of diverticulitis: combination of piperacilin and metronidazole (IV; no doses given) when admitted to surgical ward; amoxicillin–clavulanic acid (IV; no doses given) when admitted to the internal medicine or gastroenterology wards. Continued for 7-10 days depending on clinical status	NR	NR	IV	7-10 days
	No intervention (non-placebo)	Restriction of oral intake, intravenous fluid rehydration and observation. When symptoms resided, a normal diet was started. No specific foods were avoided. Analgesics were given as appropriate, starting with acetaminophen and nonsteroid anti-inflammatory drugs (NSAIDs) as needed.	NR	NR	NR	NR
DIABOLO Trial, Sweden, Nonindustry	No intervention (non-placebo)	No antibiotic	NR	NR	NR	NR
	Antibiotics: Amoxicillin + Clavulanate	IV amoxicillin–clavulanic acid was chosen as broad-spectrum antibiotic treatment of choice. Was switched to oral administration after 10 days if tolerated. In the event of allergy, a switch was made to the combination of ciprofloxacin and metronidazole.	1200 mg	4/day	IV for 10 days, switched to oral after if tolerated	10 days

Author, Year, PMID, Study Name, Country	Arm	Arm Description	Dose	Frequency	Route	Duration of intervention
Etzioni, 2010, 20484998, USA	Fluoroquinolone + metronidazole	Most commonly used	NR	NR	Oral	N/A
	Antibiotic duration: 14+ days	N/A	N/A	N/A	N/A	N/A
	Antibiotic duration: 10-13 days	N/A	N/A	N/A	N/A	N/A
	Antibiotic duration: <10 days	N/A	N/A	N/A	N/A	N/A
	Multiple (discretionary or undefined)	trimethoprim/sulfamethoxazole, amoxicillin, extended-spectrum beta-lactamases, clindamycin, doxycycline, and cephalosporins	NR	NR	Oral	N/A
Hjern, 2007, 17190761, Sweden	No intervention (non-placebo)	Careful observation, iv fluids, restriction of oral intake, no antibiotics				
	Antibiotics: Cephalosporin + Metronidazole	Careful observation, iv fluids, restriction of oral intake, antibiotics			Oral cephalosporine and metronidazole given iv, followed by oral administration of quinolone with metronidazole	10-14 days
Jaung, 2019, 32240832, STAND, New Zealand and Australia	Antibiotics: po amoxicillin/clavulanic +- IV cefuroxime & po metronidazole	Initial regimen (IV cefuroxime 750 mg every 6 hours and oral metronidazole 400 mg three times a day), and oral antibiotics (amoxicillin/clavulanic acid 625 mg three times a day). Use of "IV regimen" at the discretion of the surgical team.	cefuroxime 750 mg; metronidazole 400 mg; amoxicillin/clavulanic acid 625 mg	cefuroxime every 6 hours; oral metronidazole 3 t.i.d; amoxicillin/clavulanic acid t.i.d	first iv and oral, then oral	5-7 days (outpatient after first approximately 2 days)
	Placebo	N/A	N/A	N/A	N/A	5-7 days (outpatient after first approximately 2 days)
Kellum, 1992, 1638578, USA	Antibiotics: Gentamicin-Clindamycin		1 to 1.4 gm	Every 8 hours	IV	NR
	Antibiotics: Cefoxitin		1 to 2 gm	Every 6 hours	IV	NR

Author, Year, PMID, Study Name, Country	Arm	Arm Description	Dose	Frequency	Route	Duration of intervention
Kim, 2019, 31267222, S Korea	Placebo	Admitted, administered IV fluids, and given bowel rest for at least 3 days (and up to 5 days)				
	Antibiotics: Cephalosporin + Metronidazole	Antibiotics	Ceftriaxone, 2 g and metronidazole, 500 mg	Ceftriaxone, once daily and metronidazole, three times daily	IV was first used, then changed to oral when oral intake was toleratedIV	10 days
Park, 2019, 31290747, S Korea	Antibiotics: Cephalosporin + Metronidazole	1-day group	Cefmetazole (2000mg/day) and metronidazole (1500 mg/day)		IV	1 day
	Antibiotics: Cephalosporin + Metronidazole	4-day group	Cefmetazole (2000mg/day) and metronidazole (1500 mg/day)		57 received 4 days of IV; 32 received 3 days of IV and 1 day oralIV	4 day
Ribas, 2010, 20526718, Spain	Antibiotics: Amoxicillin + Clavulanate	antibiotics intravenously administered at first and then orally administered when symptoms improved (pain decrease, less tenderness, and absence of fever)	amoxicillin plus clavulanic acid 1g every 8h	3/day	inpatients (IV+oral) then outpatient (oral)IV	inpatients (IV (1-2 days) + oral (2-3 days)) then outpatient (oral) (10 days)
	Antibiotics: Amoxicillin + Clavulanate	antibiotics intravenously administered	amoxicillin plus clavulanic acid 1g every 8h	3/day	inpatients (IV only) then outpatient (oral)IV	inpatients (IV) (8-9 days) then outpatient (oral) (5 days)
Ridgway, 2009, 19016815, Ireland	Antibiotics: Ciprofloxacin + Metronidazole	Oral	500 mg, 400 mg	NR	Conversion to IV as per attending physicianIV	
	Antibiotics: Ciprofloxacin + Metronidazole	IV	400 mg, 500 mg	NR	Conversion to IV as per attending physicianIV	

Author, Year, PMID, Study Name, Country	Arm	Arm Description	Dose	Frequency	Route	Duration of intervention
Scarpa, 2015, 25960972, Switzerland	Antibiotics: short course IV	All patients received an IV antibiotic treatment of ceftriaxone (2,000 mg/day) and metronidazole (1,500 mg/day) except when contraindicated. Antibiotic treatment for 5 days or less.	IV: ceftriaxone (2,000 mg/day); metronidazole (1,500 mg/day); oral: ciprofloxacine (1,000-mg/day); metronidazole (1,500-mg/day)	IV: ceftriaxone (2,000 mg/day); metronidazole (1,500 mg/day); oral: ciprofloxacine (1,000-mg/day); metronidazole (1,500-mg/day)	OralIV	up to 5 days for IV (followed by 5 days oral antibiotics) (NB. results report mean length of treatment 4.7 days)
	Antibiotics: long course IV	All patients received an IV antibiotic treatment of ceftriaxone (2,000 mg/day) and metronidazole (1,500 mg/day) except when contraindicated. Antibiotic treatment for 6 days, possibly up to 14 days.	ceftriaxone (2,000 mg/day); metronidazole (1,500 mg/day)	ceftriaxone (2,000 mg/day); metronidazole (1,500 mg/day)	IV	6-14 days for IV (NB. results report mean length of treatment 8.7 days)
Schug-Pass, 2010, 20140619, Germany	Antibiotic: Ertapenem	4 days	1 g	1/day	IV	4 days
	Antibiotic: Ertapenem	7 days	1 g	1/day	IV	7 days

Table B-2-3. Antibiotics: Baselines

Author, Year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Number of Prior Episodes of Diverticulitis, %	History of (Prior) Complicated Diverticulitis %	Time Since Last Episode of Diverticulitis, Mean (SD)
AVOD Trial, Sweden	Antibiotics: Multiple (discretionary or undefined)	35	NR	57.4 (12.8)	100/0	at least one episode 35.6	NR	NR
	Placebo (IV fluids only)	36	NR	57.1 (13.2)	100/0	at least one episode 44.8	NR	NR
de Korte, 2012, 21689302, Netherlands	Antibiotics: Multiple (discretionary or undefined)	29	NR	61 [Range 27–92]	0/100	NR	NR	NR
	No intervention (non-placebo)	46.4	White 94%, Black 3.8%, Hispanic/Latino 16.6%, Asian 0.3%, Other 1.9%	56.1 (11.04)	NR	none 0.5, one 59.7, two 22.7, four to five 5.8, six to ten 1.9	NR	16.5 weeks [range 0, 122 weeks]
DIABOLO Trial, Sweden,	No intervention (non-placebo)	50.6	NR	57.4	NR	NR	NR	NR
	Antibiotics: Amoxicillin + Clavulanate	54.7	NR	59.4 (12.1)	NR	NR	NR	NR
Etzioni, 2010, 20484998, USA	Total	46	NR	58.5	NR	NR	NR	NR
Hjern, 2007, 17190761, Sweden	No intervention (non-placebo)	35	NR	59	NR	NR	30	NR
	Antibiotics: Cephalosporin + Metronidazole	37	NR	60	NR	NR	25	NR
Jaung, 2019, 32240832, STAND, New Zealand and Australia	Antibiotics: po amoxicillin/clavulanic +- IV cefuroxime & oral metronidazole	40	NR	Probably Median 56 (probably IQR 53-59)	0	71	NR	NR
	Placebo	44	NR	Probably Median 59 (probably IQR 57-62)	0	68	NR	NR

Author, Year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Number of Prior Episodes of Diverticulitis, %	History of (Prior) Complicated Diverticulitis %	Time Since Last Episode of Diverticulitis, Mean (SD)
Kellum, 1992, 1638578, USA	Antibiotics: Cefoxitin	NR	NR	64.5 (SE 2)	NR	NR	12	NR
	Antibiotics: Gentamicin-Clindamycin	NR	NR	60.8 (SE 3)	NR	NR	NR	NR
Kim, 2019, 31267222, S Korea	Placebo (admitted, administered IV fluids, and given bowel rest for at least 3 days (and up to 5 days))	57.8	NR	38.9 (9.5)	100/0	NR	NR	NR
	Antibiotics: Cephalosporin + Metronidazole	65.6	NR	37.9 (8.4)	100/0	NR	NR	NR
Park, 2019, 31290747, S Korea	Antibiotics: Cephalosporin + Metronidazole (1-day group)	54.0	NR	42.0 (11.1)	100/0	none 100	0	NR
	Antibiotics: Cephalosporin + Metronidazole (4-day group)	55.1	NR	40.2 (11.2)	100/0	none 100	0	NR
Ribas, 2010, 20526718, Spain	Antibiotics: Amoxicillin + Clavulanate (IV then Oral)	52	NR	56 (95%CI 50, 62)	100/0	Mean 1.2 (95%CI 0.9, 1.5)	NR	NR
	Antibiotics: Amoxicillin + Clavulanate (IV)	52	NR	56 (95%CI 45, 57)	100/0	Mean 1.5 (95%CI 0.9, 2.1)	NR	NR
Ridgway, 2009, 19016815, Ireland	Antibiotics: Ciprofloxacin + Metronidazole (Oral)	39.02	NR	Median 68 [Range 31-84]	NR	NR	NR	NR
	Antibiotics: Ciprofloxacin + Metronidazole (IV)	44.74	NR	Median 66 [Range 41-86]	NR	NR	NR	NR

Author, Year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Number of Prior Episodes of Diverticulitis, %	History of (Prior) Complicated Diverticulitis %	Time Since Last Episode of Diverticulitis, Mean (SD)
Scarpa, 2015, 25960972, Switzerland	Antibiotics: short course IV	47.8	NR	Median 55.5 [Range 24–81]	100/0	none 100	0	NR
	Antibiotics: long course IV	51.0	NR	Median 60 [Range 30–86]	100/0	none 100	0	NR
Schug-Pass, 2010, 20140619, Germany	Antibiotic: Ertapenem (4 days)	54	NR	60.6 (12.2)	NR	NR	NR	NR
	Antibiotic: Ertapenem (7 days)	55.4	NR	58.5 (11.9)	NR	NR	NR	NR

Table B-2-4. Antibiotics: Risk of Bias Randomized Comparative Studies

Author, Year, PMID, Study Name, Country	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel/ care providers (performance bias)	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)	Were eligibility/selection criteria for the study population prespecified and clearly described?	Was the test/service/intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all
AVOD Trial, Sweden	Low	Low	High	High	Low	Low	Yes	Yes	Yes
DIABOLO Trial, Sweden,	Low	Low	High	High	Low	Low	Yes	Yes	Yes
Jaung, 2019, 32240832, STAND, New Zealand and Australia	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes
Kellum, 1992, 1638578, USA	Low	Low	High	High	Low	Low	Yes	Yes	Yes
Kim, 2019, 31267222, S Korea	Low	Low	High	High	Low	Low	Yes	Yes	Yes
Park, 2019, 31290747, S Korea	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes
Ribas, 2010, 20526718, Spain	Low	Low	High	High	Low	Low	Yes	Yes	Yes
Ridgway, 2009, 19016815, Ireland	Low	Unclear	Unclear	High	Low	Low	Yes	Yes	Yes
Schug-Pass, 2010, 20140619, Germany	Unclear	Unclear	High	High	Low	Unclear	Yes	Yes	Yes

KQ = Key Question, PMID = PubMed Identifier. Ratings are color coded for emphasis only. See Table C-2a-2 for full legend.

Table B-2-5. Antibiotics: Risk of Bias Nonrandomized Comparative Studies

Author, Year, PMID, Study Name, Country	Bias due to confounding	Bias in selection of participants into the study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of personnel/ care providers (performance bias)	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)	Were eligibility/selection criteria for the study population prespecified and clearly described?	Was the test/service/intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
de Korte, 2012, 21689302, Netherlands	Yes	No	N/A	N/A	No	No	Unsure	Yes	No	No
Etzioni, 2010, 20484998, USA	Low	No			No	No	No	Yes	No	Yes
Hjern, 2007, 17190761, Sweden	Yes	No								
Scarpa, 2015, 25960972, Switzerland	Yes	No	N/A	N/A	No	No	Yes	Yes	Yes	Yes

KQ = Key Question, PMID = PubMed Identifier.

Table B-2-6. Antibiotics: Mortality

Outcome	Study	Time	Arm	n/N (%)	OR (95% CI)	Reported P Value
Antibiotics vs. none						
All-cause mortality	AVOD	30 d	Multiple antibiotics*	1/314 (0.3)	2.96 (0.12, 73.0)	
			Placebo	0/309 (0)		
		11 y	Multiple antibiotics*	28/275 (10.0)	1.06 (0.60, 1.86)	
			Placebo	26/275 (9.5)		
	STAND	30 d	Oral amoxicillin / clavulanate +- IV cefuroxime & oral metronidazole	1/84	3.40 (0.14, 84.48)	0.3
			Placebo	0/84		
Diverticulitis-related mortality	DIABOLO	24 mo	Amoxicillin/clavulanate	1/266 (0.4)	0.33 (0.03, 3.15)	0.43
			No antibiotics	3/262 (1.1)		

Abbreviations: CI = confidence interval, d=days, mo = months, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial.

* Discretionary.

Table B-2-7. Antibiotics: Treatment Failure

Outcome	Study	Time	Arm	n/N (%)	OR (95% CI)	Reported P Value
Antibiotics vs. none						
Nonrecovery and/or readmission	Kim, 2019, 31267222	10 d	Cephalosporin + metronidazole	1/61 (1.6)	0.34 (0.03, 3.35)	0.62
			Placebo	3/64 (4.7)		
Need for procedural intervention	STAND	30 d	Po Amoxicillin/clavulanate +- IV cefuroxime & po metronidazole	2/84	5.73 (0.27, 121.02)	0.1
			Placebo	0/94 (0)		
No return to normal bowel function	DIABOLO	6 mo	Amoxicillin/clavulanate	18/266 (6.7)	0.61 (0.33, 1.13)	0.18
			No antibiotics	28/262 (10.7)		
Time to recovery	DIABOLO	6 mo	Amoxicillin/clavulanate	Median 12 (IQR 7, 30)		
			No antibiotics	Median 14 (IQR 6, 35)		
Different regimens						
Treatment failure	Ribas, 2010, 20526718	4-8 d	Amoxicillin/clavulanate (IV and oral)	2/22 (9.1)	2.10 (0.18, 25.0)	
			Amoxicillin/clavulanate (oral)	1/22 (4.5)		
Treatment failure	Ridgway, 2008, 19016815	30 d	Ciprofloxacin + metronidazole (IV)	1/38 (2.6)	1.08 (0.07, 17.9)	
			Ciprofloxacin + metronidazole (oral)	1/41 (2.4)		
Treatment failure	Park, 2019, 31290747	30 d	Cephalosporin + metronidazole (4 days)	19/89 (21.3)	1.30 (0.61, 2.77)	0.49
			Cephalosporin + metronidazole (1 day)	15/87 (17.2)		
Treatment failure	Etzioni, 2010, 20484998	60 d	Fluoroquinolone + metronidazole	34/589 (5.8)	1.05 (0.38, 2.92) Adjusted	
			Multiple (undefined)	5/104 (4.8)		
Treatment failure	Etzioni, 2010, 20484998	60 d	≥14 d antibiotics	5/101 (5.0)	0.68 (0.20, 2.35) Adjusted	
			10-13 d antibiotics	27/485 (5.6)	0.72 (0.29, 1.78) Adjusted	
			<10 d antibiotics	7/107 (6.5)	Reference	

Abbreviations: Adj = adjusted, CI = confidence interval, d=days, IQR=interquartile range, IV = intravenous, mo = months, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial.

Table B-2-8. Antibiotics: Surgery for diverticulitis

Outcome	Time	Study	Arm	n/N (%)	OR (95% CI)	P value, Reported
Antibiotics vs. none						
Elective surgery	6 mo	DIABOLO	Amoxicillin/clavulanate	3/266 (1.1)	0.36 (0.10, 1.38)	0.25
			No antibiotics	8/262 (3.1)		
Sigmoid resection	12 mo	AVOD	Multiple antibiotics*	2/292 (0.6)	0.33 (0.07, 1.63)	0.15
			Placebo	6/290 (1.9)		
Different regimens						
Elective Surgery	>6 wk	Kellum, 1992, 1638578	Cefoxitin	6/30 (20.0)	11.4 (0.61, 215)	
			Gentamicin and clindamycin	0/21 (0)		
Elective Surgery	<12 mo	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	21/48 (42.9)	1.31 (0.57, 3.04)	NS
			Ertapenem (4 days)	16/43 (37.2)		

Abbreviations: CI = confidence interval, mo = months, NS = not statistically significant, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, wk = weeks.

* Discretionary

Table B-2-9. Antibiotics: Hospitalization or rehospitalization

Outcome	Time	Study	Arm	n/N (%)	OR (95% CI)	P value, Reported
Antibiotics vs. none						
Readmission	1 wk	STAND	Po Amoxicillin/clavulanate +- IV cefuroxime & po metronidazole	5/84 (6.0)	OR 5.89 (0.67, 51.44)	0.07
			Placebo	1/94 (1.1)		
Readmission	30 d	STAND	Po Amoxicillin/clavulanate +- IV cefuroxime & po metronidazole	5/84 (6.0)	OR 0.53 (0.17, 1.62)	0.3
			Placebo	10/94 (10.6)		
Rehospitalization for diverticulitis	6 mo	DIABOLO	Amoxicillin/clavulanate	32/266 (12.0)	0.64 (0.39, 1.05)	0.15
			No antibiotics	46/262 (17.6)		
Rehospitalization for diverticulitis	24 mo	DIABOLO	Amoxicillin/clavulanate	35/266 (13.2)	OR 0.71 (0.44, 1.15)	0.15
			No antibiotics	66/262 (25.2)		

Abbreviations: CI = confidence interval, d= days, wk= weeks, m = months, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, y = years.

Table B-2-10. Antibiotics: Length of hospital stay

Outcome	Study	Arm	Mean or Median	Reported P Value
Antibiotics vs. none				
Length of hospital (or intensive care unit) stay (days)	AVOD	Multiple *	Mean 2.9 (SE 1.9) Median 3 (Range 0, 25)	0.72
		Placebo	Mean 2.9 (SE 1.6) Median 3 (Range 0, 25)	
Length of hospital stay (days)	Kim, 2019, 31267222	Cephalosporin + metronidazole	Mean 5.3 (SD 0.8)	0.96
		Placebo	Mean 5.3 (SD 0.8)	
Length of hospital (or intensive care unit) stay (days)	DIABOLO	Amoxicillin/clavulanate	Median 3 (IQR 2, 3)	0.006
		No antibiotics	Median 2 (IQR 1, 3)	
Length of hospital stay	STAND	Po Amoxicillin/clavulanate +- IV cefuroxime & po metronidazole	Median 40 (IQR 24.4, 57.6)	
		Placebo	Median 45.8 (IQR 26.5, 60.2)	
Different regimens				
Length of hospital (or intensive care unit) stay (days)	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	Mean 9.7 (SD 3.2)	0.002
		Ertapenem (4 days)	Mean 7.8 (SD 2.8)	

Abbreviations: CI = confidence interval, IQR = interquartile range, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, SD = standard deviation, SE = standard error.

* Discretionary

Table B-2-11. Antibiotics: Recurrence of diverticulitis

Outcome	Time	Study	Arm	n/N (%)	OR (95% CI)	P value, Reported
Antibiotics vs. none						
Recurrence	≥6 wk	Kim, 2019, 31267222	Cephalosporin + metronidazole	5/64 (7.8)	1.00 (0.27, 3.64)	0.69
			Placebo	5/64 (7.8)		
Recurrence	6 mo	DIABOLO	Amoxicillin/clavulanate	8/266 (3.0)	0.87 (0.33, 2.29)	0.49
			No antibiotics	9/262 (3.4)		
Recurrence	≥12 mo	AVOD	Multiple antibiotics*	46/292 (15.8)	0.97 (0.62, 1.51)	0.88
			Placebo	47/290 (16.2)		
Recurrence	24 mo	DIABOLO	Amoxicillin/clavulanate	36/241 (14.9)	0.96 (0.58, 1.60)	0.89
			No antibiotics	35/227 (15.4)		
Recurrence	11 y	AVOD	Multiple antibiotics*	88/281 (31.3)	1.00 (0.70,1.43)	0.49
			Placebo	86/275 (31.3)		
Recurrence and/or subsequent surgery	Mean 30 m	Hjern, 2007, 17190761	Cephalosporin + metronidazole	NR	Adj 1.03 (0.61, 1.74)	
			No antibiotics	NR		
Recurrence	Mean 50 m	de Korte, 2012, 21689302	Multiple antibiotics*	12/81 (15.0)	Adj 2.04 (0.83, 4.75)	
			No antibiotics	14/191 (7.0)		
Different regimens						
Recurrence	1 y	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	5/48 (10.4)	1.43 (0.32, 5.46)	NS
			Ertapenem (4 days)	3/40 (7.5)		
Failure of treatment	1 y	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	2/56 (3.6)	0.58 (0.09, 3.62)	NS
			Ertapenem (4 days)	3/50 (6.0)		
Recurrence	>12 mo	Scarpa, 2015, 25960972	Long course IV (6 to 14 days)	52/210 (25.0)	1.05 (0.59, 2.21) Unadjusted (NRCS)	0.90
			Short course IV (</=5 days)	11/46 (24.0)		

Abbreviations: Adj = adjusted, CI = confidence interval, d=days, IV = intravenous, m = months, NR = not reported, NRCS = nonrandomized comparative study, NS = not statistically significant, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, y = years.

* Discretionary # Unadjusted

Table B-2-12. Antibiotics: Diverticulitis-related morbidities

Outcome	Time	Study	Arm	n/N (%)	P value, Reported
Antibiotics vs. none					
Abscess	30 d	AVOD	Multiple antibiotics *	0/314 (0)	0.08
			Placebo	3/309 (0.9)	
Abscess >5 cm	6 mo	DIABOLO	Amoxicillin/clavulanate	2/266 (0.7)	0.68
			No antibiotics	2/262 (0.8)	
Abscess >5 cm	24 m	DIABOLO	Amoxicillin/clavulanate	3/241 (1.2)	
			No antibiotics	2/227 (0.9)	
Fistula	6 mo	DIABOLO	Amoxicillin/clavulanate	0/266 (0)	0.55
			No antibiotics	1/262 (0.4)	
Fistula	24 mo	DIABOLO	Amoxicillin/clavulanate	1/241 (0.4)	
			No antibiotics	1/227 (0.4)	
Obstruction	6 mo	DIABOLO	Amoxicillin/clavulanate	2/266 (0.7)	0.44
			No antibiotics	4/262 (1.5)	
Obstruction	24 mo	DIABOLO	Amoxicillin/clavulanate	2/241 (0.8)	
			No antibiotics	4/227 (1.8)	
Different regimens					
Abscess	1 y	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	0/48 (0)	NS
			Ertapenem (4 days)	1/43 (2.3)	
Fistula, interenteric	1 y	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	1/43 (2.3)	NS
			Ertapenem (4 days)	0/48 (0)	
Post-inflammatory stenosis	1 y	Schug-Pass, 2010, 20140619	Ertapenem (7 days)	1/48 (2.1)	NS
			Ertapenem (4 days)	1/40 (2.5)	

Abbreviations: CI = confidence interval, m = months, NS = not statistically significant, PMID = PubMed identifier, RCT = randomized controlled trial, y = years.

* Discretionary

Table B-2-13. Antibiotics: Pain or tenderness

Outcome Measurement	Time	Study	Arm	n/N (%)	OR (95% CI)	P value, Reported
Antibiotics vs. none						
Pain, Visual Analog Scale (0 to 10)	1-5 d	AVOD	Multiple antibiotics*		NR	All NS
			Placebo			
Tenderness (0 to 4)	1-5 d	AVOD	Multiple antibiotics*	Mean 1.0 (SD NR)	MD 0.2 (0.008, 0.39)	0.041
			Placebo	Mean 0.8 (SD NR)		
Abdominal pain, Visual Analog Scale (0 to 10)	<10 d	DIABOLO	Amoxicillin/clavulanate	79/219 (36.1)	OR 0.99 (0.60, 1.46)	0.37
			No antibiotic	75/210 (35.7)		
Pain Visual Analog Scale (0 to 10)	30 d	STAND	Po Amoxicillin/clavulanate +- IV cefuroxime & po metronidazole	Median 2 (1,3)		0.9
			Placebo	Median 3 (2,3)		
Severe periodic pain	12 mo	AVOD	Multiple antibiotics*	12/292 (4.2)	OR 0.99 (0.44, 2.25)	NS
			Placebo	12/290 (4.1)		
Chronic abdominal pain	12 mo	AVOD	Multiple antibiotics*	5/292 (1.7)	OR 1.25 (0.33, 4.69)	NS
			Placebo	4/290 (1.4)		
Chronic abdominal pain	11 y	AVOD	Multiple antibiotics*	3/281 (0.9)	OR 6.92 (0.36, 135)	NS
			Placebo	0/275 (0)		
Different regimens						
Tenderness, Wexford score	3 d	Ridgway, 2008, 19016815	Ciprofloxacin + metronidazole (IV)	Mean 1.20 (SD NR)	MD −0.06 (−0.50, 0.38)	0.79
			Ciprofloxacin + metronidazole (oral)	Mean 1.26 (SD NR)		

Abbreviations: CI = confidence interval, d = days, m = months, MD = mean difference, NR = not reported, NS = not statistically significant, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, y = years.

*Discretionary

Table B-2-14. Antibiotics: Quality of life

Outcome	Measurement Instrument	Time	Study	Arm	n/N (%) or Mean (SD)	OR (95% CI)	P value, Reported
Antibiotics vs. none							
Quality of life	EQ-5D	MES	DIABOLO	Amoxicillin/clavulanate	Mean 76.4 (SD NR)	MD 0.8	0.32
				No antibiotics	Mean 77.2 (SD NR)		
Quality of life, Emotional	GIQLI	MES	DIABOLO	Amoxicillin/clavulanate	Mean 16.5 (SD NR)	MD 0	0.89
				No antibiotics	Mean 16.5 (SD NR)		
Quality of life, Gastrointestinal symptoms	GIQLI	MES	DIABOLO	Amoxicillin/clavulanate	Mean 62.9 (SD NR)	MD 0.3	0.56
				No antibiotics	Mean 62.6 (SD NR)		
Quality of life, Physical	GIQLI	MES	DIABOLO	Amoxicillin/clavulanate	Mean 20.7 (SD NR)	MD 0	0.91
				No antibiotics	Mean 20.7 (SD NR)		
Quality of life, Social	GIQLI	MES	DIABOLO	Amoxicillin/clavulanate	Mean 16.5 (SD NR)	MD -0.1	0.69
				No antibiotics	Mean 16.6 (SD NR)		
Quality of life	SF-36	MES	DIABOLO	Amoxicillin/clavulanate	Mean 49.9 (SD NR)	MD -0.5	0.48
				No antibiotics	Mean 50.4 (SD NR)		
Quality of life, Physical	SF-36	MES	DIABOLO	Amoxicillin/clavulanate	Mean 46.5 (SD NR)	MD -0.7	0.32
				No antibiotics	Mean 47.2 (SD NR)		
Quality of life, Cumulative index score	EQ-5D	11 y	AVOD	Multiple antibiotics*	Mean 0.834 (SD NR)	MD 0.015	0.46
				Placebo	Mean 0.819 (SD NR)		
Quality of life, Anxiety/depression Level 3 (major problems)	EQ-5D	11 y	AVOD	Multiple antibiotics*	1/142 (0.7)	OR 0.05 (0.01, 0.41)	0.35
				Placebo	2/163 (1.3)		
Quality of life, Mobility Level 3 (major problems)	EQ-5D	11 y	AVOD	Multiple antibiotics*	0/142 (0)	OR 0.28 (0.01, 6.35)	0.34
				Placebo	0/163 (0)		
Quality of life, Pain/discomfort Level 3 (major problems)	EQ-5D	11 y	AVOD	Multiple antibiotics*	3/142 (2.1)	OR 7.01 (0.35, 141.2)	0.77
				Placebo	5/163 (3.1)		
Quality of life, Self-care Level 3 (major problems)	EQ-5D	11 y	AVOD	Multiple antibiotics*	2/281 (0.7)	OR 0.39 (0.07, 2.01)	0.83
				Placebo	16/275 (5.7)		
Quality of life, Usual activities Level 3 (major problems)	EQ-5D	11 y	AVOD	Multiple antibiotics*	3/142 (2.1)	OR 0.20 (0.06, 0.70)	0.72
				Placebo	3/163 (1.9)		

Abbreviations: CI = confidence interval, d = days, EQ-5D= EuroQoL General Health-related Quality of Life Scale measured in 5 dimensions, GIQLI = Gastrointestinal Quality of Life Index, MD = mean difference, MES=Mean estimated scores over 3, 6, 12, and 24 months, with adjustments for baseline scores, NR = not reported, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial, SD = standard deviation, SF-36=short form 36, y = years.

* Discretionary

Table B-2-15 Antibiotics: Adverse events

Outcome	Time	Study	Arm	n/N (%)	OR (95% CI)	P value, Reported
Antibiotics vs. none						
Any	30 d	AVOD	Multiple antibiotics*	3/314 (0.9)	0.49 (0.12, 1.97)	0.30
			Placebo	6/309 (1.9)		
Complications after treatment	6 mo	DIABOLO	Amoxicillin/clavulanate	8/241 (3.3)	0.67 (0.27, 1.71)	0.40
			No antibiotics	11/227 (4.8)		
Different regimens						
Serious	<12 mo	Schug-Pass, 2010, 20140619,	Ertapenem (7 days)	0/56 (0)		
			Ertapenem (4 days)	0/50 (0)		
Allergic reaction	<12 mo	Schug-Pass, 2010, 20140619,	Ertapenem (7 days)	0/56 (0)		
			Ertapenem (4 days)	1/50 (2.0)		
Headache	<12 mo	Schug-Pass, 2010, 20140619,	Ertapenem (7 days)	0/56 (0)		
			Ertapenem (4 days)	2/50 (4.0)		
Any	<12 mo	Schug-Pass, 2010, 20140619,	Ertapenem (7 days)	0/56 (0)		
			Ertapenem (4 days)	3/50 (5.1)		

Abbreviations: CI = confidence interval, d = days, m = months, NR = not reported, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial.

* Discretionary

Table B-3. Interventional Radiology

Table B-3-1. Interventional Radiology: Design and Arm Details

Study, Year, PMID, Country, Funding	Design	Population Description	Arm	Arm Details	Age, Sex	Number of Prior Episodes of Diverticulitis
Lambrichts, 2019, 30811050, Netherlands, NR	NRCS (Retrospective)	CT-diagnosed abscess (Hinchey 1b/II); (Hinchey III/IV), sepsis, or fistula excluded	Interventional radiology	Percutaneous drainage	Mean 63 (SD 13), 62.6% male	None: 61.7% ≥1: 38.3%
			No intervention	No percutaneous drainage	Mean 60 (SD 13), 58.1% male	None: 72.0% ≥1: 28.0%
Mali, 2019, 31320921, Finland, Non-industry	NRCS (Retrospective)	CT-diagnosed abscess ≥4 cm; colon cancer excluded	Interventional radiology	Percutaneous drainage	Median 60 (IQR 50, 69), 61% male	None: 56% ≥1: 44%
			Antibiotics: Multiple	Discretionary, undefined antibiotics oral or IV	Median 67, (IQR 55, 78), 39% male	None: 67% ≥1: 33%

Abbreviations: CT = computed tomography, IQR = interquartile range, IV = intravenous, NR = not reported, NRCS = nonrandomized comparative study, PMID = PubMed identifier, SD = standard deviation.

Table B-3-2. Interventional Radiology: Risk of Bias Assessment NRCSs, Assessment of Confounding and Selection Bias

Study, Year, PMID	1.1 Potential for Any Confounding?	1.2 Potential for Time-Varying Confounding?	1.3 Intervention Switches Related to Prognostic Factors?	1.4 Appropriate Analysis Method for Confounding?	1.5 Appropriate Confounding Variables Used?	1.6 Inappropriate Control of Post-Intervention Variables?	**Judgement – Risk of Bias Related to Confounding**	2.1 Participant Selection Based on Post-Intervention Variables?	2.2 Post-Intervention Variables Associated with Intervention?	2.3 Post-Intervention Variables Associated with Outcome?	2.4 Start and Follow-Up (Duration) Coincide	2.5 Appropriate Adjustment for Selection Bias	**Judgement – Risk of Bias Related to Selection Bias**
Lambrichts, 2019, 30811050	Yes	No	N/A	Yes	Yes	No	**Low**	No	N/A	N/A	Yes	N/A	**Low**
Mali, 2019, 31320921	Yes	No	N/A	Yes	Yes	No	**Low**	No	N/A	N/A	Yes	N/A	**Low**

KQ = Key Question, NRCS = nonrandomized comparative studies, PMID = PubMed Identifier, Responses to Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) signaling questions 1.1 to 1.6 and 2.1 to 2.5 are in regular font. Each item rated as Yes, PY (probably yes), NI (no information), PN (probably no), No, or N/A (not applicable). Judgements about confounding and selection bias are in **bold font**. (each item rated as **Low**, **Moderate**, **Serious**, or **Critical**).

Table B-3-3. Interventional Radiology: Risk of Bias Assessment NRCSs, Assessment of Remaining Biases and Quality

Study, Year, PMID	Blinding of Participants	Blinding of Personnel/ Care Providers	Blinding of Outcome Assessors (Objective Outcomes)	Blinding of Outcome Assessors (Subjective Outcomes)	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias	Eligibility Criteria Prespecified and Clearly Described	Intervention Clearly Described and Consistently Delivered	Outcomes Prespecified, Clearly Defined, Valid, Reliable, and Consistently Assessed
Lambrichts, 2019, 30811050	High	High	Unclear	Unclear	Low	Unclear	Low	Yes	Yes	Yes
Mali, 2019, 31320921	High	High	High	High	Low	Low	Low	Yes	Yes	Yes

KQ = Key Question, NRCS = nonrandomized comparative study, PMID = PubMed Identifier. Ratings are color coded for emphasis only. See Table C-2a-2 for full legend.

Table B-3-4. Interventional Radiology: All outcomes

Outcome	Study Year, PMID	Time	Intervention	n/N (%)	Effect Size (95% CI)	Reported P-value
Diverticulitis-related mortality, short-term	Mali 2019,[102] 31320921	30 d	Percutaneous drainage	1/18 (5.6)	OR 1.00 (0.06, 17.3)	1.00
			Antibiotics	1/18 (5.6)		
All-cause mortality, long-term	Lambrichts 2019,[101] 30811050	6 yr	Percutaneous drainage	12/115 (10.4)	Unadj OR 2.30 (1.05, 5.02)	NR
			No drainage	16/332 (4.8)		
Sigmoid resection, short-term	Lambrichts 2019,[101] 30811050	30 d	Percutaneous drainage	16/115 (13.9)	Adj OR 1.29 (0.56, 2.99)	0.55
			No drainage	24/332 (7.2)		
	Mali 2019,[102] 31320921	During initial admission	Percutaneous drainage	5/18 (27.8)	OR 1.00 (0.23, 4.30)	1.00
			Antibiotics	5/18 (27.8)		
Sigmoid resection, long-term	Lambrichts 2019,[101] 30811050	6 yr	Percutaneous drainage	37/115 (32.2)	Adj OR 1.08 (0.69, 1.69)	0.74
			No drainage	87/332 (26.2)		
	Mali 2019,[102] 31320921	71 mo	Percutaneous drainage	9/12 (75.0)	OR 1.50 (0.25, 8.84)	1.00
			Antibiotics	8/12 (66.7)		
Stoma	Mali 2019,[102] 31320921	30 d	Percutaneous drainage	2/12 (16.7)	OR 0.60 (0.08, 4.45)	NR
			Antibiotics	3/12 (25.0)		
Treatment failure (Death or need for surgery)	Lambrichts 2019,[101] 30811050	30 d	Percutaneous drainage	41/115 (35.7)	Adj OR 1.47 (0.81, 2.68)	0.19
			No drainage	79/332 (23.8)		
	Mali 2019,[102] 31320921	30 d	Percutaneous drainage	6/18 (33.3)	OR 0.63 (0.16, 2.41)	0.49
			Antibiotics	8/18 (44.4)		
Readmission, short-term	Mali 2019,[102] 31320921	30 d	Percutaneous drainage	2/18 (11.1)	OR 0.63 (0.09, 4.28)	1.00
			Antibiotics	3/18 (16.7)		
Length of hospital stay	Mali 2019,[102] 31320921	30 d	Percutaneous drainage	6 d (3, 12)*	Median Difference = 0	0.73
			Antibiotics	6 d (3, 10)*		
Recurrence of diverticulitis, Any, long-term	Lambrichts 2019,[101] 30811050	6 yr	Percutaneous drainage	29/115 (25.2)	Unadj OR 0.87 (0.53, 1.41)	NR
			No drainage	93/332 (28.0)		
	Mali 2019,[102] 31320921	71 mo	Percutaneous drainage	1/12 (8.3)	OR 0.45 (0.04, 5.81)	1.00
			Antibiotics	2/12 (16.7)		
Recurrence of diverticulitis, Complicated, long-term	Mali 2019,[102] 31320921	71 mo	Percutaneous drainage	1/12 (8.3)	OR 1.00 (0.06, 18.1)	1.00
			Antibiotics	1/12 (8.3)		

Abbreviations: Adj = adjusted, CI = confidence interval, d = days, IQR = interquartile range, mo = months, NR = not reported, OR = odds ratio, PMID = PubMed identifier, Unadj = unadjusted (analysis of unmatched nonrandomized comparative study), yr = years.

* Median (interquartile range)

Colonoscopy and Elective Surgery After Acute Colonic Diverticulitis: A Systematic Review

Commented [EB1]: Suggestions for a better title?

Ethan M. Balk, MD, MPH[1]; Gaelen P. Adam, MLIS[1]; …

[1] Brown Evidence-based Practice Center, Center for Evidence Synthesis in Health, Brown School of Public Health, Brown University, Providence, RI

Ethan M. Balk, M.D., M.P.H.	All	
Gaelen P. Adam, M.L.I.S., M.P.H.	Elective surgery/	All
Wangnan Cao, Ph.D.	Colonoscopy	
Kristin Danko	Outpatient	
Monika Reddy Bhuma, B.D.S, M.P.H.	Antibiotics	
Shivani Mehta, B.A.	5-ASA	
Ian J. Saldanha, M.B.B.S., M.P.H., Ph.D.	IR	
Michael D. Beland, M.D.	?	
Nishit Shah, M.D.	All?	0

Corresponding Author:
Ethan Balk, MD MPH
Box G-S121-8
Brown School of Public Health
Providence, RI 02912, USA
ethan_balk@brown.edu

Running Title: Medical management of acute diverticulitis systematic review

Word Count:
Total XXXX

Tables: 3
Figures: 4
Supplements: 1 file

Disclaimer: This report is based on research conducted by the Brown Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Acknowledgment: The authors gratefully acknowledge the contribution of Lionel Bañez, MD, our AHRQ Task Order Officer.

Conflict of Interest: None of the authors have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this article.

Financial Support: This project was funded under contract No. 290-20-1500002 I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, Rockville, MD 20850, www.ahrq.gov

Key words: colonic diverticulitis, colonoscopy, colorectal cancer, elective surgery, systematic review, meta-analysis

PROSPERO registration number CRD42020151246

Abstract:

Background: The value of interventions used after acute colonic diverticulitis are unclear.

Purpose: Evaluate post-diverticulitis colonoscopy, nonsurgical treatments and elective surgery to prevent recurrent diverticulitis.

Data Sources: MEDLINE, Cochrane Central Trials Registry, Cochrane Database of Systematic Reviews, Embase, CINAHL, and ClinicalTrial.gov from January 1990 through November 16, 2020.

Study Selection: Randomized trials and multivariable-adjusted nonrandomized comparative studies of interventions of interest reporting clinical or patient-centered outcomes. Larger single group studies to evaluate prevalence of colonoscopy findings and to evaluate harms.

Data Extraction: Six researchers extracted study data and risk of bias, verified by an independent researcher. The team assessed strength of evidence (SoE) across studies.

Data Synthesis: Based on 21 eligible studies, patients with recent acute diverticulitis may be at increased risk of colorectal cancer (CRC) compared with the general population (low SoE), but risks of CRC diagnoses are similar with or without colonoscopy soon after acute diverticulitis. Patients older than 50 years may be at increased risk of CRC (moderate SoE) or premalignant lesions (low to high SoE). Colonoscopy after acute diverticulitis rarely results in complications or incomplete procedures (high SoE). Six trials reported that mesalamine (5-ASA) does not reduce risk of recurrence (high SoE). Evidence regarding other nonsurgical interventions to prevent recurrence is insufficient. Across three studies, elective surgery reduces recurrence in patients with prior complicated or smoldering/frequently recurrent diverticulitis (high SoE), but there is no evidence regarding which patients may benefit most from surgery. In 19 studies, serious surgical complications are not uncommon.

Limitations: Few RCTs provide evidence. Studies did not adequately assess heterogeneity of treatment effect.

Conclusions: Patients with recent episodes of acute diverticulitis may be at increased risk of CRC and high-risk lesions, but the effect of colonoscopy on clinical outcomes is unclear. 5-ASA is ineffective to prevent recurrence; other nonsurgical treatments have inadequate evidence. Elective surgery reduces recurrence in patients with prior complicated or smoldering/frequently recurrent diverticulitis, but it is unclear which patients benefit most.

Registration: PROSPERO CRD42020151246

Funding Source: Agency for Healthcare Research and Quality.

Reproducible Research Statement: Data set: Available at https://srdr.ahrq.gov/projects/1520/

Abstract: 332 words (275 max)
MSS: ~5244 words (4000 max)

Commented [KC2]: Authors seeking input on where to trim.

Controversies remain regarding best management of patients with a history of acute colonic diverticulitis. In particular, regarding the need for colonoscopy following a resolved episode of diverticulitis to detect occult colonic malignancy (1), the value of treatments aimed to reduce the risk of diverticulitis recurrence (2), and the benefits and harms of elective colectomy to prevent recurrence (3).

During episodes of acute diverticulitis, features seen on computed tomography (CT) may mimic colorectal cancer (CRC) (4). Thus professional societies have recommended follow-up colonoscopy to exclude CRC after an episode of acute diverticulitis (5). However, particularly for patients with uncomplicated diverticulitis, a potentially low prevalence of CRC has called into question the need for routine colon evaluation for these patients (1, 6). There also remain concerns that colonoscopy soon after an episode of acute diverticulitis may have increased risk of bowel perforation or failed procedures (1).

Strategies to reduce (or eliminate) diverticulitis recurrence have evolved. Despite very low quality of evidence (2, 7), various pharmacologic treatments, particularly mesalamine (5-ASA) are used in clinical practice, although uncertainty remains as to their effectiveness.

The rationale for elective surgery has been to prevent future complications, but recent studies have found that nonsurgical, continued medical treatment of diverticulitis is safe, with low rates of subsequent surgery (8). More recent literature has increasingly revealed that diverticulitis is not a progressive disease as once thought, and that increasing number of episodes do not lead to more complications or the need for urgent operative management (9, 10). Indeed, studies have found that the greatest risk of free perforation and peritonitis is during the first episode of the disease (11). Moreover, the risk of recurrence is likely much lower than previously thought (12); although, even if not complicated, unpredictable recurrences of diverticulitis can be a great source of distress to patients.

To address these controversies, we conducted a systematic review (SR) under the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program in support the American College of Physicians' (ACP) effort to create a new clinical practice guideline on management of acute diverticulitis (13). Here we address colonoscopy soon after an episode of acute diverticulitis, nonsurgical interventions to prevent recurrence of diverticulitis, and elective, prophylactic surgery In a companion article, we address the effectiveness, comparative effectiveness, and harms of hospitalization for acute uncomplicated diverticulitis, antibiotics use for acute complicated or uncomplicated diverticulitis, and interventional radiology techniques for acute complicated diverticulitis (14).

Methods

The Brown EPC used established SR methodologies as outlined in AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (15). The PROSPERO registration number is CRD42020151246. Description of our methods are presented in our companion article (14) and detailed descriptions of the systematic review and methods can be found in the full report (13) and Supplemental material. Here we report our methods in brief.

For the AHRQ report (13), we conducted literature searches in multiple databases restricted to 1990 through June 1, 2020 to capture contemporary evidence. Subsequently, the searches were updated through November 16, 2020. Abstracts and full text articles were screened in duplicate. We extracted data and assessed for methodological quality into a customized form in the Systematic Review Data Repository (SRDR; https://srdr.ahrq.gov/projects/1520). Study quality

Commented [KC3]: 3 new studies added since AHRQ report. No substantive differences.

was assessed with items from the Cochrane risk of bias tool for RCTs (16), the ROBINS-I Tool (17), and the National Heart, Lung, and Blood Institute (NHLBI) tool (18).

When feasible and appropriate, we conducted restricted maximum likelihood random effects model meta-analyses with the *metaan* package in Stata 14.2 (StataCorp). We evaluated odds ratios (OR) for categorical outcomes, differences or net differences (difference-in-differences) for continuous outcomes, and proportions of participants with colonoscopy findings, as data allowed. Proportions were meta-analyzed with the Freeman-Tukey arcsine transformation.

We graded the strength of evidence (SoE) as per the AHRQ Methods Guide (19). For each SoE assessment, we considered the number of studies, their study designs, study limitations/quality, the directness of the comparisons to the research question, consistency of study results, precision of estimates of effect, likelihood of reporting bias, and other limitations. Based on these assessments, we assigned a SoE rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect.

Study Selection

We included studies of adults with a history of acute complicated or uncomplicated left-sided colonic diverticulitis, excluding studies of diverticulosis or symptomatic uncomplicated diverticular disease. Studies had to evaluate either colonoscopy conducted after an episode of resolved acute diverticulitis, prophylactic nonsurgical treatments (pharmacological or nonpharmacological) to prevent recurrence of diverticulitis, or elective surgery.

We included comparisons of colonoscopy with other imaging or no imaging and single group (noncomparative studies), whether prospective or retrospective. Randomized controlled trials (RCTs) needed at least 10 participants and observational studies needed at least 200 participants. Outcomes of interest included CRC, CRC death, high-risk colonic premalignant lesions, including adenoma with high-grade dysplasia, adenoma ≥10 mm, villous adenoma, serrated polyp, and ≥3 adenomas/patient. We also evaluated procedure completion and complications.

We included pharmacologic treatments and nonpharmacologic interventions, including medical nutrition therapy. We included comparisons with other nonsurgical interventions or no intervention (or placebo). RCTs needed at least 10 participants and nonrandomized comparative studies (NRCSs) needed to account for potential confounders and include at least 30 participants. Single group studies were evaluated only for harms and needed at least 100 participants.

For elective surgery, we included comparisons of elective colonic surgery with no surgery. We excluded comparisons of different surgical techniques and excluded delayed surgery for management of acute diverticulitis. Requirements for RCTs and NRCSs were the same as for nonsurgical treatments. Single group studies were also evaluated for harms only and needed at least 500 participants.

Role of the Funding Source

This topic was nominated by the ACP for systematic review by an Evidence-based Practice Center in partnership with AHRQ. ACP members joined panels of key informants and technical experts, which provided perspectives that led to revisions to the key questions and protocol. AHRQ program officers, ACP members, and other reviewers (both invited and public) provided comments on draft versions of the protocol and full evidence report. ACP and AHRQ did not participate in the literature search, determination of study eligibility criteria, data analysis, or interpretation of findings. After completion of the AHRQ report (13), we discussed draft versions of the manuscript with ACP members to ensure it met the needs of the guideline

development committee and adequately conveyed our conclusions. However, the ACP did not draft any portion of the manuscript or attempt to alter our conclusions.

Results

The literature database searches yielded 17,133 citations (for all topics addressed in the full report (13)). We found 744 citations to retrieve for further screening (Supplemental Figure 1). Ultimately we found 21 eligible studies addressing colonoscopy, 12 eligible studies (addressing nonsurgical treatments to prevent recurrence, and 19 eligible studies addressing elective surgery.

Colonoscopy After Acute Diverticulitis

There is low SoE that patients with recent acute diverticulitis may be at about 3-times the risk of finding CRC on colonoscopy than healthy controls, but the finding is not statistically significant (Table 1). With low SoE, studies comparing patients who underwent colonoscopy soon after an episode of acute diverticulitis (within about 2-12 months) with those who did not undergo colonoscopy, found no evidence of differences in ultimate rates of CRC; however, no studies evaluated comparative risks of CRC death. Among these patients, about 2% have CRC, 7% have advanced colonic neoplasia (CRC or advanced adenoma), and between 1% and 4% have specific premalignant lesions (moderate to high SoE). There is also variable SoE (low to high) that older patients (≥50 years) and patients with recent complicated diverticulitis are at particularly high risk of CRC and various premalignant lesions. There is high SoE that procedural complications are rare (fewer than 1% of patients) and that incomplete colonoscopies are also uncommon (4.1%) soon after acute diverticulitis.

Overall, 21 studies addressed use of colonoscopy after episodes of acute diverticulitis for the purpose of assessing risk of colorectal cancer (CRC). Three of these compared colonoscopy to no colonoscopy in patients with recent diverticulitis (20-22), three compared colonoscopy in patients with recent diverticulitis to healthy controls (23-25), one compared early (in-hospital) colonoscopy with later colonoscopy (26), one compared colonoscopy with flexible sigmoidoscopy (27), and 13 were single-group studies of patients who underwent colonoscopy (28-40). Details, including risk of bias assessment and study results, are in Supplements B and C.

Colonoscopy Versus No Colonoscopy

Three NRCSs, all retrospective (20-22), evaluated colonoscopy compared with no colonoscopy in patients with recent acute diverticulitis. All study participants had recent acute colonic diverticulitis confirmed by CT. None of the studies reported on family history of CRC. In two NRCSs (20, 21) 8% and 24% of patients had abscesses and 2% and 0.3% had fistulas; in the third NRCS (22), only patients with uncomplicated diverticulitis were included. Across studies, participants who underwent colonoscopy were on average in their 50s and about half were men. The studies are at high risk of bias since they did not adjust for differences between groups. None of the studies reported funding sources.

The three studies used different comparators as the no colonoscopy arm, as described in Supplemental Table B-3-2. Colonoscopies were conducted at a median was 9 weeks after hospital discharge (22), a mean of 4 months after hospital discharge (21), or within 1 year of diagnostic CT scan (20).

None of the comparative studies reported on rates of CRC death. All three studies reported on CRC findings (Supplemental Figure C-1). Under the assumption that the three studies were sufficiently similar to each other, the summary unadjusted OR for CRC was 1.54 (95% CI 0.73

to 3.27; I^2 =0%), suggesting no evidence of a difference in rates of CRC ultimately diagnosed among those who did or did not have interval colonoscopy. Since the studies were unadjusted, the suggestion that those who underwent colonoscopy may be at increased risk for having CRC may be due to underlying biases regarding who completed their colonoscopy.

Colonoscopy After Diverticulitis Versus Healthy Controls

Three NRCS (23-25), all retrospective, evaluated colonoscopy among patients with diverticulitis and compared findings with matched healthy controls who also underwent colonoscopy. Across studies, the majority of diverticulitis patients had uncomplicated diverticulitis (86% to 92%). Age and sex were generally comparable between two arms within each study. The mean ages of participants ranged from 47 to 61 years old, and males accounted for 41 to 60 percent of the participants. Two studies (23, 24) adjusted their analysis of advanced adenomas; one (25). reported only unadjusted analyses. Two studies were explicitly not funded by industry (24, 25); one did not report funding source (23).

For diverticulitis patients, colonoscopies were performed within 6 months (24, 25) or 1 year (23) of the diverticulitis episode; 8% had pericolic abscesses in one study (24) and 10% and 14% had complicated diverticulitis in the other two studies. In two studies, 10% and 14% of diverticulitis participants had a family history of CRC. The third study (25) matched diverticulitis patients with people with a family history of CRC or colorectal adenoma.

None of the comparative studies reported on rates of CRC death. All three studies reported on unadjusted analyses of CRC findings (Supplemental Figure C-2). Under the assumption that the three studies were sufficiently similar to each other, the summary unadjusted OR for CRC was 3.35 (95% CI 0.84 to 13.4), with some heterogeneity among studies (I^2 =53%), overall suggesting possible evidence of a difference in CRC rates among adults with a recent history of diverticulitis and the general population. However, a large difference in CRC rates cannot be excluded.

All three NRCSs reported high-risk colonic premalignant lesions, but findings were inconsistent. Daniels 2015 found lower rates of various high-risk lesions than in the general population, opposite in direction to their (statistically nonsignificant) findings about relative of CRC. The crude (unadjusted) ORs for serrated polyps, large adenomas (≥10 mm), adenomas with high-grade dysplasia, advanced adenomas, and advanced colonic neoplasias (CRC or advanced adenoma) were between 0.14 and 0.34, all highly statistically significant. However, the authors note that the statistically significant difference in rates of advanced adenomas (P=0.036) became just nonsignificant after adjustment for age, family history of CRC, smoking, BMI, and cecal intubation (P=0.052); although, no adjusted effect size was reported. Similarly, Lecleire 2014 found lower risks of premalignant lesions among those with recent diverticulitis. The unadjusted ORs for large adenomas (≥10 mm) and advanced adenomas were similar (advanced adenoma 0.39, 95% CI 0.19 to 0.80; large adenoma 0.38, 95% CI 0.17 to 0.83). The OR for adenomas with high-grade dysplasias was similar, but near imprecise (OR 0.33, 95% CI 0.07 to 164). In contrast, Choi 2014 reported higher rates of advanced adenoma in the diverticulitis group than the general population (OR 5.14, 95% CI 0.99 to 26.8) and of advanced colonic neoplasia (OR 8.84, 2.90 to 2.7.0). These findings were consistent with the higher rates of CRC also found.

Rates of Colorectal Cancer and Abnormal Lesions on Colonoscopy

We combined the 21 comparative and single group studies, all retrospective, to estimate rates of abnormal findings on colonoscopy. The studies were mostly conducted at a single center and all patients received follow-up colonoscopy after treatment of acute diverticulitis treatment. Among the six studies that reported data, the majority of the participants had uncomplicated diverticulitis (ranging from 70% to 82%). Although these studies were conducted in seven different countries, they were similar in terms of participants' age, sex, and the course of diverticulitis.

The studies were at generally low risk of bias with regards to reporting rates of colonoscopy findings, with clear descriptions of eligibility criteria and outcomes, and no evidence of selection bias (except in regard to which patients were willing to undergo colonoscopy). Two studies (24, 25) were explicitly not funded by industry; the rest did not report funding source.

Two studies reported on CRC death (30, 37), with estimates of 0.5% (95% CI 0.1 to 2.0, N=402) at 2 to 4 years of followup (30) and 0.8% (95% CI 0.3 to 1.8, N=645) at a median 39 month followup (37). Figure 1 and Table 1 summarize the lesions for which meta-analysis was conducted (i.e., all outcomes except CRC death and serrated polyps). Across analyses, no clear patterns in prevalence was seen based on country (or continent). Of note, most studies defined advanced adenomas as either large (≥10 mm), villous, or of high grade (we excluded a single patient with CRC (25) and two studies that included serrated adenomas (29, 31)).

Subgroup Analyses

Ten studies compared rates of CRC and other dysplasias among subgroups of participants (22, 23, 29, 30, 32, 33, 35, 37, 39, 40). Of primary interest, we sought comparisons by age, sex, and recent complicated (vs. uncomplicated) diverticulitis. Only three studies conducted multivariable analyses (23, 29, 32); the other studies are at high risk of bias due to potentially unadjusted differences between compared subgroups.

Figure 2 summarizes the comparisons between subgroups for which meta-analysis was conducted. The comparison-specific forest plots are included in Supplement C. Patients 50 years or older were more likely to have CRC. Patients with complicated diverticulitis were at higher risk of CRC, advanced colonic neoplasia, and, possibly, advanced adenomas. Comparisons that were not meta-analyzed included analyses by age (risk of advanced adenoma nonsignificantly higher among those ≥50 years), recent complicated versus uncomplicated diverticulitis (adenomas with high-grade dysplasia nonsignificantly higher with complicated diverticulitis), sex (no evidence of a difference in risk of CRC or advanced colonic neoplasia), alarm symptoms (unintentional weight loss, a change in bowel habits, bloody stool and/or persistent abdominal pain) greatly increased the risk of CRC (odds ratio 20.2; 95% CI 2.54, 160) (37), anemia and prior diverticulitis (each with no association with advanced colonic neoplasia).

Colonoscopy: Complications, Tolerance, Feasibility, and Completion of Procedure

Five studies explicitly reported no major complications (35, 39) or (overall) no complications (23, 26, 27) related to colonoscopy across 998 patients overall, implying a confidence interval of 0 to 0.8 percent (Supplemental Figure C-. Colonoscopies were conducted within 6 to 7 weeks (26, 39), 4 months (35), or 1 year (23) after the episode of acute diverticulitis (one study (27) did not report timing).

Four studies reported on rates of failed/incomplete colonoscopy procedure (26, 27, 32, 40). Combination of the four cohorts that performed colonoscopy after hospital discharge (within 1 year, at approximately 6 weeks, or not reported) yielded a summary estimate that 4.1 percent (95% CI 2.8 to 5.7) of patients had a failed or incomplete procedure (Supplemental Figure C-12).

One study (Lahat 2007 (26)) reported a nonsignificantly higher rate of incomplete colonoscopies among those with in-hospital rather than later (6 weeks after discharge) colonoscopies The study found colonoscopy (17.8% vs. 7.3%; P = 0.16). However, the study also found that only 3/45 (6.7%) of those with inpatient colonoscopy failed to show (or refused) colonoscopy, as opposed to 10/41 (24.4%) who did not show for their 6 week colonoscopy (P=0.03). In total 34/45 (75.6%) of in-hospital colonoscopy patients had a completed colonoscopy. One NRCS (Abdulazeez 2020 (27) that compared colonoscopy with flexible sigmoidoscopy (implicitly with barium enema) provided an imprecise comparison of incomplete procedure rates in an unadjusted analysis (5/120 vs. 3/120, OR 1.70, 95% CI 0.40 to 7.26).

Commented [EB4]: Strictly we should ignore the flex sig arm. This was an unadjusted analysis. Therefore, more correct to include this as just a single group study of colonoscopy.
As I write this comment, I think this would be better. It would not change conclusions since, as the next sentence suggests, their comparison of colonoscopy with flex sig does not yield a meaningful result.

Commented [EB5]: They also reported 0/120 CRC on flex sig and 0 complications with flex sig. These data have been omitted.

Nonsurgical Interventions to Prevent Recurrence

There is high SoE that 5-ASA does not reduce the risk of recurrence and is not more harmful than placebo (Table 2). Evidence for other interventions (rifaximin, combination 5-ASA and rifaximin, combination 5-ASA and probiotics, probiotics, and burdock tea) is too sparse to make conclusions (insufficient). No studies evaluated medical nutrition therapy.

Twelve studies (10 RCTs, one NRCS, and one single-group study) evaluated nonsurgical (pharmacologic and nonpharmacologic) interventions to prevent recurrent diverticulitis (41-50). Details, including risk of bias assessment and study results, are in Supplement C. With a small number of exceptions, all study participants had a documented prior episode of acute diverticulitis. Five RCTs were funded by industry (43, 44, 46, 47), and one was explicitly not funded by industry (48); the remaining six studies did not report their funding sources.

5-ASA Versus Placebo

5-ASA is an anti-inflammatory drug typically used for inflammatory bowel disease (ulcerative colitis and Crohn's disease). Six RCTs (in four publications (42, 46-48)) compared 5-ASA (in a variety of doses) with placebo in a total of 1836 participants, In addition, one single-group study reported harms in 45 patients receiving 4.8 g/day of 5-ASA (50).

All six RCTs reported on recurrence of diverticulitis. By meta-analysis, the summary OR for diverticulitis recurrence with 5-ASA, across doses, was 1.15 (95% CI 0.92, 1.44), suggesting 5-ASA may *increase* the risk of recurrence by a small amount (Figure 3). There was no statistical evidence of heterogeneity across studies; we did not see evidence that effects differ by dose, which may also suggest a lack of effect.

Three RCTs (42, 46, 48) reported on time to recurrence (in days) but had conflicting results. Parente 2013 reported *worse* outcomes with 5-ASA: patients receiving 1.6 g/day of 5-ASA (10 d/mo) had a *shorter* mean time to recurrence than patients receiving placebo (mean difference [MD] −151 days, 95% CI −366 to −66). The other two trials found no statistically significant differences between 5-ASA and placebo (Parente 2013 (46): HR 1.02 for 3 g/d and 0.74 for 1.5 g/d; DIVA (48): 209 days *longer* before recurrence with 5-ASA, but reported as NS, implying a very wide confidence interval).

Two RCTs reported on symptom scores, the Therapy Impact Questionnaire (TIQ) (46) and the Global Symptom Score (GSS) (48). Parente 2013 (46) found a mean difference in the TIQ score at 24 months of –2.9 (95% CI –4.8, –1.0) favoring 5-ASA, but we found no information

regarding what a minimal clinically important difference would be. There was also concern about selective outcome reporting, since follow-up data on the quality of life component of the TIQ were omitted. The analysis of GSS, which was developed for the DIVA study was also incompletely reported but found that GSS scores were mostly nonsignificantly lower (better) with 5-ASA than placebo at all followup timepoints, but mostly nonsignificantly so (48). The study did not claim any differences were clinically significant.

Other Nonsurgical Interventions

Single, generally small RCTs provided insufficient evidence of comparisons of other interventions. These included placebo comparisons of probiotics (43), rifaximin (44), combination 5-ASA and probiotics (48), and burdock tea (45); 5-ASA versus rifaximin (41); combination 5-ASA and rifaximin versus rifaximin (49); combination 5-ASA and probiotics versus 5-ASA (48); and combination 5-ASA and probiotics versus probiotics (51).

Adverse Events

Five RCTs (PREVENT-1 (47), PREVENT-2 (47), SAG-37 (42), Parente 2013 (46), Stollman 2013 (48)) evaluated a variety of doses of 5-ASA (ranging from 0.8 to 4.8 g/day) and reported adverse events that the authors named as serious. However, none defined the outcome. Serious adverse event rates ranged between 8% and 14% percent across 5-ASA arms. But in all trials, similar serious adverse event rates were seen in the placebo groups. Three RCTs (SAG-37 (42), Parente 2013 (46), Stollman 2013 (48)) reported higher likelihood of discontinuation due to adverse events with 5-ASA than placebo, but only one SAG-37 trial found a statistically significant difference. Three RCTs (PREVENT-1 (47), PREVENT-2 (47), Stollman 2013 (48)) reported similar rates of specific adverse events (sepsis, acute myocardial infarction, and urinary tract infections) with 5-ASA or placebo. Studies of other interventions did not report on adverse events.

Elective Surgery

There is high SoE that elective surgery reduces the risk of recurrence of diverticulitis among patients with prior complicated or frequently recurrent diverticulitis, but no evidence regarding which patients may benefit most from surgery (Table 3). There was low to moderate SoE that serious adverse events are uncommon with elective surgery, including that fewer than 1% of patients die postoperatively.

Two small RCTs (52-55) and one large NRCS (56) with adjusted analyses evaluated elective surgery (laparoscopic sigmoid colectomy (52), laparoscopic sigmoidectomy (53-55), and colectomy (56)) compared to nonoperative management. Nonoperative management was described as conservative management (53-55), observation (52), or simply nonoperative management (56). The NRCS conducted propensity score adjusted analyses. Details, including risk of bias assessment and study results, are in Supplements B and C. The two RCTs included different patients. The DIRECT trial (53) included patients with uncomplicated disease who had either smoldering symptoms (persisting >3 months) or frequent recurring symptoms (≥3 within 2 years) while You 2018 (52) evaluated patients with a history of complicated diverticulitis manifested as extraluminal air with or without abscess. The NRCS (56) included 7072 patients with a history of an acute diverticular abscess (complicated diverticulitis). Participant ages were similar across studies, with participants in their mid 50s, and between 28 and 54 percent male. One RCT was industry funded (52), the other was non-industry funded; the NRCS did not report

funding source. Both RCTs were of low risk of bias for randomization, incomplete outcome data, and selective reporting, but high risk of bias for blinding. The NRCS had a low risk of bias for confounding and selection bias.

The RCTs had only a single death (in a nonoperative arm) at 3 and 5 years. The NRCS (56) reported an unadjusted analysis of diverticulitis-related death but found a large difference. The death rate was substantially lower in the elective surgery group (0.2%) at 5 years than the nonsurgical treatment group (1.9%), implying an unadjusted OR of 0.13 (95% CI 0.03 to 0.29), suggesting the number needed to treat (NNT) to prevent one death was 57 (95% CI 46 to 76).

Risk of recurrence was much lower among participants who had elective surgery. While the NRCS reported only an unadjusted analysis, *post hoc*, we decided to meta-analyze the three studies given their similar results. The summary OR was 0.16 (95% CI 0.09,0.27) (Figure 4). The implied summary NNT to prevent one recurrence is 4.6 (95% CI 2.7 to 7.9).

The DIRECT 2017 RCT reported on quality of life and pain in 109 participants. Across four scales (Gastrointestinal Quality of Life Index [GIQLI], Short Form [SF]-36 mental and physical, and EuroQol-5D), people in the elective surgery group had greater improvements in quality of life and pain measures at both 6 months and 5 years, compared with baseline. Regarding GIQLI, the study was powered to detect a minimal clinical important difference of 10 points. At 6 months, the net difference between arms from baseline was 13.6 units (95% CI 5.2 to 22.0), favoring surgery, and at 5 years, 9.3 (95% CI 1.3, to 17.3). SF-36 mental and physical health scales were mostly statistically and clinically significantly better after surgery (mental: 4.1 units [95% CI −0.4, 8.6] at 6 months, 6.4 [95% CI 2.2, 10.6] at 5 years; physical: 3.9 units [95% CI 1.1, 6.7] at 6 months, 4.9 units [95% CI 1.5, 8.3] at 5 years). Similar findings were reported for the EQ-5D scale: at both 6 months and 5 years, the net differences between arms from baseline were 0.16 units (95% CI 0.08, 0.24). Likewise, the visual analog scale for pain (100 points) favored elective surgery: net difference at 6 months was −18.4 units (95% CI −26.4, −10.4) and at 5 years −11.0 (95% CI −20.1, −1.9).

Notably, none of the eligible studies reported subgroup (or similar) analyses to evaluate potential heterogeneity of treatment effect of the benefits of elective surgery (which patients might fare best with elective surgery).

Serious adverse events associated with elective surgery were reported in 19 studies (2 RCTs (52-55), 1 NRCS (56), and 16 eligible single-group studies (57-73)). In general, composite adverse events (of multiple events) were common, but individual adverse event rates were low. Each specific adverse event was reported by only a small subset of the 19 included studies. Adverse events are summarized in Supplemental Table C-4c-4. Across four studies, the summary risk of serious adverse events (various composites or not defined) was 25.1% (95% CI 3.7, 57.0). The summary risk of 30-day mortality was 0.7% (95% CI 0.3, 1.4; 9 studies). One study, Sheer 2011 (67), in a study of Medicare beneficiaries with an overall 30-day death rate of 1.22%, found that the OR for the oldest (85 years and older) compared to the youngest (65 to 69 years) age groups was 10.2 (95% CI 6.49, 16.0), and the odds increased with every age in between.

Commented [EB6]: Many more AEs we could list

Conclusions

Comparative studies do not provide definitive evidence regarding whether colonoscopy after an episode of acute diverticulitis affects rates of CRC death or likelihood of uncovering CRC compared with routine screening. There is low SoE that patients who undergo colonoscopy soon after an episode of acute diverticulitis (~2-12 months) may, ultimately, have similar rates of CRC than those who do not undergo colonoscopy. However, there is also low SoE that patients with

recent diverticulitis (within 6-12 months) may have an increased likelihood of having undiagnosed CRC. There was no eligible evidence regarding CT colonography or other cancer screening tests post-diverticulitis. The evidence suggests that among people with recent acute diverticulitis, those 50 or older or who had complicated diverticulitis are at increased risk of having CRC or premalignant lesions on colonoscopy. Colonoscopies conducted within 1.5 to 12 months after acute diverticulitis rarely have complications or incomplete tests.

Among nonsurgical interventions to prevent recurrence of diverticulitis, only 5-ASA has been adequately evaluated. There is high SoE that 5-ASA does not reduce the risk of diverticulitis, and there is even a suggestion that people using 5-ASA may be at a small *increased* risk of recurrence. There is, though, also high SoE that 5-ASA does not cause important adverse events. Notably, no eligible study evaluated nutritional therapies.

Among patients with either a history of complicated diverticulitis or smoldering or frequently recurring diverticulitis, there is a high SoE indicated that elective surgery resulted in much lower rates of diverticulitis recurrence than nonsurgical interventions. However, no eligible studies evaluated the relative effect of elective surgery for patients with nonrecurrent uncomplicated diverticulitis. Serious adverse events, including 30-day mortality (at 0.7%), were not uncommon. The evidence is sparse to evaluate risk of long-term death, but there is some indication that at 5 years of followup, patients who underwent elective surgery were at reduced risk of death. A single trial suggests improved quality of life and reduced pain among those having elective surgery. However, none of the studies provided evidence regarding which patients would most benefit from surgery.

We believe that our literature search was complete and did not systematically miss studies. It appears that the large majority of studies that were unavailable to us were conference abstracts, so we might have missed some cutting-edge studies. We restricted the evidence base to the past 30 years, based on changing diagnostic criteria for acute diverticulitis in the 1990s. We might have, thus, missed some important older studies that might still be pertinent. However, none of the stakeholders we collaborated with knew of such studies or were concerned by the choice of dates. While we restricted some study designs based on sample sizes, we do not believe the smaller studies would have altered conclusions.

We were fairly liberal about decisions to perform meta-analyses. However, where one might have reasonably chosen not to meta-analyze studies (because of clinical heterogeneity of included studies or *post hoc* decisionmaking), we explicitly point this out. We chose to use meta-analysis mostly as an indicator of possible effect (or of likelihood of an outcome or finding) rather than to provide precise estimates. In particular, for evaluations of elective surgery complications, we acknowledge that we did not adequately account for the differences across studies of surgery or patient characteristics. However, no clear patterns were seen across studies to explain the statistically large differences in surgical complication rates.

The evidence base appeared to be generally applicable to patients with a recent history of acute diverticulitis. Most studies described their eligibility criteria sufficiently to determine that the included participants are those for whom the interventions are potentially appropriate. However, many studies did not provide sufficient detail to understand the detailed level of severity of disease or of potential risk factors for poor outcomes. And, as already noted, studies rarely evaluated subgroups and failed to address heterogeneity of treatment effect. Such analyses could allow a better understanding of whom the findings are most applicable to.

There is a clear need for high-quality research to address all covered issues. Ideally, large-scale, multicenter RCTs should be conducted in unrestricted populations (i.e., without eligibility

restrictions that may reduce applicability) with appropriate subgroup analyses. RCTs should be large enough to evaluate potential clinically important differences in rates of the most important outcomes to patients (e.g., death, recurrence rate, and time to recurrence, CRC) and important harms, adverse events, and complications.

Many questions remain inadequately answered regarding the best management of patients with a recent history of acute diverticulitis. Patients with recent episodes of diverticulitis are at risk of having undiagnosed CRC or advanced colonic neoplasia, particularly if they are at least 50 years of age or have had complicated diverticulitis; however, the effect of colonoscopy follow-up after diverticulitis on clinical outcomes remains unclear. The use of 5-ASA does not reduce (and may increase) the risk of recurrence of diverticulitis but is not more harmful than placebo. Patients with a history of complicated diverticulitis or who have smoldering or frequently recurring diverticulitis who undergo elective surgery are at greatly reduced risk of recurrent diverticulitis; serious surgery-related adverse events are uncommon. However, for elective surgery in particular, and for all other evaluated interventions, the evidence does not adequately address which patients would benefit most from a given intervention. There is a compelling need for future, well-conducted studies that address both effectiveness (and harms) of interventions and heterogeneity of treatment effect.

References

1. Agarwal AK, Karanjawala BE, Maykel JA, Johnson EK, Steele SR. Routine colonic endoscopic evaluation following resolution of acute diverticulitis: is it necessary? World J Gastroenterol. 2014;20(35):12509-16.
2. Stollman N, Smalley W, Hirano I. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology. 2015;149(7):1944-9.
3. Simianu VV, Flum DR. Rethinking elective colectomy for diverticulitis: a strategic approach to population health. World J Gastroenterol. 2014;20(44):16609-14.
4. Balthazar EJ, Megibow A, Schinella RA, Gordon R. Limitations in the CT diagnosis of acute diverticulitis: comparison of CT, contrast enema, and pathologic findings in 16 patients. AJR Am J Roentgenol. 1990;154(2):281-5.
5. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 1999;94(11):3110-21.
6. Sharma PV, Eglinton T, Hider P, Frizelle F. Systematic review and meta-analysis of the role of routine colonic evaluation after radiologically confirmed acute diverticulitis. Ann Surg. 2014;259(2):263-72.
7. Carabotti M, Annibale B, Severi C, Lahner E. Role of Fiber in Symptomatic Uncomplicated Diverticular Disease: A Systematic Review. Nutrients. 2017;9(2).
8. Garfinkle R, Kugler A, Pelsser V, Vasilevsky CA, Morin N, Gordon P, et al. Diverticular Abscess Managed With Long-term Definitive Nonoperative Intent Is Safe. Dis Colon Rectum. 2016;59(7):648-55.
9. Buchs NC, Konrad-Mugnier B, Jannot AS, Poletti PA, Ambrosetti P, Gervaz P. Assessment of recurrence and complications following uncomplicated diverticulitis. Br J Surg. 2013;100(7):976-9; discussion 9.
10. Lahat A, Avidan B, Sakhnini E, Katz L, Fidder HH, Meir SB. Acute diverticulitis: a decade of prospective follow-up. J Clin Gastroenterol. 2013;47(5):415-9.
11. Ritz JP, Lehmann KS, Frericks B, Stroux A, Buhr HJ, Holmer C. Outcome of patients with acute sigmoid diverticulitis: multivariate analysis of risk factors for free perforation. Surgery. 2011;149(5):606-13.
12. Hall JF, Roberts PL, Ricciardi R, Read T, Scheirey C, Wald C, et al. Long-term follow-up after an initial episode of diverticulitis: what are the predictors of recurrence? Dis Colon Rectum. 2011;54(3):283-8.
13. Balk EM, Adam GP, Cao W, Danko K, Bhuma MR, Mehta S, et al. Management of Colonic Diverticulitis. Comparative Effectiveness Review No. 233. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015- 00002-I.) AHRQ Publication No. 20(21)-EHC025. Rockville, MD: Agency for Healthcare Research and Quality; October 2020. DOI: https://doi.org/10.23970/AHRQEPCCER233. Posted final reports are located on the Effective Health Care Program search page.
14. Balk EM. Medical Management of Acute Colonic Diverticulitis: A Systematic Review. submitted. 2021.
15. Agency for Healthcare Research and Quality Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No.

10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
16. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
17. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
18. National Heart, Lung, and Blood Institute. Study Quality Assessment Tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools . Accessed December 5, 2020.
19. Berkman ND, Lohr KN, Ansari MT, Balk EM, Kane R, McDonagh M, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015;68(11):1312-24.
20. Lau KC, Spilsbury K, Farooque Y, Kariyawasam SB, Owen RG, Wallace MH, et al. Is colonoscopy still mandatory after a CT diagnosis of left-sided diverticulitis: can colorectal cancer be confidently excluded? Dis Colon Rectum. 2011;54(10):1265-70.
21. Sallinen V, Mentula P, Leppaniemi A**.** Risk of colon cancer after computed tomography-diagnosed acute diverticulitis: is routine colonoscopy necessary? Surg Endosc. 2014;28(3):961-6.
22. Soh NYT, Chia DKA, Teo NZ, Ong CJM, Wijaya R**.** Prevalence of colorectal cancer in acute uncomplicated diverticulitis and the role of the interval colonoscopy. Int J Colorectal Dis. 2018;33(7):991-4.
23. Choi YH, Koh SJ, Kim JW, Kim BG, Lee KL, Im JP, et al. Do we need colonoscopy following acute diverticulitis detected on computed tomography to exclude colorectal malignancy? Dig Dis Sci. 2014;59(9):2236-42.
24. Daniels L, Unlu C, de Wijkerslooth TR, Stockmann HB, Kuipers EJ, Boermeester MA, et al. Yield of colonoscopy after recent CT-proven uncomplicated acute diverticulitis: a comparative cohort study. Surg Endosc. 2015;29(9):2605-13.
25. Lecleire S, Nahon S, Alatawi A, Antonietti M, Chaput U, Di-Fiore A, et al. Diagnostic impact of routine colonoscopy following acute diverticulitis: A multicenter study in 808 patients and controls. United European Gastroenterol J. 2014;2(4):301-6.
26. Lahat A, Yanai H, Menachem Y, Avidan B, Bar-Meir S**.** The feasibility and risk of early colonoscopy in acute diverticulitis: a prospective controlled study. Endoscopy. 2007;39(6):521-4.
27. Abdulazeez Z, Kukreja N, Qureshi N, Lascelles S**.** Colonoscopy and flexible sigmoidoscopy for follow-up of patients with left-sided diverticulitis. Ann R Coll Surg Engl. 2020;102(9):744-7.
28. Alcantar DC, Rodriguez C, Fernandez R, Kumar S, Junia C**.** The Necessity of a Colonoscopy after an Acute Diverticulitis Event in Adults Less Than 50 Years Old. Cureus. 2019;11(9):e5666.
29. Brar MS, Roxin G, Yaffe PB, Stanger J, MacLean AR, Buie WD**.** Colonoscopy following nonoperative management of uncomplicated diverticulitis may not be warranted. Dis Colon Rectum. 2013;56(11):1259-64.
30. Elmi A, Hedgire SS, Pargaonkar V, Cao K, McDermott S, Harisinghani M**.** Is early colonoscopy beneficial in patients with CT-diagnosed diverticulitis? AJR Am J Roentgenol. 2013;200(6):1269-74.

31. Studniarek A, Kochar K, Warner C, Eftaiha S, Naffouj S, Borsuk DJ, et al. Findings on Colonoscopy after Diverticulitis: A Multicenter Review. Am Surg. 2019;85(12):1381-5.
32. Andrade P, Ribeiro A, Ramalho R, Lopes S, Macedo G**.** Routine Colonoscopy after Acute Uncomplicated Diverticulitis - Challenging a Putative Indication. Dig Surg. 2017;34(3):197-202.
33. Horesh N, Saeed Y, Horesh H, Berger Y, Speter C, Pery R, et al. Colonoscopy after the first episode of acute diverticulitis: challenging management paradigms. Tech Coloproctol. 2016;20(6):383-7.
34. Khoury T, Mahamid M, Lubany A, Safadi M, Farah A, Sbeit W, et al. Underlying Colorectal Cancer Was Rarely Detected After an Episode of Acute Diverticulitis: a Retrospective Analysis of 225 Patients. J Gastrointest Cancer. 2019.
35. Meireles LC, Fernandes SR, Ribeiro LC, Velosa J**.** Role of endoscopy after an acute episode of diverticulitis: analysis of a cohort of Portuguese patients from a tertiary referral center. Eur J Gastroenterol Hepatol. 2015;27(12):1429-32.
36. O'Donohoe N, Chandak P, Likos-Corbett M, Yee J, Hurndall K, Rao C, et al. Follow up colonoscopy may be omissible in uncomplicated left-sided acute diverticulitis diagnosed with CT- a retrospective cohort study. Sci Rep. 2019;9(1):20127.
37. Ramphal W, Schreinemakers JMJ, Seerden TCJ, Gobardhan PD**.** Tumour Characteristics of Patients with Colorectal Cancer after Acute Uncomplicated Diverticulitis. Dig Dis. 2018;36(5):362-8.
38. Schout PJ, Spillenaar Bilgen EJ, Groenen MJ**.** Routine screening for colon cancer after conservative treatment of diverticulitis. Dig Surg. 2012;29(5):408-11.
39. Seoane Urgorri A, Zaffalon D, Pera Roman M, Batlle Garcia M, Riu Pons F, Dedeu Cusco JM, et al. Routine lower gastrointestinal endoscopy for radiographically confirmed acute diverticulitis. In whom and when is it indicated? Rev Esp Enferm Dig. 2018;110(9):571-6.
40. Suhardja TS, Norhadi S, Seah EZ, Rodgers-Wilson S**.** Is early colonoscopy after CT-diagnosed diverticulitis still necessary? Int J Colorectal Dis. 2017;32(4):485-9.
41. Festa V, Spila Alegiani S, Chiesara F, Moretti A, Bianchi M, Dezi A, et al. Retrospective comparison of long-term ten-day/month rifaximin or mesalazine in prevention of relapse in acute diverticulitis. Eur Rev Med Pharmacol Sci. 2017;21(6):1397-404.
42. Kruis W, Kardalinos V, Eisenbach T, Lukas M, Vich T, Bunganic I, et al. Randomised clinical trial: mesalazine versus placebo in the prevention of diverticulitis recurrence. Aliment Pharmacol Ther. 2017;46(3):282-91.
43. Kvasnovsky CL, Bjarnason I, Donaldson AN, Sherwood RA, Papagrigoriadis S**.** A randomized double-blind placebo-controlled trial of a multi-strain probiotic in treatment of symptomatic uncomplicated diverticular disease. Inflammopharmacology. 2017.
44. Lanas A, Ponce J, Bignamini A, Mearin F**.** One year intermittent rifaximin plus fibre supplementation vs. fibre supplementation alone to prevent diverticulitis recurrence: a proof-of-concept study. Dig Liver Dis. 2013;45(2):104-9.
45. Mizuki A, Tatemichi M, Nakazawa A, Tsukada N, Nagata H, Kinoshita Y**.** Effects of Burdock tea on recurrence of colonic diverticulitis and diverticular bleeding: An open-labelled randomized clinical trial. Sci Rep. 2019;9(1):6793.
46. Parente F, Bargiggia S, Prada A, Bortoli A, Giacosa A, Germana B, et al. Intermittent treatment with mesalazine in the prevention of diverticulitis recurrence: a randomised

multicentre pilot double-blind placebo-controlled study of 24-month duration. Int J Colorectal Dis. 2013;28(10):1423-31.
47. Raskin JB, Kamm MA, Jamal MM, Marquez J, Melzer E, Schoen RE, et al. Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials. Gastroenterology. 2014;147(4):793-802.
48. Stollman N, Magowan S, Shanahan F, Quigley EM**.** A randomized controlled study of mesalamine after acute diverticulitis: results of the DIVA trial. J Clin Gastroenterol. 2013;47(7):621-9.
49. Tursi A, Brandimarte G, Daffina R**.** Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. Dig Liver Dis. 2002;34(7):510-5.
50. Silva Sanchez SD, Wan H, Streck P, Willshire D, Raskin JB**.** Long-term safety of once-daily multimatrix mesalazine: a pooled clinical trials analysis. Journal of gastroenterology and hepatology (australia). 2014;29:106-7.
51. Tursi A, Brandimarte G, Giorgetti GM, Elisei W, Aiello F**.** Balsalazide and/or high-potency probiotic mixture (VSL#3) in maintaining remission after attack of acute, uncomplicated diverticulitis of the colon. Int J Colorectal Dis. 2007;22(9):1103-8.
52. You K, Bendl R, Taut C, Sullivan R, Gachabayov M, Bergamaschi R**.** Randomized clinical trial of elective resection versus observation in diverticulitis with extraluminal air or abscess initially managed conservatively. Br J Surg. 2018;105(8):971-9.
53. van de Wall BJM, Stam MAW, Draaisma WA, Stellato R, Bemelman WA, Boermeester MA, et al. Surgery versus conservative management for recurrent and ongoing left-sided diverticulitis (DIRECT trial): an open-label, multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2017;2(1):13-22.
54. Bolkenstein HE, de Wit GA, Consten ECJ, Van de Wall BJM, Broeders I, Draaisma WA**.** Cost-effectiveness analysis of a multicentre randomized clinical trial comparing surgery with conservative management for recurrent and ongoing diverticulitis (DIRECT trial). Br J Surg. 2019;106(1365-2168 (Electronic)):448-57.
55. Bolkenstein HE, Consten ECJ, van der Palen J, van de Wall BJM, Broeders I, Bemelman WA, et al. Long-term Outcome of Surgery Versus Conservative Management for Recurrent and Ongoing Complaints After an Episode of Diverticulitis: 5-year Follow-up Results of a Multicenter Randomized Controlled Trial (DIRECT-Trial). Ann Surg. 2019;269(4):612-20.
56. Aquina CT, Becerra AZ, Xu Z, Justiniano CF, Noyes K, Monson JRT, et al. Population-based study of outcomes following an initial acute diverticular abscess. Br J Surg. 2019;106(4):467-76.
57. Bhakta A, Tafen M, Glotzer O, Canete J, Chismark AD, Valerian BT, et al. Laparoscopic sigmoid colectomy for complicated diverticulitis is safe: review of 576 consecutive colectomies. Surg Endosc. 2016;30(4):1629-34.
58. Bordeianou L, Cauley CE, Patel R, Bleday R, Mahmood S, Kennedy K, et al. Prospective Creation and Validation of the PREVENTT (Prediction and Enaction of Prevention Treatments Trigger) Scale for Surgical Site Infections (SSIs) in Patients With Diverticulitis. Ann Surg. 2019;270(6):1124-30.
59. Ilyas MI, Zangbar B, Nfonsam VN, Maegawa FA, Joseph BA, Patel JA, et al. Are there differences in outcome after elective sigmoidectomy for diverticular disease and for cancer? A national inpatient study. Colorectal Dis. 2017;19(3):260-5.

60. Lidor AO, Schneider E, Segal J, Yu Q, Feinberg R, Wu AW**.** Elective surgery for diverticulitis is associated with high risk of intestinal diversion and hospital readmission in older adults. J Gastrointest Surg. 2010;14(12):1867-73; discussion 73-4.
61. Masoomi H, Buchberg B, Nguyen B, Tung V, Stamos MJ, Mills S**.** Outcomes of laparoscopic versus open colectomy in elective surgery for diverticulitis. World J Surg. 2011;35(9):2143-8.
62. Moghadamyeghaneh Z, Carmichael JC, Smith BR, Mills S, Pigazzi A, Nguyen NT, et al. A comparison of outcomes of emergent, urgent, and elective surgical treatment of diverticulitis. Am J Surg. 2015;210(5):838-45.
63. Papageorge CM, Kennedy GD, Carchman EH**.** National Trends in Short-term Outcomes Following Non-emergent Surgery for Diverticular Disease. J Gastrointest Surg. 2016;20(7):1376-87.
64. Perez NP, Chang DC, Goldstone RN, Bordeianou L, Ricciardi R, Cavallaro PM**.** Relationship Between Diverticular Disease and Incisional Hernia After Elective Colectomy: a Population-Based Study. J Gastrointest Surg. 2020.
65. Pessaux P, Muscari F, Ouellet JF, Msika S, Hay JM, Millat B, et al. Risk factors for mortality and morbidity after elective sigmoid resection for diverticulitis: prospective multicenter multivariate analysis of 582 patients. World J Surg. 2004;28(1):92-6.
66. Russ AJ, Obma KL, Rajamanickam V, Wan Y, Heise CP, Foley EF, et al. Laparoscopy improves short-term outcomes after surgery for diverticular disease. Gastroenterology. 2010;138(7):2267-74, 74.e1.
67. Sheer AJ, Heckman Je Fau - Schneider EB, Schneider Eb Fau - Wu AW, Wu Aw Fau - Segal JB, Segal Jb Fau - Feinberg R, Feinberg R Fau - Lidor AO, et al. Congestive heart failure and chronic obstructive pulmonary disease predict poor surgical outcomes in older adults undergoing elective diverticulitis surgery. Dis Colon Rectum. 2011;54(11):1430-7.
68. Silva-Velazco J, Stocchi L, Costedio M, Gorgun E, Kessler H, Remzi FH**.** Is there anything we can modify among factors associated with morbidity following elective laparoscopic sigmoidectomy for diverticulitis? Surg Endosc. 2016;30(8):3541-51.
69. Simianu VV, Sinanan MN, Bastawrous AL, Billingham RP, Fichera A, Florence MG, et al. The impact of delaying elective resection of diverticulitis on laparoscopic conversion rate. American Journal of Surgery. 2015;209(5):913-9.
70. Tsilimparis N, Haase O, Wendling P, Kipfmuller K, Schmid M, Engemann R, et al. [Laparoscopic "fast-track" sigmoidectomy for diverticulitis disease in Germany. Results of a prospective quality assurance program]. Dtsch Med Wochenschr. 2010;135(36):1743-8.
71. Valizadeh N, Suradkar K, Kiran RP**.** Specific Factors Predict the Risk for Urgent and Emergent Colectomy in Patients Undergoing Surgery for Diverticulitis. Am Surg. 2018;84(11):1781-6.
72. Varma S, Mehta A, Canner JK, Azar F, Efron DT, Efron J, et al. Surgery After an Initial Episode of Uncomplicated Diverticulitis: Does Time to Resection Matter? J Surg Res. 2019;234:224-30.
73. von Strauss und Torney M, Moffa G, Kaech M, Haak F, Riss S, Deutschmann E, et al. Risk of Emergency Surgery or Death After Initial Nonoperative Management of Complicated Diverticulitis in Scotland and Switzerland. JAMA Surg. 2020;155(7):600-6.

Table 1. Evidence profile for colonoscopy after acute diverticulitis

Comparison	Outcome	No. Studies (Subjects*)	Risk of Bias	Consistency	Precision	Directness	Other	Overall SoE	Findings and Conclusions
Colonoscopy vs. no colonoscopy	CRC death	0							No evidence
	CRC	3 (1851)	Moderate	Consistent	Imprecise	Direct	None	Low	No evidence of a difference OR 1.54 (0.73, 3.26)
Diverticulitis vs. general population	CRC death	0							No evidence
	CRC	3 (954)	Moderate	Inconsistent	Precise	Direct	None	Low	Possible increased risk after diverticulitis OR 3.35 (0.84, 13.4)
	Premalignant lesions	3 (954)	Moderate	Inconsistent	Imprecise	Direct	None	Insufficient	No conclusion regarding colonoscopy in diverticulitis vs. general population
Rates of abnormal findings (no comparison)	CRC death	2 (1047)	Low	Consistent	Imprecise	Direct	Sparse	Low	0.5% or 0.8%
	CRC	21 (6325)	Low	Inconsistent	Precise	Direct	None	Moderate	1.9% (1.2, 2.7)
	ACN	3 (766)	Low	Inconsistent	Precise	Direct	None	Moderate	7.4% (5.2, 10.0)
	Advanced adenoma	6 (1675)	Low	Consistent	Precise	Direct	None	High	4.5% (2.7, 6.7)
	High-grade dysplasia	7 (2419)	Low	Inconsistent	Precise	Direct	None	Moderate	1.3% (0.3, 3.0)
	Adenoma ≥10 mm	4 (1210)	Low	Consistent	Precise	Direct	None	High	2.6 (1.8, 3.6)
	Serrated polyp	2 (617)	Low	Inconsistent	Imprecise	Direct	Sparse	Insufficient	Estimate unclear
Age ≥50 vs. <50 y	CRC	4 (1158)	Low	Inconsistent	Precise	Direct	None	Moderate	Older at increased risk OR 3.31 (1.58, 6.95)
	ACN	3 (650)	Low	Consistent	Precise	Direct	None	High	Older at increased risk OR ~8 to 9
	Advanced adenoma	2 (398)	Low	Consistent	Imprecise	Direct	Sparse	Low	Possibly older at increased risk OR 1.7 or 3.3, but imprecise or NS
Complicated vs. uncomplicated	CRC	7 (1965)	Low	Consistent	Precise	Direct	None	High	Hx of complicated at increased risk OR 5.72 (2.73, 12.0)
	ACN	4 (866)	Low	Consistent	Precise	Direct	None	High	Hx of complicated at increased risk OR 3.44 (1.99, 5.94)
	Advanced adenoma	3 (671)	Low	Consistent	Imprecise	Direct	None	Moderate	Hx of complicated maybe at increased risk OR 1.95 (0.91, 4.17)
	High-grade dysplasia	1 (427)	Low	N/A	Precise	Direct	Sparse	Insufficient	No conclusion regarding complicated vs. uncomplicated
Complications (no comparison)	Complications	5 (998)	Low	Consistent	Precise	Direct	None	High	0% (0 to 0.9)
Feasibility (no comparison)	Incomplete colonoscopy	4 (692)	Low	Consistent	Precise	Direct	None	High	4.1% (2.8, 5.7)

Abbreviations: ACN = advanced colonic neoplasia, CRC = colorectal cancer, Hx of = history of (recent), NS = not statistically significant, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

* With recent acute diverticulitis

Table 2. Evidence profile for nonsurgical interventions to prevent recurrence

Topic	No. Studies (Subjects)	Risk of Bias	Consistency	Precision	Directness	Other	Overall SoE	Conclusion statements
5-ASA to prevent recurrence (vs. placebo)	6 (1898)	Low	Consistent	Precise	Direct	None	High	5-ASA does not reduce the risk of recurrence OR 1.15 (0.92, 1.44), nominally favoring placebo
5-ASA adverse events	6 (1898)	Low	Consistent	Precise	Direct	None	High	Adverse events are no more common with 5-ASA than placebo
Other treatments to prevent recurrence*	7 (30-218)	Moderate	N/A	Mixed	Direct	Sparse†	Insufficient	No conclusions

Abbreviations: N/A = not applicable, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

* Rifaximin, probiotics, combination 5-ASA and rifaximin, combination 5-ASA and probiotics, and burdock tea
† Each study made a unique comparison.

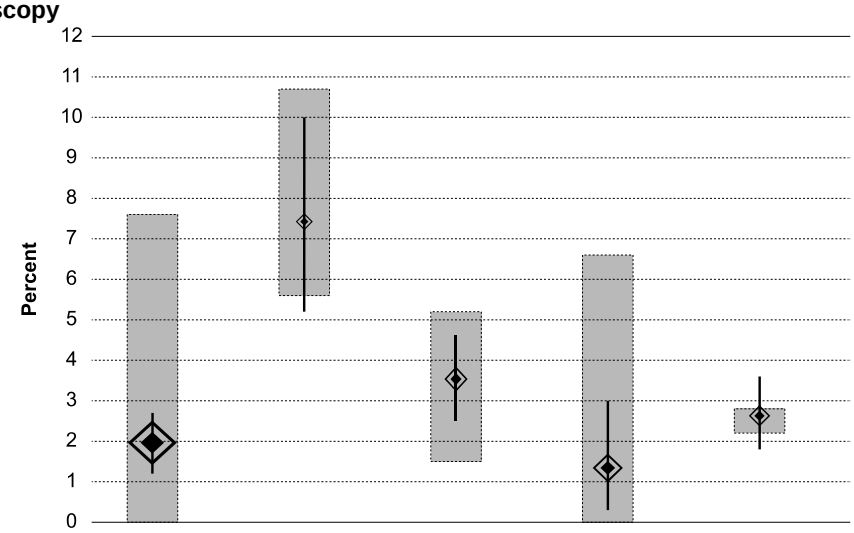
Table 3. Evidence profile for elective surgery

Topic	Outcome	No. Studies (Subjects)	Risk of Bias	Consistency	Precision	Directness	Other	Overall SoE	Conclusion statements
Elective surgery vs. nonoperative management	Death	3 (7288)	Moderate	Unclear*	Precise	Direct	None	Insufficient †	No conclusion regarding surgery vs. no surgery. Rare events.
	Recurrence	3 (7288)	Moderate	Consistent	Precise	Direct	None	High ‡	Elective surgery has lower recurrence OR 0.16 (0.09, 0.27) #
	Length of hospital stay	2 (7179)	High	Inconsistent	Imprecise	Direct	Sparse	Insufficient	No conclusion regarding surgery vs. no surgery.
Adverse events	Total serious AE	4 (2928)	Low	Inconsistent	Imprecise	Indirect §	None	Insufficient	Estimate unclear
	30-day mortality	9 (199,915)	Low	Inconsistent	Precise	Direct	None	Moderate	0.7% (0.3, 1.4)
	Reoperation	6 (49,004)	Low	Inconsistent	Imprecise	Direct	None	Low	5.5% (3.1, 8.5)
	Anastomotic leakage	6 (15,367)	Low	Inconsistent	Imprecise	Direct	None	Low	4.3% (2.2, 6.9)
	Sepsis	7 (82,597)	Low	Inconsistent	Precise	Direct	None	Moderate	1.6% (1.0, 2.3)
	Site infection	4 (3272)	Low	Inconsistent	Precise	Direct	None	Moderate	1.4% (0.8, 1.9)
	MI	5 (65,459)	Low	Inconsistent	Precise	Direct	None	Moderate	0.7% (0.1, 1.6)
	DVT	4 (36,970)	Low	Inconsistent	Precise	Direct	None	Moderate	0.6% (0.2, 1.1)
	Pulmonary embolism	5 (43,818)	Low	Inconsistent	Precise	Direct	None	Moderate	0.3% (0.1, 0.6)
Predictors of AE	Various AE	4 (25,233)	Low	Inconsistent	Imprecise	Direct	Sparse	Insufficient	Estimate unclear

Abbreviations: AE = adverse events, DVT = deep vein thrombosis, MI = myocardial infarction, OR = odds ratio (with 95% confidence interval), SoE = strength of evidence.

* The two RCTs were underpowered, but the NRCS found a very large association.
† Only one unadjusted NRCS provided adequate data. The two RCTs were underpowered, with one death between them. Thus the conclusions are based on a single study only.
‡ Although, the studies had some risk of bias, it was unlikely to be severe enough to change the conclusions of the very strong effect size
# For patients with a history of complicated diverticulitis (2 studies) or smoldering or frequently recurrent diverticulitis after an episode of uncomplicated diverticulitis (1 study). No study evaluated patients with single episode of uncomplicated diverticulitis.
§ It was unclear what was meant by total serious adverse events for several studies.

Figure 1. Summary meta-analysis estimates of colonic lesions found on colonoscopy

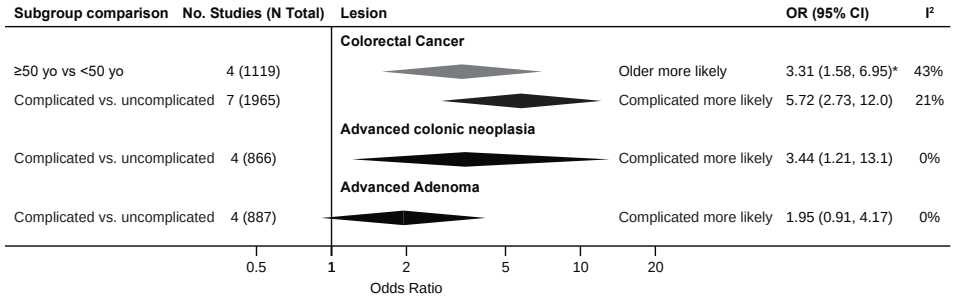


Lesion	CRC	ACN	AA	HGD	≥10 mm
MA est (95% CI)	1.9% (1.2, 2.7)	7.4% (5.2, 10.0)	3.5% (2.5, 4.6)	1.3% (0.3, 3.0)	2.6% (1.8, 3.6)
[Range]	[0-7.6%]	[5.6-10.7%]	[1.5-5.2%]	[0-6.6%]	[2.2-2.8%]
No. studies (Total N)	21 (6325)	3 (766)	6 (1426)	7 (2419)	4 (1210)
I^2	78%	37%	15%	89%	0%

Summary estimates (by meta-analysis) and range of estimates across studies for each lesion. The diamond and vertical line indicate the summary estimate and 95% CI across studies. The size of the diamond is scaled to the total number of individuals across studies. The grey boxes indicate the range of estimates across studies.

Abbreviations: ≥10 mm = large adenomas (≥10 mm), AA = advanced adenoma, ACN = advanced colonic neoplasia, CI = confidence interval, CRC = colorectal cancer, HGD = (adenoma with) high-grade dysplasia, I^2 = estimate of the statistical heterogeneity across studies (which ranges from 0-100%, where higher values indicate greater heterogeneity across studies), MA est = meta-analysis (summary) estimate.

Figure 2. Summary meta-analysis estimates of subgroup analyses

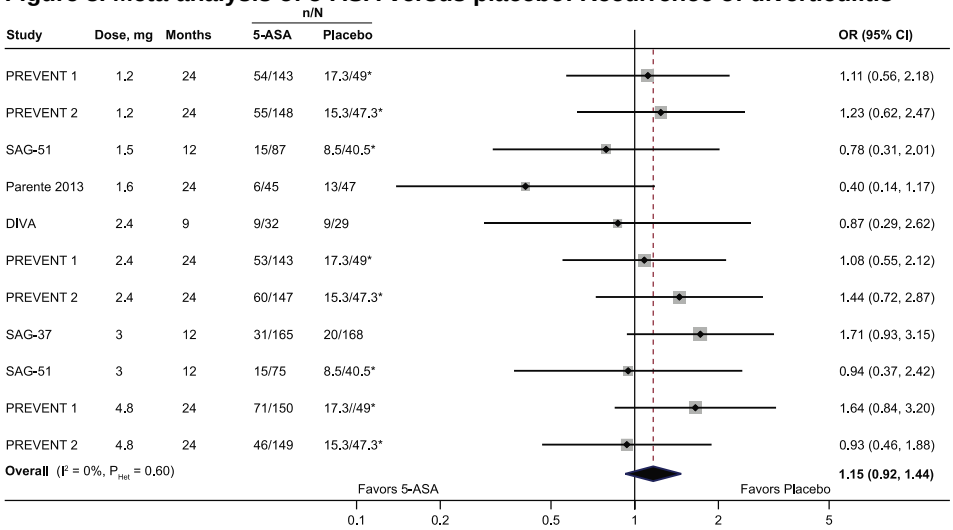


Summary estimates (by meta-analysis) for each subgroup analysis. Each diamond indicates the summary estimate and 95% CI across studies.

Abbreviations: CI = confidence interval, I^2 = estimate of the statistical heterogeneity across studies (which ranges from 0-100%, where higher values indicate greater heterogeneity across studies), OR = odds ratio, yo = years old.

* Peto odds ratio

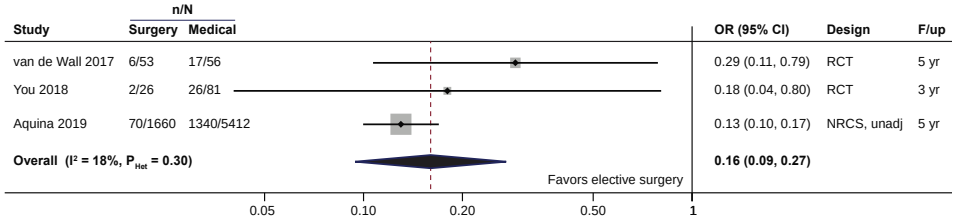
Figure 3. Meta-analysis of 5-ASA versus placebo: Recurrence of diverticulitis



Abbreviations: 5-ASA = 5-aminosalicylic acid, CI = confidence interval, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), mg = milligrams, OR = odds ratio, P_{Het} = statistical heterogeneity P value.

* The numbers of participants in placebo groups were divided by the number of nonplacebo groups to avoid double counting.

Figure 4. Meta-analysis of elective surgery for diverticulitis versus no surgery: Recurrence of diverticulitis



Abbreviations: CI = confidence interval, F/up = followup, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NRCS, unadj = unadjusted nonrandomized comparative study, OR = odds ratio, P_{Het} = statistical heterogeneity P value.

Supplement A. Methods

Literature Search Strategies

Note that the full search strategy included searches for research questions about CT as a diagnostic tool and management of acute diverticulitis. These can be found in Appendix A of the full report (see article for reference).

All searches restricted to January 1990 to November 16, 2020 (final search date)

Medline (via PubMed)
(“Diverticulitis”[Mesh] OR "Diverticulosis, Colonic"[Mesh] OR diverticulitis [tiab] OR diverticulosis [tiab] OR diverticular [tiab])
AND
(Hospital OR hospitals OR hospitalization OR "Hospitalization"[Mesh] OR Inpatient* OR discharge* OR outpatient OR "Ambulatory Care"[Mesh] OR antibiotic* OR "Anti-Bacterial Agents"[Mesh] OR medication* OR medical OR "Radiology, Interventional"[Mesh] OR interventional radiology)

NOT
(“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or "comment on" or ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murinae)

Embase
#30 (#6 OR #28) AND ([article]/lim OR [article in press]/lim)
#29 #6 OR #28
#28 #8 AND #27
#27 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#26 'elective surgery'/de
#25 'lactobacillus casei'/de
#24 'balsalazide'/de
#23 'probiotic agent'/de
#22 'rifaximin'/de
#21 'fiber'/de
#20 'diet therapy'/de
#19 'aminosalicylic acid'/de
#18 'mesalazine'/de
#17 'colonography'/de
#16 'colonoscopy'/de
#15 'interventional radiology'/de

#14 'drug therapy'/de
#13 'antibiotic agent'/de
#12 'ambulatory care'/de
#11 'outpatient'/de
#10 'hospital patient'/de
#9 'hospitalization'/de
#8 #1 OR #2Diverticulitis
#7 #4 AND #5 AND ([article]/lim OR [article in press]/lim)
#6 #4 AND #5
#5 #1 OR #2 OR #3
#4 'computer assisted tomography'/de
#3 'acute abdomen'/de
#2 'diverticulosis'/de
#1 'diverticulitis'/de

Cochrane
((Diverticulitis OR diverticulosis OR diverticular OR “acute abdomen” OR ((acute or nonspecific OR non-specific OR emergen*) AND (abdome* OR abdomi*) AND pain) OR peritonitis)
AND
(“CT scan” OR “cat scan” OR tomography)) OR (Diverticulitis OR diverticulosis OR diverticular)

CINAHL 1961 to June 1, 2020
((Diverticulitis OR diverticulosis OR diverticular OR “acute abdomen” OR ((acute or nonspecific OR non-specific OR emergen*) AND (abdome* OR abdomi*) AND pain) OR peritonitis) AND (“CT scan” OR “cat scan” OR tomography))
OR
(Diverticulitis OR diverticulosis OR diverticular)

Inclusion/Exclusion Criteria Details

Study Eligibility Criteria for Colonoscopy (Full Report Key Question 3)

Population(s)

- Adults with history of (resolved) acute diverticulitis
- Exclude: Active diverticulitis
- Exclude: History of related condition (only), e.g., complicated diverticulosis, SUDD
- Exclude: Meckel's diverticula (unless concurrent acute diverticulitis)
- Exclude: Non-colonic diverticulitis

Interventions:

- Elective colonoscopy (full colon)
- Elective CT colonography

Comparators:

- No colon cancer screening
- Flexible sigmoidoscopy and barium enema
- Limited colonoscopy (e.g., left-sided)
- Virtual colonoscopy
- Stool guaiac testing (etc.)
- Other colon cancer screens (e.g., DNA tests)
- Different intervals, Different initial colonoscopy timing after acute episode
- No comparator

Outcomes:

- Colorectal cancer death
- Colorectal cancer
- High-risk colonic premalignant lesions
  - Adenoma, high grade dysplasia
  - Adenoma ≥10 mm
  - Adenoma, villous
  - Serrated polyp
- Tolerance, feasibility, and completion of procedure; technical adequacy
- Harms, adverse events, and side effects of colonoscopy (e.g. perforation, bleeding)

Modifiers/Subgroups of interest:

- Patient characteristics (e.g., age, family history)
- Course of illness (e.g., prior complicated vs. uncomplicated diverticulitis)
- Alarm symptoms
- Other factors (e.g., timing since last episode of acute diverticulitis)

Timing:

- Start of colorectal cancer screening after resolution of acute disease

Setting:

- Outpatient

Design:

- Randomized controlled trials
  - N≥10/arm

- Nonrandomized comparative studies
  - No restriction based on analytic methods
  - Including comparisons with healthy (non-diverticulitis) people
  - N≥200 (total)
- Single group studies
  - N≥200 (receiving colonoscopy or CT colonography)
- Case-control studies
  - Including comparisons with healthy (non-diverticulitis) people
  - N≥100/arm
- Prospective or retrospective
- Publication since 1990
- Exclude: Case reports (and series of case reports)

Study Eligibility Criteria for Prevention of Recurrence (Full Report Key Question 4)

Population(s):

- Adults with history of (resolved) acute diverticulitis
- Exclude: Ongoing acute diverticulitis
- Exclude: History of related condition (only), e.g., complicated diverticulosis, SUDD
- Exclude: Meckel's diverticula (unless concurrent acute diverticulitis)
- Exclude: Non-colonic diverticulitis

Interventions:

- Pharmacological treatments
  - Any class, route, regimen, treatment duration, or initiation time
- Non-pharmacological interventions
  - Any class/type, route/method, regimen, treatment duration, or initiation time
- Elective surgery
  - Laparoscopic, open, robot-assisted, or any other type of colon surgery conducted as an elective (non-emergent) procedure
- Exclude: Natural history or undefined/unspecified intervention or undefined/unspecified comparator

Comparators:

- Pharmacological and non-pharmacological intervention comparisons:
  - Alternative pharmacologic or non-pharmacologic intervention (or regimen)
    - Pharmacologic vs. non-pharmacologic intervention
    - Other class/type
    - Other intervention within class/type
    - Same intervention different treatment duration
    - Same intervention, different initiation time
  - No intervention
    - Placebo
    - "Usual care" (needs to be defined)
- Elective surgery comparisons:
  - No or deferred elective surgery
  - Exclude: Comparisons with other surgical approaches or techniques

- All:
    - Exclude: Natural history or undefined/unspecified intervention or comparator

Outcomes:

- Recurrent diverticulitis
- Acute complicated diverticulitis
- Surgery for diverticulitis (avoidance; except for elective surgery comparisons)
    - Including colostomy (avoidance)
- Hospitalization for diverticulitis or diverticulitis-related complications (e.g., fistula, stricture)
- Quality of life/Functional outcomes
- All categorical "effectiveness" outcomes include time to outcome
- Harms, adverse events, or side effects of interventions (e.g., surgical complications)
    - From single-group studies of elective surgery, only serious, major, or clinically important adverse events/complications

Modifiers/Subgroups of interest:

- Patient characteristics (e.g., age)
- Course of illness (e.g., prior complicated vs. uncomplicated diverticulitis)
- Other factors (e.g., time since last episode of diverticulitis)

Timing:

- No minimum duration of follow-up
- Hospitalization, unit stay, post-hospitalization

Setting:

- Inpatient, emergency department (or equivalent), outpatient

Design:

- Randomized controlled trials
    - N≥10/arm
- Nonrandomized comparative studies
    - Restrict to studies that use modeling or other analytic methods to minimize selection bias (due to inherent differences between people who receive one or the other intervention)
    - N≥30/arm
- Single group studies
    - Only for adverse events
    - Elective surgery
        - N≥500
    - Other interventions
        - N≥100
- Longitudinal (Exclude: cross-sectional)
- Prospective or retrospective
- Publication since 1990
- Exclude: Case reports (and series of case reports)

Data Synthesis and Analysis (Details)

Meta-Analysis

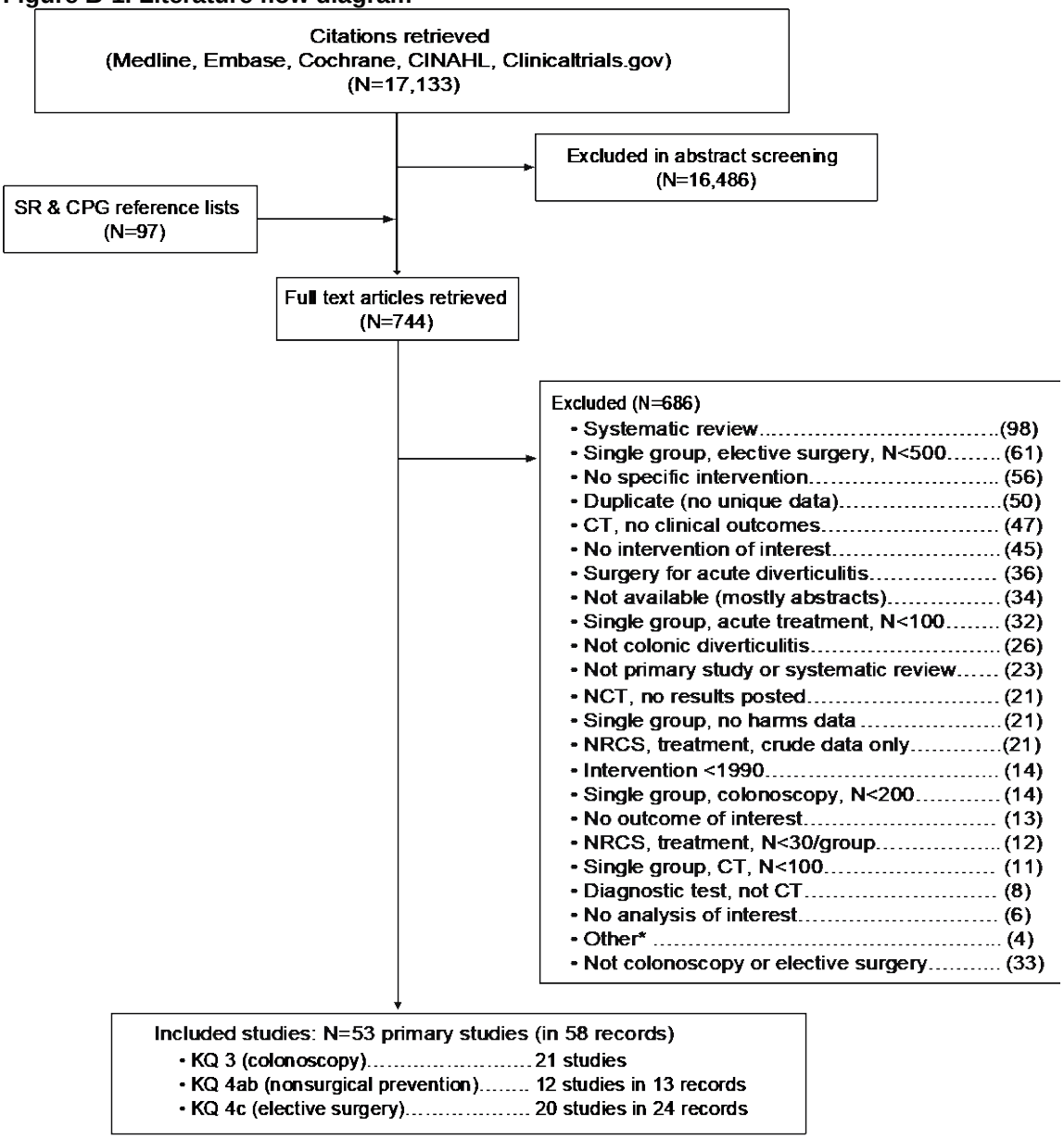
For the colonoscopy topic, we conducted REML meta-analyses of ORs for comparisons between groups (either study groups or subgroups). In one instance, with very rare events across studies, we estimated the summary Peto OR, also in metaan. To combine estimates of proportions, we used the Freeman-Tukey double arcsine transformation to overcome the nonnormal distribution of proportion estimates (because values are truncated at 0). Proportions were converted to percentages. For this, we used the metaprop program in Stata 15.1.

For the elective surgery topic, we meta-analyzed all included adverse events, regardless of the clinical heterogeneity between studies (or groups). As an example, we meta-analyzed adverse events from studies that evaluated different types of elective surgery. In addition, we ran meta-analyses of only two studies. The proportions (adverse event rates) were again meta-analyzed with the Freeman-Tukey double arcsine transformation.

Supplement B

Search Results

Figure B-1. Literature flow diagram



Abbreviations: CPG = clinical practice guideline, CT = computed tomography (imaging), KQ = Key Question, NCT = ClinicalTrials.gov record, NRCS = nonrandomized comparative study, SR = systematic review.

* CT of pre-diagnosed groups, not for diagnosis or staging (N=1); randomized controlled trial, N<10/arm (N=1); antibiotics used for both complicated and uncomplicated diverticulitis, not separated (N=1); study design not of interest, focus group (N=1).

Study Design Details and Arms, Risk of Bias

Colonoscopy (Key Question 3)

Table B-3-1. KQ3 Design Details

Author, Year, PMID, Country	Study Design	Funder	Years	Inclusion criteria	Exclusion criteria
Abdulazeez, 2020, 32820657, UK	NRCS, Retrospective	Not reported (or unclear)	2016, 2019	Left-sided acute diverticulitis, ≥18 years, follow-up colonoscopy or flexible sigmoidoscopy	Extensive or right-sided diverticulitis
Alcantar, 2019, 31720142, USA	Single group, Retrospective	Not reported (or unclear)	2007, 2017	Patients between the ages of 18 and 49 years with acute diverticulitis	Patients without CT verification of diverticulitis, and patients greater than 50 years old were excluded
Andrade, 2017, 27941344, Portugal	Single group,	Not reported (or unclear)	2008, 2013	patients who underwent a colonoscopy within 1 year after the conservative management of CT-proven acute diverticulitis	emergency surgery, incomplete colonoscopy
Brar, 2013, 24105001, Canada	Single group, Retrospective	Not reported (or unclear)	2007, 2010	patients successfully treated nonoperatively for acute left-sided diverticulitis, and all endoscopy reports before index admission and within 1 year after admission	patients underwent endoscopies more than 1 year after admission, patients underwent complete colonoscopy within the 2 years before admission
Choi, 2014, 24723071, S Korea	NRCS, Retrospective	Not reported (or unclear)	2001, 2013	underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from among healthy individuals who underwent screening colonoscopy.	colorectal cancer, colorectal surgery, underwent colonoscopy 1 year prior to the diagnosis of diverticulitis.

Author, Year, PMID, Country	Study Design	Funder	Years	Inclusion criteria	Exclusion criteria
Daniels, 2015, 25472747, Netherlands	NRCS, Retrospective	Non-industry (fully)	2009, 2013	Primary colonoscopy screening population: Only those participants who were randomly invited for primary colonoscopy screening and decided to participate were included in the current study, 50-75 years. Uncomplicated Diverticulitis Population: adult patients, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial. Patients who had undergone follow up colonoscopy within 6 months were included int his study.	Primary colonoscopy screening population: not willing to participate Uncomplicated Diverticulitis Population: excluded based on DIABOLO trial exclusion criteria
Elmi, 2013, 23701063, USA	Single group, Retrospective	Not reported (or unclear)	2000, 2004	>49 years, acute diverticulitis, evaluation of the colon using colonoscopy	history of colorectal cancer
Horesh, 2016, 27170283, Israel	Single group, Retrospective	Not reported (or unclear)	2008, 2012	patients admitted for a first episode of acute diverticulitis diagnosed based on clinical signs and CT findings and were successfully treated conservatively	patients who underwent colonoscopy during the year prior to presentation
Khoury, 2019, 30632029, Israel	Single group, Retrospective	Not reported (or unclear)	2014, 2018	>16 years, acute diverticulitis, patients who underwent colonoscopy in the period of 6 months following the diagnosis with acute diverticulitis, or patients who performed virtual CT colonography in the case of contraindication to colonoscopy.	Exclusion criteria included patients with undetermined diagnosis of acute diverticulitis; patient who did not complete colonoscopy in the scheduled time; history of inflammatory bowel conditions such as inflammatory bowel disease, collagenous colitis, microscopic colitis, and eosinophilic colitis; patients with oncological diseases; and patients with immunosuppressive therapy.
Lahat, 2007, 17554647, Israel	RCT	Not reported (or unclear)	2004, 2006	All patients underwent abdominal CT, and only those with characteristic findings on CT compatible with the diagnosis of acute diverticulitis	Patients with CT findings of pericolonic air or fluid adjacent to a diverticulum and, obviously, patients with free perforation; patients with a lesion seen on CT scan that was suspicious of colonic cancer; patients who had undergone a colonoscopy within the year prior to the current episode of acute diverticulitis
Lau, 2011, 21904141, Australia	NRCS, Retrospective	Not reported (or unclear)	2003, 2009	diverticulitis confirmed by CT, colonoscopy patients only included who had a follow up colonoscopy within 1 year from the date of CT scan	colonoscopy >1 year from the date of CT scan

Author, Year, PMID, Country	Study Design	Funder	Years	Inclusion criteria	Exclusion criteria
Lecleire, 2014, 25083288, France	NRCS, Retrospective	Non-industry (fully)	2005, 2011	Group 1: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode Group 2: sex and age matched with a familial history of colorectal adenoma or neoplasia	patients with haematochezia, recent change in bpwel habits, personal history of colorectal neoplasia, undergone colonoscopy within the 2 years before the episode of diverticulitis
Meireles, 2015, 26378691, Portugal	Single group, Retrospective	Not reported (or unclear)	2004, 2013	patients subjected to endoscopy following the primary episode of diverticulitis	patients with a history of colorectal cancer, diverticular bleeding, or who underwent emergency surgery
O'Donohoe, 2019, 31882879, United Kingdom	Single group, Retrospective	Not reported (or unclear)	2014, 2017	Patients over the age of 18 with CT-diagnosed uncomplicated left-sided diverticulitis (with a modified Hinchey classification of 0 or 1a), admitted 2014–2017, with a follow-up colonoscopy 4–6 weeks after admission	Patients with right sided diverticulitis or complicated diverticulitis
Ramphal, 2018, 29945147, Netherlands	Single group, Retrospective	Not reported (or unclear)	2008, 2013	Hinchey 0 and 1	Hinchey II-IV, previous colorectal cancer, previous episodes of diverticulitis
Sallinen, 2014, 24178863, Finland	NRCS, Retrospective	Not reported (or unclear)	2006, 2010	Clinically and CT diagnosed acute diverticulitis	NR
Schout, 2012, 23171930, Netherlands	Single group, Retrospective	Not reported (or unclear)	2000, 2010	Patients who underwent radiological or surgical abscess drainage only without colon resection	patients who underwent surgical treatment, had a history of colon cancer, had another underlying disease which caused an intra-abdominal abscess, or underwent colonoscopy in the diagnostic process of the episode of diverticulitis
Seoane Urgorri, 2018, 29900742, Spain	Single group, Retrospective	Not reported (or unclear)	2005, 2013	Colonoscopy performed after CT-confirmed diagnosis of acute diverticulitis.	Endoscopy within 2 years prior to episode of acute diverticulitis
Soh, 2018, 29663068, Singapore	NRCS, Retrospective	Not reported (or unclear)	2007, 2011	first episode of CT-proven acute diverticulitis with no complications	NR
Studniarek, 2019, 31908222, USA	Single group, Retrospective	Not reported (or unclear)	2005, 2017	A history of acute diverticulitis as the indication for the colonoscopy, and colonoscopy performed within one year from the initial diagnosis of diverticulitis	NR

Author, Year, PMID, Country	Study Design	Funder	Years	Inclusion criteria	Exclusion criteria
Suhardja, 2017, 28035461, Australia	Single group, Retrospective	Not reported (or unclear)	2011, 2013	Patients diagnosed with acute colonic diverticulitis on CT scan and received follow-up colonoscopy	NR

NR: Not reported

Table B-3-2. KQ 3 Arm Details

Author, Year, PMID, Country	Arm	Colon imaging type	Time since bout of diverticulitis, Mean (SD)
Abdulazeez, 2020, 32820657, UK	Colonoscopy	Full colonoscopy 100%	NR
Abdulazeez, 2020, 32820657, UK	Flexible sigmoidoscopy	Flexible sigmoidoscopy, 100%	NR
Alcantar, 2019, 31720142, USA	Colonoscopy	Full colonoscopy 100%	
Andrade, 2017, 27941344, Portugal	Colonoscopy	Full colonoscopy 100%	16 weeks (11.4 weeks)
Brar, 2013, 24105001, Canada	Colonoscopy	Full colonoscopy 98.4%; Flexible sigmoidoscopy 1.6%;	Median 90 days
Choi, 2014, 24723071, S Korea	Diverticulitis with colonoscopy	Full colonoscopy 100%	
Choi, 2014, 24723071, S Korea	Healthy sex matched controls	Full colonoscopy 100%	
Daniels, 2015, 25472747, Netherlands	Diverticulitis patients (DIABOLO trial)	Full colonoscopy 100%	Median 55 days
Daniels, 2015, 25472747, Netherlands	Screening individuals (COCOS trial)	Full colonoscopy 100%	
Elmi, 2013, 23701063, USA	Colonoscopy	Full colonoscopy 100%	5.3 years; 34.8% in first 6 months
Horesh, 2016, 27170283, Israel	Colonoscopy	Full colonoscopy	Median 3.25 months (range 0.5, 24 months)
Khoury, 2019, 30632029, Israel	Colonoscopy	Full colonoscopy; CT colonography (if there is a contraindication to colonoscopy)	6 months after the diagnosis of acute diverticulitis
Lahat, 2007, 17554647, Israel	Colonoscopy (early; in-hospital)	Full colonoscopy 100%	Median 5.2 days (range 3, 11)
Lahat, 2007, 17554647, Israel	Colonoscopy (late, 6 weeks later)	Full colonoscopy 100%	Median 7.8 days (range 6, 19)
Lau, 2011, 21904141, Australia	Colonoscopy	Full colonoscopy 95%; Flexible sigmoidoscopy 5%; incomplete colonoscopy 6.6%	
Lau, 2011, 21904141, Australia	No colonoscopy	No record of colonoscopy available	
Lecleire, 2014, 25083288, France	Acute diverticulitis	Full colonoscopy	
Lecleire, 2014, 25083288, France	Sex and age matched controls	Full colonoscopy	
Meireles, 2015, 26378691, Portugal	Colonoscopy	Full colonoscopy	Median 4.0 months (IQR 1.2, 7.1)
O'Donohoe, 2019, 31882879, United Kingdom	Colonoscopy	Full colonoscopy 100%	Median 37 days (range 27, 68)
Ramphal, 2018, 29945147, Netherlands	Colonoscopy		The patients who underwent colonoscopy between 6 weeks and 3 months after their acute episode of diverticulitis were eligible for analysis.
Sallinen, 2014, 24178863, Finland	Colonoscopy	Full colonoscopy 100%	122 days (180 days)

Author, Year, PMID, Country	Arm	Colon imaging type	Time since bout of diverticulitis, Mean (SD)
Sallinen, 2014, 24178863, Finland	No colonoscopy	Numerous reasons, including prior colonoscopy within or beyond 2 years, patient declined, patient "too old/frail", no record of colonoscopy performed, others	
Schout, 2012, 23171930, Netherlands	Colonoscopy	Full colonoscopy; Flexible sigmoidoscopy; Barium enema; CT colonography	6-10 weeks after discharge
Seoane Urgorri, 2018, 29900742, Spain	Colonoscopy	Full colonoscopy 100%	Median 6-7 weeks
Soh, 2018, 29663068, Singapore	Colonoscopy	Full colonoscopy 98.5%; Barium enema 0.7%; CT colonography 0.7%	Range 6, 8 weeks
Soh, 2018, 29663068, Singapore	No colonoscopy	Did not have scheduled colonoscopy	
Studniarek, 2019, 31908222, USA	Colonoscopy	Full colonoscopy 100%	
Suhardja, 2017, 28035461, Australia	Colonoscopy	Full colonoscopy 100%	100% in first year

Table B-3-3. KQ3 Baselines

Author, Year, PMID, Study Name, Country	Arm	Male %	Participant age, mean (SD)	Age ≥50, %	Complicated/ Uncomplicated diverticulitis %
Abdulazeez, 2020, 32820657, UK	Colonoscopy	35	70 (10.2) [range 46, 90]	NR	NR
Abdulazeez, 2020, 32820657, UK	Flexible sigmoidoscopy	37	72 (13.9) [range 28, 91]	NR	NR
Alcantar, 2019, 31720142, USA	Colonoscopy	60.3	40.7	NR	22.5/77.5
Andrade, 2017, 27941344, Portugal	Colonoscopy	49.2	Median 55 [IQR 11.1]	NR	NR
Brar, 2013, 24105001, Canada	Colonoscopy	49	55 [range 27, 90]; 63.5% >55	63.5	29.7/70.3
Choi, 2014, 24723071, S Korea	Diverticulitis with colonoscopy	59.7	48.6 (16.5)	NR	14.1/85.9
Choi, 2014, 24723071, S Korea	Healthy sex matched controls	59.9	46.6 (16.6)	NR	8.2/91.8
Daniels, 2015, 25472747, Netherlands	Diverticulitis patients (DIABOLO trial)	47.6	Median 57 [range 49, 65]	NR	NR
Daniels, 2015, 25472747, Netherlands	Screening individuals (COCOS trial)	50.9	Median 60 [range 55, 65]	NR	NR
Elmi, 2013, 23701063, USA	Colonoscopy	42	100% >55	100	NR
Horesh, 2016, 27170283, Israel	Colonoscopy	45.4	62.6 [range 21, 98]; 30.6% >55	30.6	18.5/81.5
Khoury, 2019, 30632029, Israel	Colonoscopy	62	55.73 (13.81) [range 24, 93]	NR	NR
Lahat, 2007, 17554647, Israel	Colonoscopy (early)	31.1	60.5 (11.4)	NR	NR
Lahat, 2007, 17554647, Israel	Colonoscopy (late)	34.1	60.3 (14.7)	NR	NR

Author, Year, PMID, Study Name, Country	Arm	Male %	Participant age, mean (SD)	Age ≥50, %	Complicated/ Uncomplicated diverticulitis %
Lau, 2011, 21904141, Australia	Colonoscopy	53	15-39y: 7.2%, 40-64y: 55.5%, 65+: 37.3%	NR	NR
Lau, 2011, 21904141, Australia	No Colonoscopy	47.6	15-39y: 8.5%, 40-64y: 54.2%, 65+: 37.3%	NR	NR
Lecleire, 2014, 25083288, France	Acute diverticulitis	41	60.9 (12.6)	NR	10.0/90.0
Lecleire, 2014, 25083288, France	Sex and age matched controls	41	60.7 (13.4)	NR	NR
Meireles, 2015, 26378691, Portugal	Colonoscopy	49.6	64.4 (13.5) [range 23, 103]	NR	28.8/81.2
O'Donohoe, 2019, 31882879, UK	Colonoscopy	28	Median 63 (range 29, 90)	NR	0/100
Ramphal, 2018, 29945147, Netherlands	Colonoscopy	NR	59	NR	NR
Schout, 2012, 23171930, Netherlands	Colonoscopy	NR	NR	NR	NR
Seoane Urgorri, 2018, 29900742, Spain	Colonoscopy	48	59 (15)	NR	27/73
Studniarek, 2019, 31908222, USA	Colonoscopy	51	Median 53 (range 22, 88)	NR	NR
Suhardja, 2017, 28035461, Australia	Colonoscopy	46.1	59.3	NR	27.4/72.6

NR = Not reported

Table B-3-4. KQ 3 Risk of Bias

Author, Year, PMID, Country	Adjusted results in arm (subgroup) differences reported	Eligibility/selection criteria prespecified	Clear outcome definition
Colonoscopy	No	Yes	Yes
Flexible sigmoidoscopy	No	Yes	Yes
Andrade, 2017, 27941344, Portugal	Yes*	Yes	Yes
Brar, 2013, 24105001, Canada	Yes*	Yes	Yes
Choi, 2014, 24723071, S Korea	Yes*	Yes	Yes
Daniels, 2015, 25472747, Netherlands	Yes †	Yes	Yes ‡
Elmi, 2013, 23701063, USA	No	Yes	Yes
Horesh, 2016, 27170283, Israel	No	Yes	Yes
Khoury, 2019, 30632029, Israel	No	Yes	Yes
Lahat, 2007, 17554647, Israel	No	Yes	Yes
Lau, 2011, 21904141, Australia	No	Yes	Yes ‡
Lecleire, 2014, 25083288, France	No	Yes	Yes ‡
Meireles, 2015, 26378691, Portugal	No	Yes	Yes ‡
O'Donohoe, 2019, 31882879, United Kingdom	No	Yes	Yes
Ramphal, 2018, 29945147, Netherlands	No	Yes	Yes
Sallinen, 2014, 24178863, Finland	No	Yes	Yes ‡
Schout, 2012, 23171930, Netherlands	No	Yes	Yes
Seoane Urgorri, 2018, 29900742, Spain	No	Yes	Yes
Soh, 2018, 29663068, Singapore	No	Yes	Yes
Studniarek, 2019, 31908222, USA	No	Yes	Yes
Suhardja, 2017, 28035461, Australia	No	Yes	Yes ‡

Abbreviations: KQ = Key Question, PMID = PubMed Identifier.

Ratings are color coded for emphasis only. Each item rated as Yes (lower risk of bias) or No (higher risk of bias).

* Conducted multivariable analyses for the outcome of advanced colonic neoplasia.
† Adjusted (e.g., age, family history of CRC) for the outcome of advanced adenomas.
‡ Did not define the outcome of high-grade dysplasia.

Nonsurgical Prevention of Recurrence (Key Questions 4a-b)

Table B-4ab-1. KQ 4ab Design Details and Arms

Study, Year, PMID, Country, Funding	Design	Population description	Arm	Arm Details	Age Sex	Number of Prior Episodes
Festa, 2017, 28387885, Italy, NR	NRCS (Retrospective)	≥18 yr, with ≥1 documented episode of acute diverticulitis in the previous 24 mo that resolved w/o surgery. History of IBD and prior abdominal surgery excluded.	Rifaximin	800 mg/d, 10 d/mo	≤65 years 45.8, >65 years 54.2, 47.2% male	One 86.1% Two or more 13.9%
			5-ASA	2.4 g/d, 10 d/mo	≤65 years 51.9, >65 years 48.1, 42.3% male	One 90.4% Two or mroe 9.6%
Kruis, 2017, 28543263, SAG-37, Germany, NR	RCT	40-80 yr old w/left-sided uncomplicated acute diverticulitis confirmed by CT or ultrasonography w/≥1 diverticulum in left colon	5-ASA (3.0 g/d)	3.0 g/d	Mean 58.8 SD 9.1 38.2% male	One 55.8% Two 30.9% Three or more 6.7%
			Placebo		Mean 58.3 SD 9.5 44% male	One 54.2% Two 30.4% Three or more 5.4%
Kruis, 2017, 28543263, SAG-51, USA/Germany, NR	RCT	30-80 yr old w/left-sided uncomplicated acute diverticulitis confirmed by CT or ultrasonography w/≥1 diverticulum in left colon	5-ASA (1.5 g/d)	1.5 g/d	Mean 55.6 SD 10.4 30.9% male	One 53.7% Two 29.3% Three or more 5.7%
			5-ASA (3.0 g/d)	3.0 g/d	Mean 55.2 SD 11.3 43.3% male	One 53.3% Two 26.7% Three or more 7.7%
			Placebo		Mean 55.4 SD 10.3 44.1% male	One 46.8% Two 36.9% Three or more 9.0%
Kvasnovsky, 2017, 28528364, International, Industry	RCT	Abdominal symptoms ≥3 mo w/uncomplicated diverticulitis	Probiotics Symprove	1 mL/kg/d	Median 60 (IQR 52, 72) 55.6% male	NR

Study, Year, PMID, Country, Funding	Design	Population description	Arm	Arm Details	Age Sex	Number of Prior Episodes
			Placebo		Median 63.5 (IQR 54, 72.5) 44.4% male	NR
Lanas, 2013, 23092785, Spain, Industry	RCT	≥18 years w/≥1 acute diverticulitis in remission at enrollment. Acute ep at recruitment excluded.	Rifaximin	Rifaximin (800 mg/d) + fiber 3.5 g/d	53.6 (12.0) 66.2% male	At least one: 100%
			Placebo	Placebo + fiber 3.5 g/d	54.7 (13.2) 62.5% male	At least one: 100%
Mizuki, 2019, 31043657, Japan, NR	RCT	Diagnosed with CDB or uncomplicated ACD and aged between 20-85 years	Burdock tea	NR	Mean 48 (Range 24, 82) 55.3% male	At least one: 18%
			No intervention (non-placebo)		Mean 53 (Range 27, 79) 47.7% male	At least one 8%
Parente, 2013, 23754545, Italy, Industry	RCT	18-85 yo w/diverticular disease of left colon and/or ep. Of uncomplicated diverticulitis. Complicated diverticulitis excluded.	5-ASA	800 mg 2/d for 10 d/mo	Mean 61.9 (Range 35, 80) SD 10 44.4% male	None 100%
			Placebo		Mean 61.1 (Range 23, 84) SD 12.2 53.2% male	None 100%
Raskin, 2014, 25038431, PREVENT-1, International, Industry	RCT	1 documented episodes of acute diverticulitis in the previous 24 mo that resolved w/o colonic resection, and w/o signs/symptoms of diverticulitis within 6 wks of enrollment. Confirmation of diverticulosis via endoscopic evaluation of the sigmoid colon w/at ≥3 diverticula noted	5-ASA (1.2 g/d)	1.2 g/d	55.3 (11.39) 52.8% male	None 0.3% One 58.1% Two 25.4% Four or five 5.5% Six to ten 2.1
			5-ASA (2.4 g/d)	2.4 g/d		
			5-ASA (4.8 g/d)	4.8 g/d		

Study, Year, PMID, Country, Funding	Design	Population description	Arm	Arm Details	Age Sex	Number of Prior Episodes
			Placebo	Daily		
Raskin, 2014, 25038431, PREVENT-2, International, Industry	RCT	1 documented episodes of acute diverticulitis in the previous 24 mo that resolved w/o colonic resection, and w/o signs/symptoms of diverticulitis within 6 wks of enrollment. Confirmation of diverticulosis via endoscopic evaluation of the sigmoid colon w/at ≥3 diverticula noted	5-ASA (1.2 g/d)	1.2 g/d	Mean 56.1 SD 11.04 46.4% male	None 0.5% One 59.7% Two 22.7% Four to Five 5.8% Six to Ten 1.9%
			5-ASA (2.4 g/d)	2.4 g/d		
			5-ASA (4.8g/d)	4.8 g/d		
			Placebo	Daily		
Silva Sanchez, 2014, International, NR	Single-group (Unclear)	NR (abstract)	5-ASA (4.8 g/d)	4.8 g/d	NR	NR
Stollman, 2013, 23426454, DIVA, USA, Industry	RCT	35-85 yr old, acute diverticulitis (first, second, or third attack) confirmed by CT scan, a GSS score ≥12 at baseline, an abdominal pain assessment score >2. Patients initially enrolled with acute diverticulitis, but randomization occurred after resolution, up to 14 days later	5-ASA + Probiotic (*Bifidobacterium infantis* 35624)	5-ASA 2.4 g/day + Probiotic: 1/day, 12 wk	Mean 59.1 SD 10.1 47.2% male	None 52.8% One 22.2% Two 25.0%
			5-ASA	2.4 g/day, 12 wk	Mean 57.7 SD 12.8 42.5% male	None 45.0% One 35.0% Two 20.0%
			Placebo	Placebos for 5-ASA and for probiotic, 12 wk	Mean 56.1 SD 11.1 53.7% male	None 51.2% One 34.1% Two 14.6%
Tursi, 2002, 12236485, Italy, NR	RCT	Diverticulitis w/≥2 attacks of acute diverticulitis in previous yr	5-ASA + Rifaximin	5-ASA (1.6 g/d) + rifaximin (800 mg/d), 7 d/mo†	Mean 66.5 59% male	Two: 82.6% Three or more: 17.4%
			Rifaximin	Rifaximin (800 mg/d), 7 d/mo	Mean 62.1 61.4% male	Two: 84.4% Three or more: 15.6%
Tursi, 2007, 17390144, Italy, NR	RCT	Uncomplicated acute diverticulitis	5-ASA + Probiotic	Balsalazide (2.25 mg/d), 10 d/mo + VSL#3 (1 bag/d), 15 d/mo*	Mean 60.1 (Range 47, 75)	Two: 83.5% Three or more: 16.5%

Study, Year, PMID, Country, Funding	Design	Population description	Arm	Arm Details	Age Sex	Number of Prior Episodes
			Probiotics	VSL#3 (1 bag/d), 15 d/mo*		

d = day, wk = weeks, mo = month, NR = not reported, PMID = PubMed identifier, y = years, g/d = grams/per day, * = During the first 10 days of treatment, patients in both groups also took rifaximin 800 g/d., † During the first 7 days of tresatment, 5-ASA 2.4 g/d + rifaximin 800 mg/d vs. rifaximin 800 mg/d.

Table B-4ab-2. KQ 4ab Risk of Bias RCTs

Author, Year, PMID, Study Name, Country	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personel, care providers, outcome assessor	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)	Other bias
Kruis, 2017, 28543263, SAG-37, Germany	Low	Low	Low	Low	Low	Low
Kruis, 2017, 28543263, SAG-57, USA/Germany	Low	Low	Low	Low	Low	Low
Kvasnovsky, 2017, 28528364, International	High	High	High	Low	High	Low
Lanas, 2013, 23092785, Spain	Low	Low	High	Low	Low	High
Mizuki, 2019, 31043657, Japan	Low	Low	Low	Low	Low	Low
Parente, 2013, 23754545, Italy	Unclear	Unclear	Low	Low	High	Low
Raskin, 2014, 25038431, PREVENT1, International	Low	Low	Low	Low	Low	Low
Raskin, 2014, 25038431, PREVENT2, International	Low	Low	Low	Low	Low	Low
Stollman, 2013, 23426454, DIVA, USA	Low	Low	Low	High	Low	Low
Tursi, 2002, 12236485, Italy	High	High	High	Low	Low	Low
Tursi, 2007, 17390144, Italy	Unclear	High	High	Low	Low	Low

KQ = Key Question, PMID = PubMed Identifier. Ratings are color coded for emphasis only. See Table B-2a-2 for full legend.

Table B-4ab-3. KQ 4ab Risk of bias NRCSs

Author, year, PMID, Study Name, Country	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personel, care providers, outcome assessor	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)	Were eligibility/selection criteria for the study population prespecified and clearly described?	Was the test/service/intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable,	No bias due to confounding	No bias in selection of participants into the study
Festa, 2017, 28387885, Italy	N/A	N/A	Low	High	High	Yes	Yes	Yes	No	Yes

KQ = Key Question, PMID = PubMed Identifier. Ratings are color coded for emphasis only. See Table B-2a-2 for full legend.

Elective Surgery (Key Question 4c)

Table B-4c-1. KQ 4c Design Details

Author, year, PMID, Study Name, Country	Study Design	Funder	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Aquina, 2019, 30335195, USA	NRCS (Retrospective)	Not reported (or unclear)	2002, 2010	at least 18 years, acute diverticular abscess	laparotomy, laparoscopy, colectomy or stoma creation within 2 days of admission; concurrent diagnosis of colorectal cancer, cirrhosis, or ascites	NR
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA	Single group (Prospective)	Non-industry (fully)	2001, 2013	diverticulitis requiring elective surgery	none	diverticulitis was defined as either a physician-documented or self-reported episode of left lower quadrant abdominal pain and tenderness, with or without fever and leukocytosis.

Author, year, PMID, Study Name, Country	Study Design	Funder	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA	Single group (Retrospective)	Not reported (or unclear)	2005, 2009	patients who underwent sigmoid resection for a diagnosis of diverticulitis	emergent resection	Acute resolving uncomplicated diverticulitis is defined as discrete episodes of left lower quadrant abdominal pain, fever, leukocytosis, and evidence of inflammation on imaging that resolve with conservative management. Chronic/ smoldering uncomplicated diverticulitis is defined as symptoms of left lower quadrant abdominal pain and evidence of inflammation (elevated white blood cell count, fever, CT evidence of inflammation) that does not improve with the traditional antibiotic regimen, or re-exacerbation with cessation of antibiotics, for at least 3 months' duration. Atypical uncomplicated diverticulitis is defined as symptoms of left lower quadrant pain and possible alterations in bowel habits for a period of at least 3 months; however, other clinical and radiographic evidence of diverticulitis is not present.
Bordeianou, 2019, 29916880, PREVENTT, USA	Single group (Prospective)	Not reported (or unclear)	2010, 2016	underwent surgery for diverticulitis	< 18 years of age, underwent a colectomy with a diagnosis of colon or rectal cancer or IBD.	NR
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA	Single group (Retrospective)	Non-industry (fully)	2004, 2011	Procedure codes were used from ICD-9 to identify patients who underwent elective sigmoid resection.	Patients with acute diverticulitis, perforated diverticulitis, preoperative weight loss and metastatic disease were excluded.	Patients with an ICD-9 diagnosis code of diverticulitis were identified. (ICD-9 codes 562.11 and 562.13)
Lidor, 2010, 20878256, USA	Single group (Retrospective)	Non-industry (fully)	2004, 2007	≥65 years old; primary admission diagnosis of diverticulitis by ICD-9	concurrent diagnosis of colorectal cancer	NR
Masoomi, 2011, 21732208, Nationwide Inpatient Sample (2002-2007), USA	Single group (Retrospective)	Non-industry (fully)	2002, 2007	Hospitalizations resulting from elective colon resection were identified with ICD procedure code and then divided into open surgery and laparoscopy groups.	Urgent colon resection	All discharges with International Classification of Disease (ICD) procedure codes [sigmoidectomy (45.76) or anterior resection (48.62, 48.63)] with a primary diagnosis of diverticulitis (codes 562.11 and 562.13) were selected from 2002 to 2007; those patients with the admission code for an elective operation were identified and utilized in the study.

Author, year, PMID, Study Name, Country	Study Design	Funder	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA	Single group (Retrospective)	Not reported (or unclear)	2012, 2013	Diverticulitis who underwent colon re-sections using procedural and diagnosis codes as specified by the ICD 9th Revision.	Underwent colon surgery without colon resection and patients < 18 yo	Colonic diverticulitis based on ICD 9 code 562.11. Colon resection based on Current Procedural Terminology codes: 44140 to 44147, 44204 to 44208, 45110, and 45113.
Novitsky, 2009, 18639223, Nationwide Inpatient Sample (2001-2002), USA	Single group (Retrospective)	Non-industry (fully)	2001, 2002	Patients with ICD codes who underwent elective surgery for diverticulitis.	Patients ?18 years and those with a diagnosis of colon cancer were excluded from the analysis.	Patients with ICD codes for diverticulitis diagnostic codes were identified. Patients with colectomy procedure codes were then cross referenced to obtain patients who underwent elective surgery for diverticulitis.
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA	Single group (Retrospective)	Not reported (or unclear)	2005, 2013	Primary procedure CPT code or one of the secondary CPT codes (from the "other procedure" variables) was for partial colectomy or colostomy.	Cases performed emergently, patients of ASA class 5 or unknown ASA class, cases performed by a surgical specialist in a field other than general surgery, presence of preoperative SIRS, sepsis or septic shock, and preoperative ventilator dependence.	Acute diverticulitis w/o hemorrhage or diverticulosis w/o hemorrhage by ICD-9 codes 562.11 and 562.1.
Perez, 2020, 32748338, New York Statewide Planning and Research Cooperative System (SPARCS), US	Single group (Retrospective)	Non-industry (fully)	2010, 2016	18 years old and older, undergoing elective open or laparoscopic sigmoid or left hemicolectomy (by ICD-9 code) for diverticulitis (by ICD-9 code)	index colectomy were excluded, as well as patients with colon cancer who had been noted to have diverticular disease at any point prior to their colectomy. prior abdominal surgeries, concurrent stoma creations, hernia repairs, or surgeries of the liver, spleen, pancreas, kidneys, or uterus during their index colectomy, abdominal operations during their index admission after their index colectomy, organ space abscess, anastomotic leak, or wound disruption/infection within 30 days after index colectomy; inflammatory bowel disease; chemotherapy within 6 months prior to or after index colectomy; radiation therapy any time prior to or within 6 months after index colectomy; history of rectal, anal, or prostate cancer; and history of congenital abdominal wall defect.	NR
Pessaux, 2004, 14639493, French Association for Surgical Research, France	Single group (Retrospective)	Not reported (or unclear)	1985, 1998	elective sigmoid resection by laparotomy at least 1.5 month after an acute episode of diverticulitis, followed by primary anastomosis with or without protective stoma.	prior colon resection, emergency resection, surgery without resection, resection without primary anastomosis, and patients undergo-ing laparoscopic resection	NR
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA	Single group (Retrospective)	Not reported (or unclear)	2005, 2008	Emergency and nonemergency cardiac and noncardiac surgery. Diverticular disease were identified by ICD-9 codes and then categorized based on procedure type using CPT codes.	Defined by the NSQIP to have undergone emergency surgery. Definition includes patients who had surgery within 12 hours of admission.	Diverticular disease were identified by ICD-9 codes

Author, year, PMID, Study Name, Country	Study Design	Funder	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
Silva-Velazco, 2016, 26541732, USA	Single group (Prospective)	Non-industry (fully)	1992, 2013	elective, restorative procedures for sigmoid diverticulitis performed using a minimally invasive approach	disease presentations requiring urgent surgery	diverticulitis was radiologically confirmed in 1032 patients (97.5 %), while outside preoperative imaging was not available in our institutional records in the remaining 27 patients
Simianu, 2015, 25773308, Surgical Care and Outcomes Assessment Program (SCOAP), USA	Single group (Prospective)	Non-industry (fully)	2010, 2013	underwent laparoscopic colon resection for diverticulitis	none	NR
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany	Single group (Prospective)	Not reported (or unclear)	2005, 2008	all patients with elective laparoscopic sigma resection for diverticulitis	emergency surgery within 24 hours of admission, ileus, perforation, <18 years old, pregnant	NR
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA	Single group (Retrospective)	Not reported (or unclear)	2012, 2013	Chronic diverticular disease or acute diverticulitis	NR	NR
van de Wall, 2017, 28404008, DIRECT trial, Netherlands	RCT	Non-industry (fully)	2010, 2014	patients aged 18–75 years who presented to trial centres with either ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed (ie, seen with CT scan, ultrasonography, or endoscopy) episode of diverticulitis.	1) previous elective or emergency surgery for acute sigmoid diverticulitis, OR 2) an absolute operation indication, OR 3) suspicion of a colorectal malignancy, OR 4) patients classified with a preoperative or postoperative risk of greater than III on the American Society of Anesthesiologists (ASA) classification	The Hinchey classification was used to classify the primary episode of diverticulitis and was based on findings of either CT scan or ultrasonography
Varma, 2019, 30527478, California State Inpatient Database 2005-13, USA	Single group (Retrospective)	Non-industry (fully)	2005, 2011	experienced an initial episode of uncomplicated diverticulitis (562.10, 562.11), were medically managed during their initial presentation, and underwent a bowel resection afterward	diagnoses for malignancy (153, 196, 197, 198), undergoing spinal cord (3.9), thorax (33.2, 34.9), ventral hernia (53.4, 53.5), and salpingo-oophorectomies (65.4, 65.6) procedures; or missing clinical factors	NR
von Strauss und Torney, 2020, 32401298, Switzerland & UK Non-industry	Single group (Retrospective)	Non-industry (fully)	2005, 2015	(ICD-10) diagnosis of primary colonic diverticulitis or diverticulosis in combination with a complication of acute diverticulitis as the primary diagnosis (eg, peritonitis or sepsis), who underwent elective interval resection.	NR	NR

Author, year, PMID, Study Name, Country	Study Design	Funder	Study Dates	Inclusion criteria	Exclusion criteria	How was diverticulitis diagnosed?
You, 2018, 29683483, USA	RCT	Industry (fully or in part)	2011, 2016	≥18 with a first episode of acute diverticulitis of the sigmoid colon complicated by extraluminal air with or without abscess, first treated with successful non-operative management and colonoscopy negative for malignancy.	history of previous diverticulitis of the sigmoid colon; history of diverticulitis of the sigmoid colon, colonic cancer at colonoscopy, immunosuppression, acute diverticulitis of the sigmoid colon complicated by peritonitis and/or distant free air, pregnancy, or inability to sign informed consent.	Not explicitly described

Table B-4c-2. KQ 4c Arm Details

Author, Year, PMID, Study Name, Country	Arm	Surgery type	Time frame of elective surgery in relation to last acute diverticulitis
Aquina, 2019, 30335195, USA	Elective surgery	Colectomy	< 6 months
	No intervention (Nonoperative management)	N/A	NR
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA	Elective surgery	Laparoscopic	NR
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA	Elective surgery (Arm 1: Acute resolving uncomplicated diverticulitis)	Sigmoidectomy (any 24%, laparoscopic 25%, hand-assisted 50%, robot-assisted 0.3%)	NR
	Elective surgery (Arm2: Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy (any 12%, laparoscopic 30%, hand-assisted 56%, robot-assisted 2%)	NR
	Elective surgery (Arm3: Atypical uncomplicated diverticulitis)	Sigmoidectomy (any 15%, laparoscopic 30%, hand-assisted 55%)	NR
Bordeianou, 2019, 29916880, PREVENTT, USA	Elective surgery	Any	NR
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA	Elective surgery	Sigmoidectomy	NR
Lidor, 2010, 20878256, USA	Elective surgery	Left colectomyLeft colectomy with ileostomy	NR
Masoomi, 2011, 21732208, Nationwide Inpatient Sample (2002-2007), USA	Elective surgery (Open surgery)	Open	NR
	Elective surgery (Laparoscopy)	Laparoscopic	NR
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA	Elective surgery (2012-2013)	Open 28%Laparoscopic (72%)	NR
Novitsky, 2009, 18639223, Nationwide Inpatient Sample (2001-2002), USA	Elective surgery	Left colectomy with ostomy	NR
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA	Elective surgery (2005/06)	Laparoscopic approach and ostomy creation, as defined by the CPT code.	NR
	Elective surgery (2007)		NR
	Elective surgery (2008)		NR
	Elective surgery (2009)		NR
	Elective surgery (2010)		NR
	Elective surgery (2011)		NR
	Elective surgery (2012)		NR
	Elective surgery (2013)		NR
Perez, 2020, 32748338, New York Statewide Planning and Research Cooperative System (SPARCS), US	Elective surgery	Open or laparoscopic sigmoid or left hemicolectomy	NR
Pessaux, 2004, 14639493, French Association for Surgical Research, France	Elective surgery (elective laparotomy for colon or rectal resection for diverticulitis)	Sigmoidectomy	> 1.5 months
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA	Elective surgery (Open procedure)	Open	NR
	Elective surgery (Laparoscopic procedure)	Laparoscopic	NR
Silva-Velazco, 2016, 26541732, USA	Elective surgery	Laparoscopic	range 6, 8 weeks
Simianu, 2015, 25773308, Surgical Care and Outcomes Assessment Program (SCOAP), USA	Elective surgery	Laparoscopic	NR
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany	Elective surgery	Laparoscopic	>1 day

Author, Year, PMID, Study Name, Country	Arm	Surgery type	Time frame of elective surgery in relation to last acute diverticulitis
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA	Elective surgery	NR	NR
van de Wall, 2017, 28404008, DIRECT trial, Netherlands	Elective surgery (Laparoscopic surgery)	Sigmoidectomy, laparoscopic	NR
	No intervention (Conservative management treatment: current daily practice)	n/a	NR
Varma, 2019, 30527478, California State Inpatient Database 2005-13, USA	Elective surgery	Any	median 3.8 months (IQR 2.3, 8.1 months; range 30 days, 2 years)
von Strauss und Torney, 2020, 32401298, Switzerland & UK Non-industry	Elective surgery	Any	NR
You, 2018, 29683483, USA	No intervention (Observation)	none	NR
	Elective surgery (underwent elective resection of the sigmoid colon with colorectal anastomosis via a minimally invasive access.)	Laparoscopic	NR

Table B-4c-3. KQ 4c Baselines

Author, year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Specific Complications of Diverticulitis %	Number of Prior Episodes of Diverticulitis, %	Time Since Last Episode of Diverticulitis, Mean (SD)
Aquina, 2019, 30335195, USA	Elective surgery	51.8	White 87.1%, Black 4.8%, Other 5.6%, Unknown 2.5%	Median 56 (IQR 47, 66); <=50 years 35.3, 51-65 years 39.2, >65 years 25.5	.		at least one 16.3	
	No intervention (non-placebo) (Nonoperative management)	46.3	White 74.2%, Black 11.9%, Other 11.1%, Unknown 2.7%	Median 58 (IQR 47, 72); <=50 years 33.8, 51-65 years 30.7, >65 years 35.6	.		at least one 10.0	
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA	Elective surgery	47		55.7	75.9/24.1	abscess 8.3, perforated diverticulitis 0.7, stricture 3.6, immunocompromised 0.5	Mean 3.1 [range 1, 12]	
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA	Elective surgery (Arm 1: Acute resolving uncomplicated diverticulitis)	45		Median 63			Median 3 [range 1, 15]	
	Elective surgery (Arm2: Chronic/ smoldering uncomplicated diverticulitis)	38		Median 66				

Author, year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Specific Complications of Diverticulitis %	Number of Prior Episodes of Diverticulitis, %	Time Since Last Episode of Diverticulitis, Mean (SD)
	Elective surgery (Arm3: Atypical uncomplicated diverticulitis)	37		Median 64				
Bordeianou, 2019, 29916880, PREVENTT, USA	Total	43.6	White 93.4%, Hispanic/Latino 3.2%	59.9 (12.7)			at least one 50	
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA	Elective surgery	45.7	White 82.3%	65.7 (13.1)				
Lidor, 2010, 20878256, USA	Elective surgery	28.9	White 95.35%, Black 3.1%, Other 1.55%	73.9 (5.9); 65-69 years 28.8, 70-74 years 29.7, 75-79 years 23.5, 80-85 years 12.6, 85+ years 5.5	.			
Masoomi, 2011, 21732208, Nationwide Inpatient Sample (2002-2007), USA	Elective surgery (Open surgery)	47.1	White 89%, Black 3.4%, Hispanic/Latino 4.9%, Asian 0.3%	57				
	Elective surgery (Laparoscopy)	47.4	White 84.9%, Black 3.7%, Hispanic/Latino 8.8%, Asian 0.1%	55				
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA	Elective surgery (2012-2013)	45.9	White 91.8%, Black 6.4%, Asian 1%, Other 0.7%	58 (12)				
Novitsky, 2009, 18639223, Nationwide Inpatient Sample (2001-2002), USA	Elective surgery	41.8		67.1 (13.8)				

Author, year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Specific Complications of Diverticulitis %	Number of Prior Episodes of Diverticulitis, %	Time Since Last Episode of Diverticulitis, Mean (SD)
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA	Elective surgery (2005/06)	48		<50 years 29.7, 65+ years 29.6				
	Elective surgery (2007)	47.6		<50 years 28.5, 65+ years 28.8				
	Elective surgery (2008)	46.8		<50 years 27.9, 65+ years 29				
	Elective surgery (2009)	45		<50 years 27.3, 65+ years 30				
	Elective surgery (2010)	44.6		<50 years 25.9, 65+ years 29.7				
	Elective surgery (2011)	45.2		<50 years 25.9, 65+ years 29.7				
	Elective surgery (2012)	46.2		<50 years 24.5, 65+ years 31.8				
	Elective surgery (2013)	44.5		<50 years 24.2, 65+ years 32.3				
Perez, 2020, 32748338, New York Statewide Planning and Research Cooperative System (SPARCS), US	Elective surgery	50.1	White 81.7%, Black 3.9%, Hispanic/Latino 7.1%, Asian 0.4%	55.9 (95% CI 55.6, 56.2)				
Pessaux, 2004, 14639493, French Association for Surgical Research, France	Elective surgery (elective laparotomy for colon or rectal resection for diverticulitis)	46.6		<58 years 37.5, 59-75 years 45.8, >76 years 16.7				[range >1.5 months]
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA	Elective surgery (Open procedure)	46.9	White 79.2%, Black 6.9%, Other 14%	59.2				
	Elective surgery (Laparoscopic procedure)	49.1	White 83.5%, Black 3.4%, Other 13.2%	55.6				
Silva-Velazco, 2016, 26541732, USA	Elective surgery	52		55 (12)		Preoperative percutaneous abscess drainage 6	.	[range 6, 8 weeks]

Author, year, PMID, Study Name, Country	Arm	Male %	Race/ethnicity	Age, mean (SD) or %	Participants with Un/Complicated Diverticulitis, %	Specific Complications of Diverticulitis %	Number of Prior Episodes of Diverticulitis, %	Time Since Last Episode of Diverticulitis, Mean (SD)
Simianu, 2015, 25773308, Surgical Care and Outcomes Assessment Program (SCOAP), USA	Elective surgery	47	White 87.2%	57.8 (12.7)		Colovesicular fistula 8.7, current GI bleed 2.3, stricture 4.4	none 13.9, one 15.2, two 14.5, at least three 52.5	
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany	Elective surgery	42		63 [Range 23, 91]; <60 years 42, 60-69 years 33, >69 years 25	100/0			
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA	Elective surgery	nr		>65 years 31.5				
van de Wall, 2017, 28404008, DIRECT trial, Netherlands	Elective surgery (Laparoscopic surgery)	28		Median 54.1 (IQR 44.6-62.1)			Mean 3.1 (SD 1.0)	
	No intervention (non-placebo) (Conservative management treatment: current daily practice)	43		Median 56.5 (IQR 48.3-63.2)			Mean 4.1 (SD 2.0)	
Varma, 2019, 30527478, California State Inpatient Database 2005-13, USA	Elective surgery	48.4	White 69.0%, Black 3.5%, Hispanic/Latino 18.9%, Other/missing 8.6%	55.3 (13.8)	89/11		one 70.8, two 21.8, at least three 7.4	[range 30d, 2y]
von Strauss und Torney, 2020, 32401298, Switzerland & UK Non-industry	Elective surgery	NR	NR	NR	0/100	NR	NR	NR
You, 2018, 29683483, USA	Placebo (Observation)	63		55.2 (13.1)		Abscess 42, extraluminal air 100	none 100	
	Elective surgery	54		53.3 (13.5)		Abscess 58, extraluminal air 100	none 100	

Table B-4B-4. KQ 4c Risk of Bias RCTs and NRCS

Author, Year, PMID, Study Name, Country	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personel, care providers, outcome assessor	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)	Were eligibility/selection criteria for the study population prespecified and clearly described?	Was the test/service/intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed	Bias due to confounding	Bias in selection of participants into the study
Aquina, 2019, 30335195, USA	High	High	High	Low	Low	Yes	Yes	Yes	Low	Low
van de Wall, 2017, 28404008, DIRECT trial, Netherlands	Low	Low	High	Low	Low	Yes	Yes	Yes	Low	Low
You, 2018, 29683483, USA	Low	Unclear	High	Low	Low	Yes	No	Yes	Low	Low

KQ = Key Question, PMID = PubMed Identifier. Ratings are color coded for emphasis only. See Table B-2a-2 for full legend.

Table B-4c-5. KQ 4c Risk of Bias Single-Group Studies

Author, year, PMID, Study Name, Country	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)	Were eligibility/ selection criteria for the study population prespecified and clearly described?	Was the test/service/ intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA	Low	Low	Yes	Yes	Yes
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA	Low	Low	Yes	Yes	Yes
Bordeianou, 2019, 29916880, PREVENTT, USA	Low	Low	Yes	No	Yes
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA	Low	Low	Yes	No	Yes
Lidor, 2010, 20878256, USA	Low	High	Yes	Yes	Yes
Masoomi, 2011, 21732208, Nationwide Inpatient Sample (2002-2007), USA	Low	Low	Yes	Yes	Yes
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA	Low	Low	Yes	Yes	Yes
Novitsky, 2009, 18639223, Nationwide Inpatient Sample (2001-2002), USA	Low	Low	Yes	Yes	Yes
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA	Low	Low	Yes	Yes	Yes
Perez, 2020, 32748338, New York Statewide Planning and Research Cooperative System (SPARCS), US	Low	Low	Yes	Yes	Yes
Pessaux, 2004, 14639493, French Association for Surgical Research, France	Low	Low	Yes	Yes	Yes
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA	Low	Low	Yes	Yes	Yes
Silva-Velazco, 2016, 26541732, USA	Low	Unclear	Yes	Yes	Yes
Simianu, 2015, 25773308, Surgical Care and Outcomes Assessment Program (SCOAP), USA	Low	Low	Yes	Yes	Yes
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany	Low	Low	Yes	Yes	Yes
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA	Low	Low	Yes	Yes	Yes
Varma, 2019, 30527478, California State Inpatient Database 2005-13, USA	Low	Low	Yes	Yes	Yes
von Strauss und Torney, 2020, 32401298, Switzerland & UK Non-industry	Low	Low	Yes	No	Yes

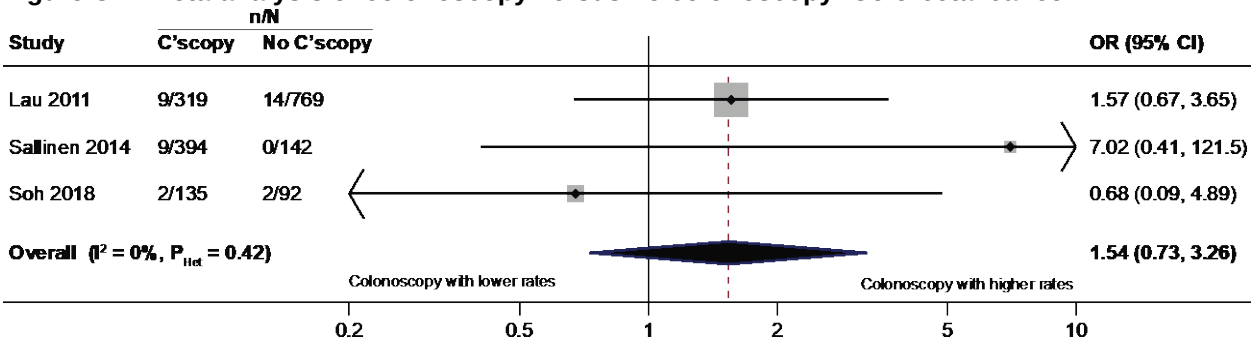
KQ = Key Question, PMID = PubMed Identifier. Ratings are color coded for emphasis only: Low/Yes, High/No, or Unclear.

Supplement C. Full Results Tables and Figures

Colonoscopy (Key Question 3)

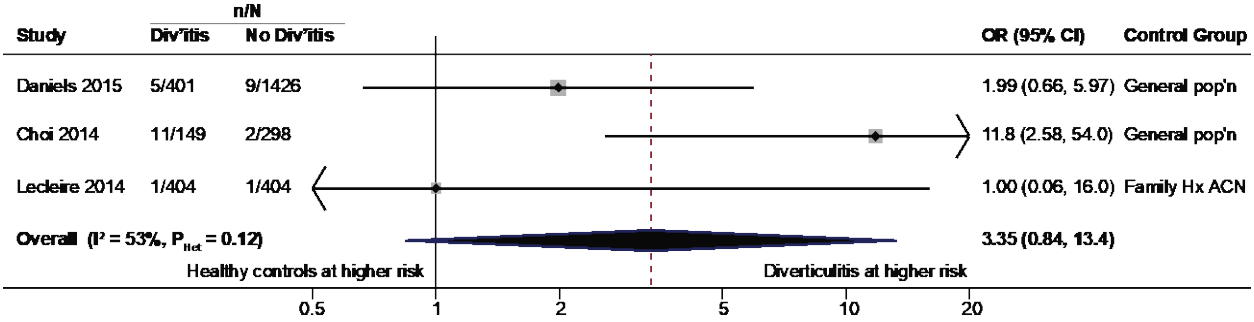
Meta-Analysis Figures

Figure C-1. Meta-analysis of colonoscopy versus no colonoscopy: Colorectal cancer



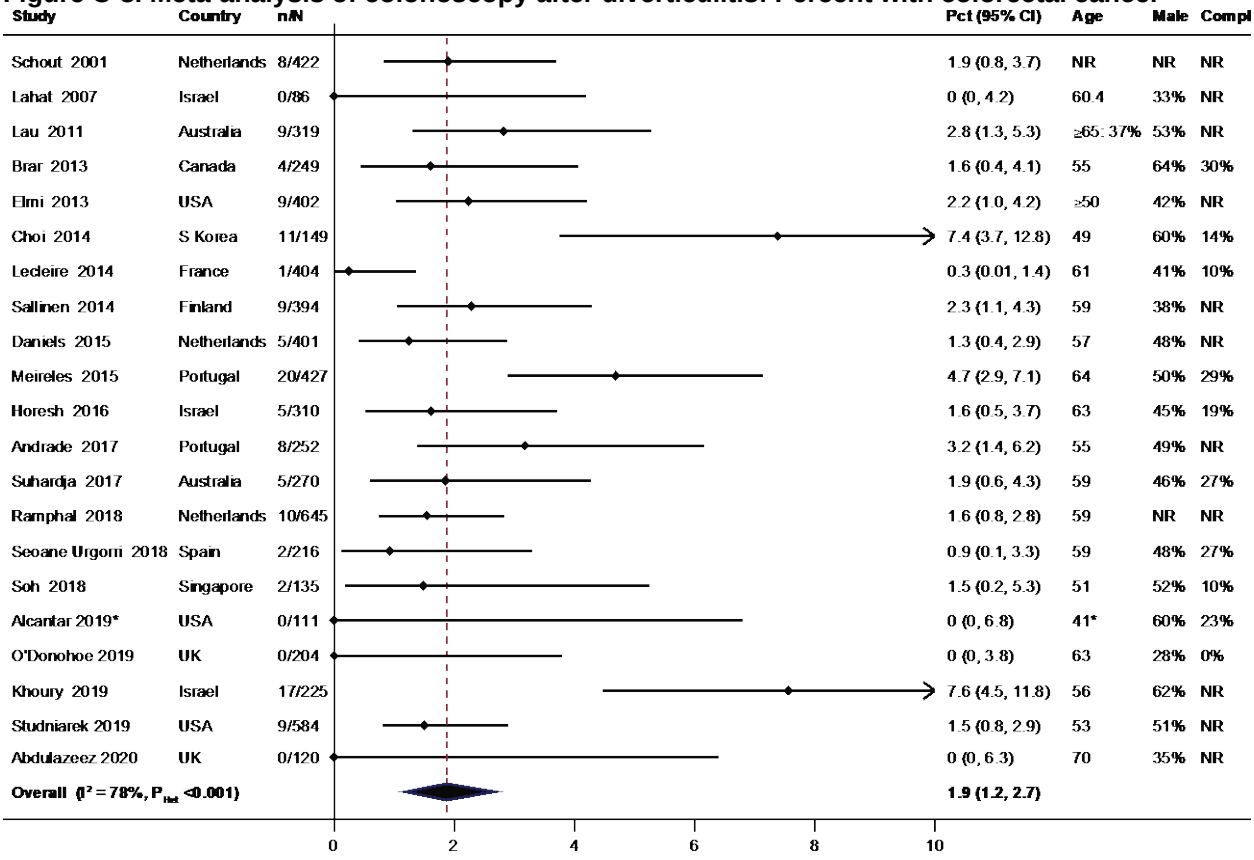
Abbreviations: CI = confidence interval, C'scopy = colonoscopy, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, P_{Het} = statistical heterogeneity P value.

Figure C-2. Meta-analysis of colonoscopy after diverticulitis versus in healthy controls: Colorectal cancer



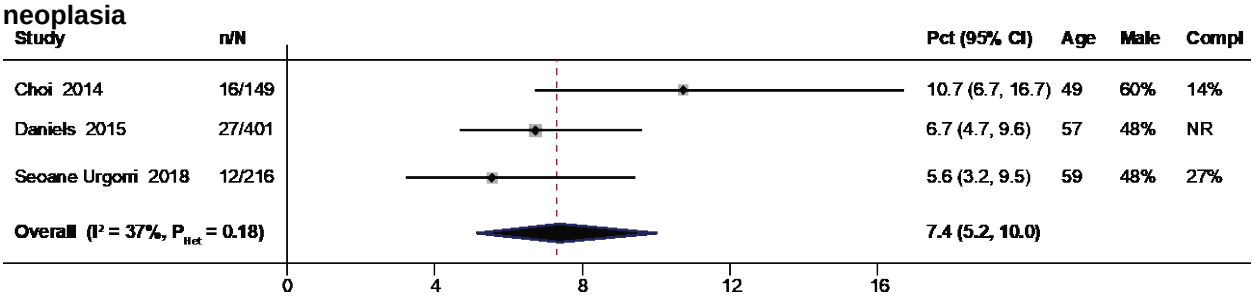
Abbreviations: CI = confidence interval, Div'it is = diverticulitis, Family Hx ACN = family history of advanced colonic neoplasia (colorectal cancer or advanced adenoma), I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, P_{Het} = statistical heterogeneity P value, pop'n = population.

Figure C-3. Meta-analysis of colonoscopy after diverticulitis: Percent with colorectal cancer



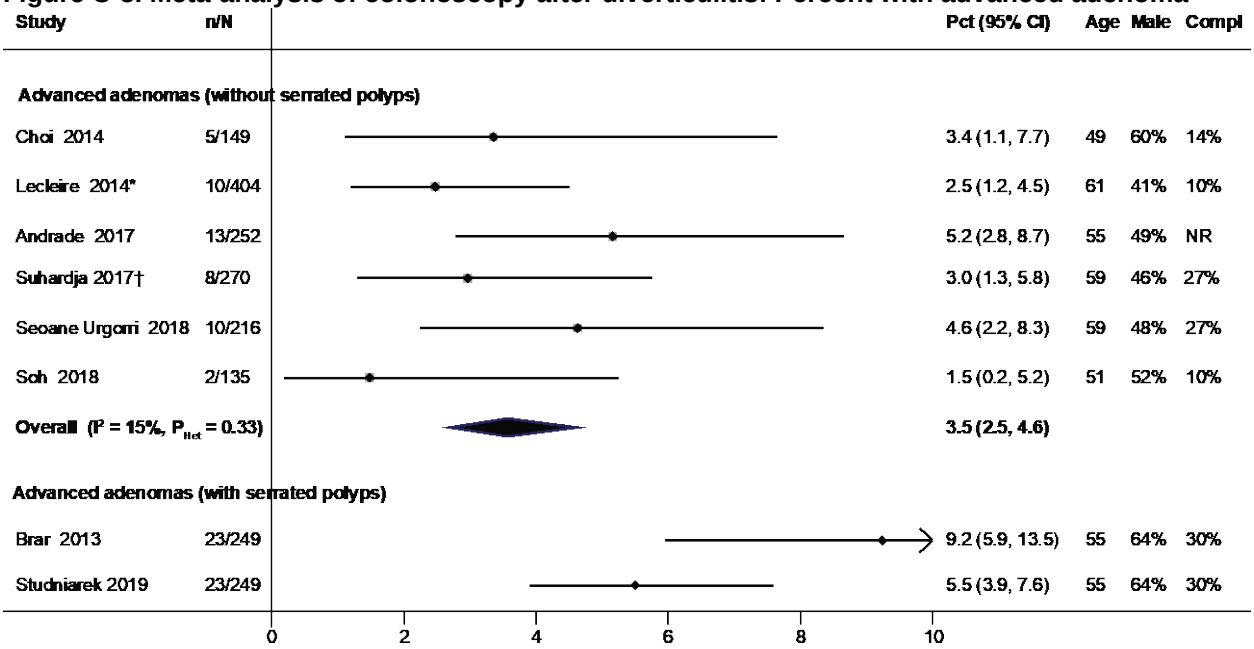
Abbreviations: CI = confidence interval, Compl = complicated diverticulitis (%), I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NR = not reported, Pct = percent, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate).

Figure C-4. Meta-analysis of colonoscopy after diverticulitis: Percent with advanced colonic neoplasia



Abbreviations: CI = confidence interval, Compl = complicated diverticulitis (%), I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NR = not reported, Pct = percent, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate).

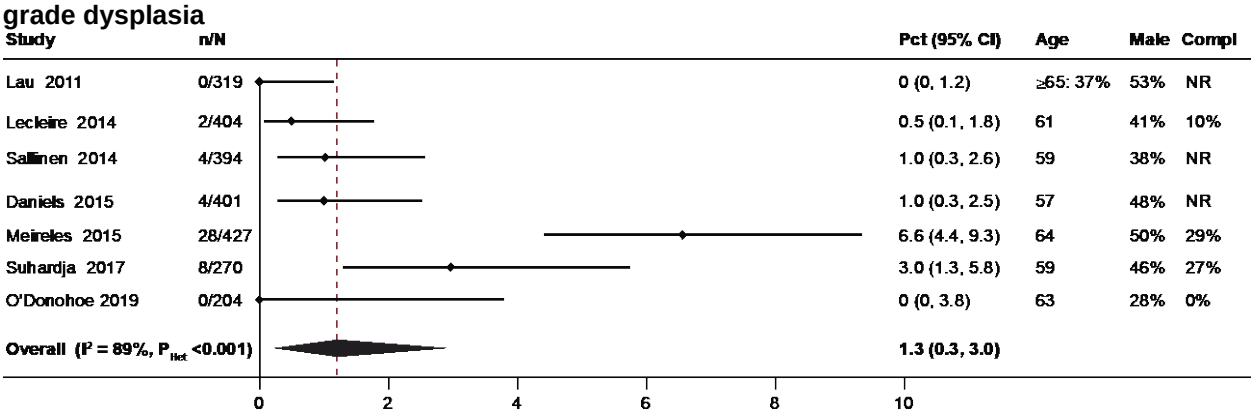
Figure C-5. Meta-analysis of colonoscopy after diverticulitis: Percent with advanced adenoma



Abbreviations: CI = confidence interval, Compl = complicated diverticulitis (%), I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NR = not reported, Pct = percent, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate).

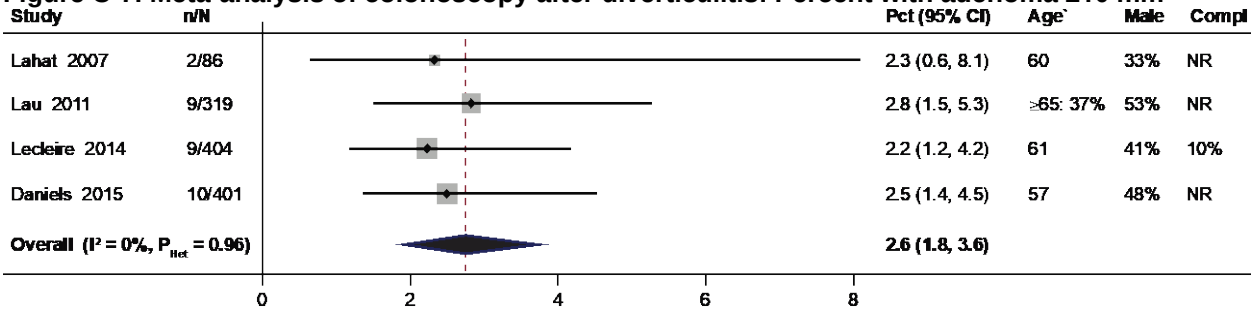
* This estimate excludes the one patient with CRC who was included by Lecleire 2014 as also having advanced adenoma.
† Suhardja 2017 did not define advanced adenoma.

Figure C-6. Meta-analysis of colonoscopy after diverticulitis: Percent with adenomas with high-grade dysplasia



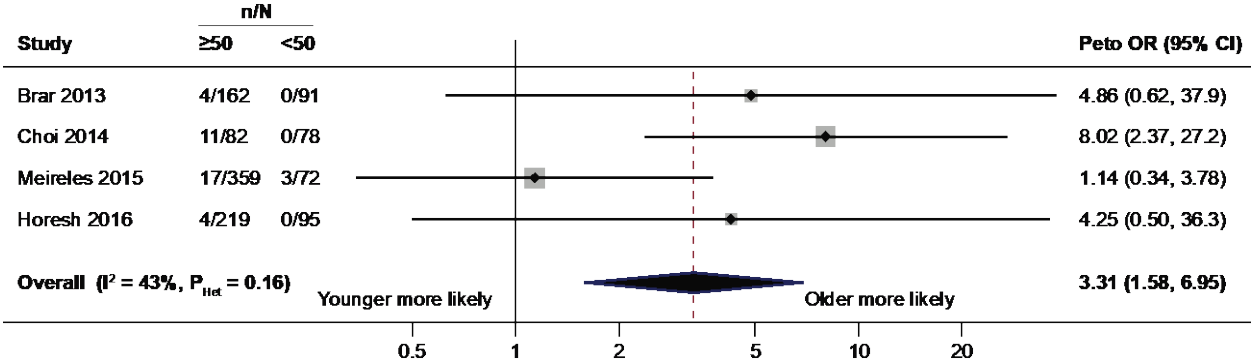
Abbreviations: CI = confidence interval, Compl = complicated diverticulitis (%), I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NR = not reported, Pct = percent, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate).

Figure C-7. Meta-analysis of colonoscopy after diverticulitis: Percent with adenoma ≥10 mm



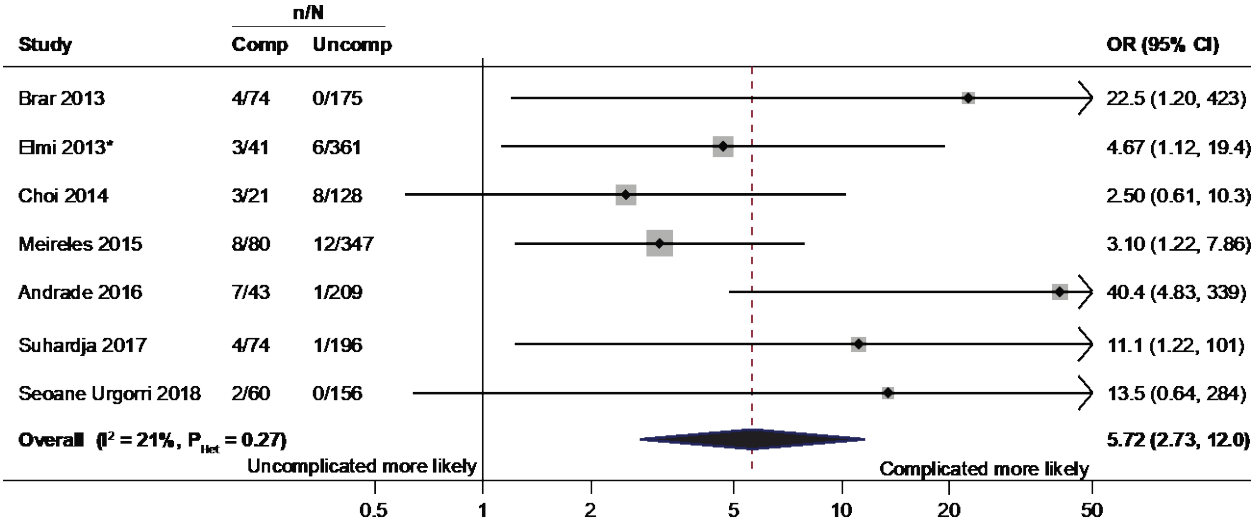
Abbreviations: CI = confidence interval, Compl = complicated diverticulitis (%), I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NR = not reported, Pct = percent, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate).

Figure C-8. Meta-analysis of older (≥50 years) versus younger adults with acute diverticulitis: Colorectal cancer



Abbreviations: CI = confidence interval, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate).

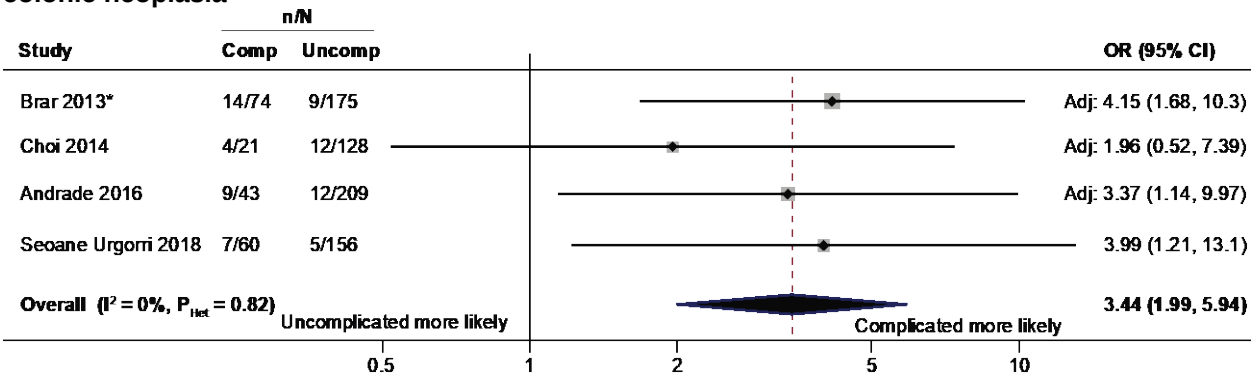
Figure C-9. Meta-analysis of complicated versus uncomplicated acute diverticulitis: Colorectal cancer



Abbreviations: CI = confidence interval, Compl = complicated diverticulitis, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate), Uncompl = uncomplicated diverticulitis.

* Comparison of abscess versus no abscess.

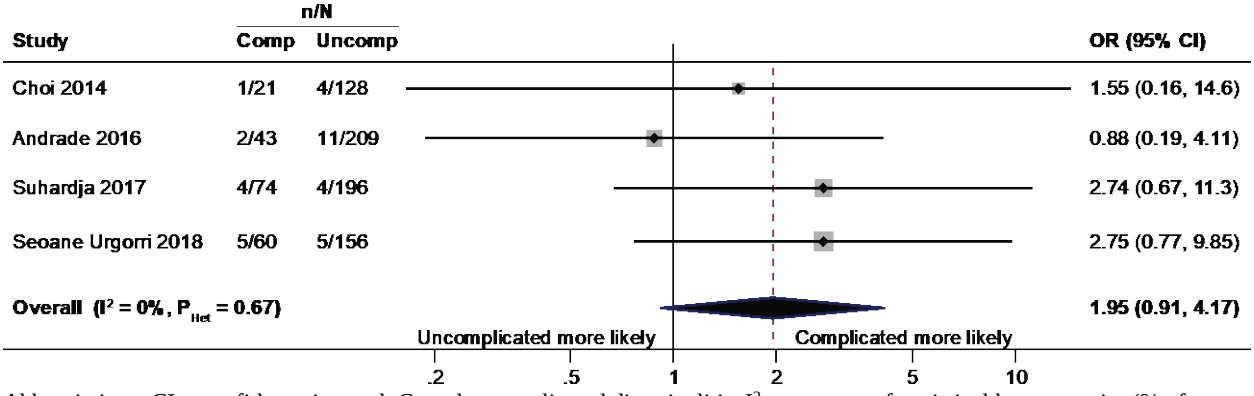
Figure C-10. Meta-analysis of complicated versus uncomplicated acute diverticulitis: Advanced colonic neoplasia



Abbreviations: CI = confidence interval, Compl = complicated diverticulitis, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate), Uncompl = uncomplicated diverticulitis.

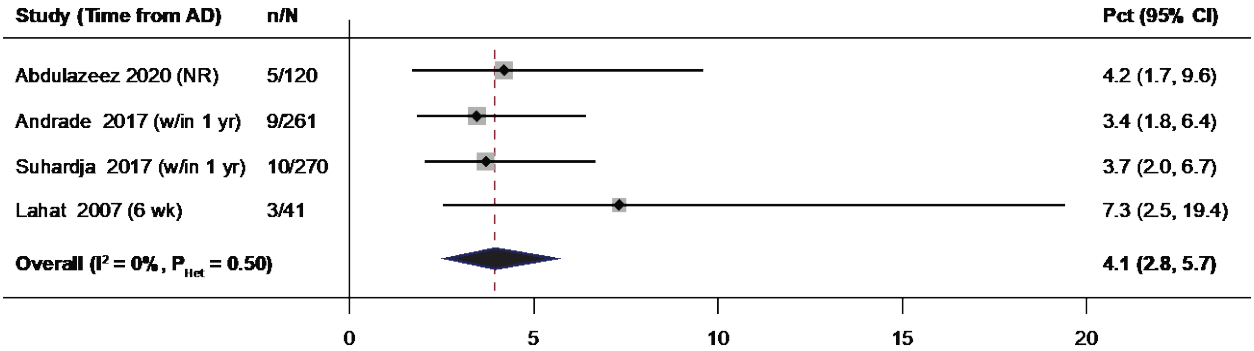
* Comparison of abscess versus no abscess.

Figure C-11. Meta-analysis of complicated versus uncomplicated acute diverticulitis: Advanced adenoma



Abbreviations: CI = confidence interval, Compl = complicated diverticulitis, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), OR = odds ratio, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate), Uncompl = uncomplicated diverticulitis.

Figure C-12. Meta-analysis of rate of incomplete colonoscopies



Abbreviations: AD = acute diverticulitis, CI = confidence interval, I^2 = measure of statistical heterogeneity (% of heterogeneity not due to random chance), NR = not reported, P_{Het} = chi-squared P value of statistical heterogeneity (not the P value of the estimate), Pct = percent.

Table C-3-1 KQ 3 Categorical outcomes, colonoscopy versus no colonoscopy after acute diverticulitis

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Colorectal cancer									
Lau, 2011, 21904141, Australia, NR	NRCS (Retrospective)	Diverticulitis confirmed by CT and had a follow up colonoscopy within 1 year from the date of CT scan. Family history of CRC: not available (claimed by the author). Multicenter.	Colorectal cancer	Colonoscopy	15-39y: 7.2%, 40-64y: 55.5%, 65+: 37.3% 53% male	NR NR	9/319 (2.8%)	OR 1.57 (0.67, 3.65)*	
				No Colonoscopy	15-39y: 8.5%, 40-64y: 54.2%, 65+: 37.3% 48% male	NR NR	14/769 (1.8%)		
Sallinen, 2014, 24178863, Finland, NR	NRCS (Retrospective)	Clinically and CT diagnosed acute diverticulitis. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	58.5 (13.9) 38% male	NR NR	9/394 (2.3%)	OR 7.02 (0.41, 121)*	
				No Colonoscopy	NR NR	NR NR	0/142 (0)		
Soh, 2018, 29663068, Singapore, NR	NRCS (Retrospective)	First episode of CT-proven acute diverticulitis with no complications. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	50.9 [range 18, 96] 52% male	NR 10.0%/90.0%	2/135 (1.5%)	OR 0.68 (0.09, 4.89)*	
				No Colonoscopy	NR NR	NR NR	2/92 (2.2%)		

Abbreviations: CRC = colorectal cancer, CT = computed tomography, Hx = history, NR = not reported, NRCS = nonrandomized controlled study, OR = odds ratio.

* Calculated by review team.

Table C-3-2 KQ 3 Categorical outcomes, colonoscopy after acute diverticulitis versus general screening (no diverticulitis)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Colorectal cancer									
Choi, 2014, 24723071, S Korea, NR	NRCS (Retrospective)	Underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from healthy individuals who underwent screening colonoscopy. Family history of CRC: 2.6% among diverticulitis patients and 3.1% among controls. Multicenter.	Colorectal cancer	Diverticulitis with colonoscopy	48.6 (16.5) 60% male	NR 14.1%/85.9%	11/149 (7.4%)	OR 11.80 (2.58, 54.0)	0.001
				Sex matched controls	46.6 (16.6) 60% male	NR 8.2%/91.8%	2/298 (0.7%)		
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Colorectal cancer	Diverticulitis patients (DIABOLO trial)	Median 57 [range 49, 65] 48% male	NR NR	5/401 (1.2%)	OR 1.99 (0.66, 5.97)*	0.673
				Screening individuals (COCOS trial)	Median 60 [range 55, 65] 51% male	NR NR	9/1426 (0.6%)		

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Colorectal cancer	Acute diverticulitis	60.9 (12.6) 41% male	NR 10.0%/90.0%	1/404 (0.3%)	OR 1.00 (0.06, 16.0)*	
				Sex and age matched controls	60.7 (13.4) 41% male	NR NR	1/404 (0.3%)		
High-risk colonic premalignant lesions									
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Adenoma ≥10 mm	Diverticulitis patients (p DIABOLO trial)	Median 57 [range 49, 65] 48% male	NR NR	10/401 (2.5%)	OR 0.36 (0.18, 0.69)*	0.002
				Screening individuals (COCOS trial)	Median 60 [range 55, 65] 51% male	NR NR	95/1426 (6.7%)		

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Adenoma ≥10 mm	Acute diverticulitis	60.9 (12.6) 41% male	NR 10.0%/90.0%	9/404 (2.2%)	OR 0.38 (0.17, 0.83)*	
				Sex and age matched controls	60.7 (13.4) 41% male	NR NR	23/404 (5.7%)		
Choi, 2014, 24723071, S Korea, NR	NRCS (Retrospective)	Underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from healthy individuals who underwent screening colonoscopy. Family history of CRC: 2.6% among diverticulitis patients and 3.1% among controls. Multicenter.	Advanced adenoma	Diverticulitis with colonoscopy	48.6 (16.5) 60% male	NR 14.1%/85.9%	5/149 (3.4%)	OR 5.14 (0.99, 26.8)	0.052
				Sex matched controls	46.6 (16.6) 60% male	NR 8.2%/91.8%	2/298 (0.7%)		

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Advanced adenoma	Acute diverticulitis	60.9 (12.6) 41% male	NR 10.0%/90.0%	11/404 (2.7%)	OR 0.39 (0.19, 0.80)*	0.01
				Sex and age matched controls	60.7 (13.4) 41% male	NR NR	27/404 (6.7%)		
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Advanced adenomas	Diverticulitis patients (DIABOLO trial)	Median 57 [range 49, 65] 48% male	NR NR	22/401 (5.5%)	OR 0.61 (0.38, 0.97)*	0.053 †
				Screening individuals (COCOS trial)	Median 60 [range 55, 65] 51% male	NR NR	124/1426 (8.7%)		

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Choi, 2014, 24723071, S Korea, NR	NRCS (Retrospective)	Underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from healthy individuals who underwent screening colonoscopy. Family history of CRC: 2.6% among diverticulitis patients and 3.1% among controls. Multicenter.	Advanced colonic neoplasia	Diverticulitis with colonoscopy	48.6 (16.5) 60% male	NR 14.1%/85.9%	16/149 (10.7%)	OR 8.84 (2.90, 27.0)	<0.001
				Sex matched controls	46.6 (16.6) 60% male	NR 8.2%/91.8%	4/298 (1.3%)		
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Advanced colonic neoplasia	Diverticulitis patients (DIABOLO trial)	Median 57 [range 49, 65] 48% male	NR NR	27/401 (6.7%)	OR 0.72 (0.47, 1.11)*	0.132
				Screening individuals (COCOS trial)	Median 60 [range 55, 65] 51% male	NR NR	130/1426 (9.1%)		

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Adenoma, high grade dysplasia	Diverticulitis patients (DIABOLO trial)	Median 57 [range 49, 65] 48% male	NR NR	4/401 (1.0%)	OR 0.41 (0.15, 1.17)*	0.111
				Screening individuals (COCOS trial)	Median 60 [range 55, 65] 51% male	NR NR	34/1426 (2.4%)		
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Adenoma, high grade dysplasia	Acute diverticulitis	60.9 (12.6) 41% male	NR 10.0%/90.0%	2/404 (0.5%)	OR 0.33 (0.07, 1.64)*	
				Sex and age matched controls	60.7 (13.4) 41% male	NR NR	6/404 (1.5%)		

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)	Effect Size	Reported P value
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Adenoma, villous	Acute diverticulitis	60.9 (12.6) 41% male	NR 10.0%/90.0%	3/404 (0.7%)	OR 1.00 (0.20, 4.98)*	
				Sex and age matched controls	60.7 (13.4) 41% male	NR NR	3/404 (0.7%)		
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Serrated polyp	Diverticulitis patients (DIABOLO trial)	Median 57 [range 49, 65] 48% male	NR NR	53/401 (13.2%)	OR 0.41 (0.30, 0.56)*	<0.001
				Screening individuals (COCOS trial)	Median 60 [range 55, 65] 51% male	NR NR	388/1426 (27.2%)		

Abbreviations: CRC = colorectal cancer, CT = computed tomography, Hx = history, NR = not reported, NRCS = nonrandomized controlled study, OR = odds ratio.

* Calculated by review team.
† The statistically significant difference in rates of advanced adenomas (P=0.036) became just nonsignificant after adjustment for age, family history of CRC, smoking, BMI, and cecal intubation (P=0.053); although, no adjusted effect size was reported.

Table C-3-3 KQ 3 Categorical outcomes, colonoscopy vs. flexible sigmoidoscopy and single group studies

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Colorectal cancer							
Abdulazeez, 2020, 32820657, UK NR	NRCS	Left sided acute diverticulitis, ≥18 years Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	70 (10.2) [range 46, 90] NR	NR NR	0/120 (0%)
				Flex sig	72 (13.9) [range 28, 91] NR	NR NR	0/120 (0%)
Alcantar, 2019, 31720142, USA, NR	Single group (Retrospective)	Patients between the ages of 18 and 49 years with acute diverticulitis. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	Mean 40.7 60.3% male	NR 22.5%/77.5%	0/111 (0%)
Andrade, 2017, 27941344, Portugal, NR	Single group (Retrospective)	Underwent a colonoscopy within 1 year after the conservative management of CT-proven acute diverticulitis. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	Median 55 [IQR 11.1] 49% male	NR NR	8/252 (3.2%)
Brar, 2013, 24105001, Canada, NR	Single group (Retrospective)	Successfully treated nonoperatively for acute left-sided diverticulitis, and all endoscopy reports before index admission and within 1 year after admission. Family history of CRC: not reported. Single center.	Colorectal cancer found within a year of admission	Colonoscopy	55 [range 27, 90]; 63.5% >55 49% male	63.5% 29.7%/70.3%	4/249 (1.6%) [A]
Choi, 2014, 24723071, S Korea, NR	NRCS (Retrospective)	Underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from healthy individuals who underwent screening colonoscopy. Family history of CRC: 2.6% among diverticulitis patients and 3.1% among controls. Multicenter.	Colorectal cancer	Colonoscopy	48.6 (16.5) 60% male	NR 14.1%/85.9%	11/149 (7.4%)
Elmi, 2013, 23701063, USA, NR	Single group (Retrospective)	Acute diverticulitis, evaluation of the colon using colonoscopy. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	100% >49 42%	100% NR	9/402 (2.2%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Colorectal cancer	Colonoscopy	Median 57 [range 49, 65] 48% male	NR NR	5/401 (1.2%)
Horesh, 2016, 27170283, Israel, NR	Single group (Retrospective)	Admitted for a first episode of acute diverticulitis diagnosed based on clinical signs and CT findings and were successfully treated conservatively. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	62.6 [range 21, 98]; 30.6% >55 45% male	30.6% 18.5%/81.5%	5/310 (1.6%)
Khoury, 2019, 30632029, Israel, NR	Single group (Retrospective)	Acute diverticulitis, patients who underwent colonoscopy in the period of 6 months following the diagnosis with acute diverticulitis, or patients who performed virtual CT colonography in the case of contraindication to colonoscopy. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	55.7 (13.8) [range 24, 93] 62% male	NR NR	17/225 (7.6%)
Lahat, 2007, 17554647, Israel, NR	RCT	Findings on CT compatible with the diagnosis of acute diverticulitis Family history of CRC: not reported. Not sure.	Colorectal cancer	Colonoscopy	60.4 33% male	NR NR	0/86 (0)
Lau, 2011, 21904141, Australia, NR	NRCS (Retrospective)	Diverticulitis confirmed by CT and had a follow up colonoscopy within 1 year from the date of CT scan. Family history of CRC: not available (claimed by the author). Multicenter.	Colorectal cancer	Colonoscopy	15-39y: 7.2%, 40-64y: 55.5%, 65+: 37.3% 53% male	NR NR	9/319 (2.8%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Colorectal cancer	Colonoscopy	60.9 (12.6) 41% male	NR 10.0%/90.0%	1/404 (0.3%)
Meireles, 2015, 26378691, Portugal, NR	Single group (Retrospective)	Subjected to endoscopy following the primary episode of diverticulitis. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	64.4 (13.5) [range 23, 103] 50% male	NR 28.8%/81.2%	20/427 (4.7%)
O'Donohoe, 2019, 31882879, United Kingdom, NR	Single group (Retrospective)	Patients over the age of 18 with CT-diagnosed uncomplicated left-sided diverticulitis (with a modified Hinchey classification of 0 or 1a), admitted 2014–2017, with a follow-up colonoscopy 4–6 weeks after admission. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	Median 63 (range 29, 90) 28% male	NR 0/100%	0/204 (0)
Ramphal, 2018, 29945147, Netherlands, NR	Single group (Retrospective)	Diagnosed with acute colonic diverticulitis (Hinchey 0 and 1) and offered colonoscopy to rule out CRC. Family history of CRC: among 10 identified colorectal cancer cases, 2 had a family history of CRC and 1 had a positive family history for Crohn's disease. Single center.	Colorectal cancer	Colonoscopy	59 NR	NR [B] NR	10/645 (1.6%)
Sallinen, 2014, 24178863, Finland, NR	NRCS (Retrospective)	Clinically and CT diagnosed acute diverticulitis. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	58.5 (13.9) 38% male	NR NR	9/394 (2.3%)
Schout, 2012, 23171930, Netherlands, NR	Single group (Retrospective)	Underwent radiological or surgical abscess drainage only without colon resection. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	NR NR	NR NR	8/422 (1.9%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Seoane Urgorri, 2018, 29900742, Spain, NR	Single group (Retrospective)	Colonoscopy performed after CT-confirmed diagnosis of acute diverticulitis. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	59 (15) 48% male	NR 27.0%/73.0%	2/216 (0.9%)
Soh, 2018, 29663068, Singapore, NR	NRCS (Retrospective)	First episode of CT-proven acute diverticulitis with no complications. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	50.9 [range 18, 96] 52% male	NR 10.0%/90.0%	2/135 (1.5%)
Studniarek, 2019, 31908222, USA, NR	Single group (Retrospective)	A history of acute diverticulitis as the indication for the colonoscopy, and colonoscopy performed within one year from the initial diagnosis of diverticulitis. Family history of CRC: not reported. Multicenter.	Colorectal cancer	Colonoscopy	Median 53 (range 22, 88) 51% male	NR NR	9/584 (1.5%)
Suhardja, 2017, 28035461, Australia, NR	Single group (Retrospective)	Diagnosed with acute colonic diverticulitis on CT scan and received follow-up colonoscopy. Family history of CRC: not reported. Single center.	Colorectal cancer	Colonoscopy	59.3 46% male	NR 27.4%/72.6%	5/270 (1.9%)
High-risk colonic premalignant lesions							
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Adenoma ≥10 mm	Colonoscopy	Median 57 [range 49, 65] 48% male	NR NR	10/401 (2.5%)
Lahat, 2007, 17554647, Israel, NR	RCT	Findings on CT compatible with the diagnosis of acute diverticulitis Family history of CRC: not reported. Not sure.	Adenoma ≥10 mm	Colonoscopy	60.4 33% male	NR NR	2/86 (2.3%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Lau, 2011, 21904141, Australia, NR	NRCS (Retrospective)	Diverticulitis confirmed by CT and had a follow up colonoscopy within 1 year from the date of CT scan. Family history of CRC: not available (claimed by the author). Multicenter.	Adenoma ≥10 mm	Colonoscopy	15-39 y: 7.2%, 40-64 y: 55.5%, 65+: 37.3% 53% male	NR NR	9/319 (2.6%)
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Adenoma ≥10 mm	Colonoscopy	60.9 (12.6) 41% male	NR 10.0%/90.0%	9/404 (2.2%)
Andrade, 2017, 27941344, Portugal, NR	Single group (Retrospective)	Underwent a colonoscopy within 1 year after the conservative management of CT-proven acute diverticulitis. Family history of CRC: not reported. Single center.	Advanced adenomas	Colonoscopy	Median 55 [IQR 11.1] 49% male	NR NR	13/252 (5.1%)
Brar, 2013, 24105001, Canada, NR	Single group (Retrospective)	Successfully treated nonoperatively for acute left-sided diverticulitis, and all endoscopy reports before index admission and within 1 year after admission. Family history of CRC: not reported. Single center.	Advanced adenomas [C]	Colonoscopy	55 [range 27, 90]; 63.5% >55 49% male	63.5% 29.7%/70.3%	19/249 (7.6%)
Choi, 2014, 24723071, S Korea, NR	NRCS (Retrospective)	Underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from healthy individuals who underwent screening colonoscopy. Family history of CRC: 2.6% among diverticulitis patients and 3.1% among controls. Multicenter.	Advanced adenoma	Colonoscopy	48.6 (16.5) 60% male	NR 14.1%/85.9%	5/149 (3.4%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Advanced adenoma	Colonoscopy	60.9 (12.6) 41% male	NR 10.0%/90.0%	11/404 (2.7%)
Seoane Urgorri, 2018, 29900742, Spain, NR	Single group (Retrospective)	Colonoscopy performed after CT-confirmed diagnosis of acute diverticulitis. Family history of CRC: not reported. Single center.	Advanced adenoma	Colonoscopy	59 (15) 48% male	NR 27.0%/73.0%	10/216 (4.6%)
Soh, 2018, 29663068, Singapore, NR	NRCS (Retrospective)	First episode of CT-proven acute diverticulitis with no complications. Family history of CRC: not reported. Single center.	Advanced adenoma	Colonoscopy	50.9 [range 18, 96] 52% male	NR 0%/100%	2/135 (1.5%)
Studniarek, 2019, 31908222, USA, NR	Single group (Retrospective)	A history of acute diverticulitis as the indication for the colonoscopy, and colonoscopy performed within one year from the initial diagnosis of diverticulitis. Family history of CRC: not reported. Multicenter.	Advanced adenoma [C]	Colonoscopy	Median 53 (range 22, 88) 51% male	NR NR	32/584 (5.4%)
Suhardja, 2017, 28035461, Australia, NR	Single group (Retrospective)	Diagnosed with acute colonic diverticulitis on CT scan and received follow-up colonoscopy. Family history of CRC: not reported. Single center.	Advanced adenoma	Colonoscopy	59.3 46% male	NR 27.4%/72.6%	8/270 (3.0%)
Choi, 2014, 24723071, S Korea, NR	NRCS (Retrospective)	Underwent CT, followed by colonoscopy within a year and diagnosed with acute diverticulitis. For each diverticulitis case, two age- (±5 years) and sex matched control individuals were identified from healthy individuals who underwent screening colonoscopy. Family history of CRC: 2.6% among diverticulitis patients and 3.1% among controls. Multicenter.	Advanced colonic neoplasia	Colonoscopy	48.6 (16.5) 60% male	NR 14.1%/85.9%	16/149 (10.7%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Advanced colonic neoplasia	Colonoscopy	Median 57 [range 49, 65] 48% male	NR NR	27/401 (6.7%)
Seoane Urgorri, 2018, 29900742, Spain, NR	Single group (Retrospective)	Colonoscopy performed after CT-confirmed diagnosis of acute diverticulitis. Family history of CRC: not reported. Single center.	Advanced colonic neoplasia	Colonoscopy	59 (15) 48% male	NR 27.0%/73.0%	12/216 (5.5%)
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Adenoma, high grade dysplasia	Colonoscopy	Median 57 [range 49, 65] 48% male	NR NR	4/401 (1.0%)
Lau, 2011, 21904141, Australia, NR	NRCS (Retrospective)	Diverticulitis confirmed by CT and had a follow up colonoscopy within 1 year from the date of CT scan. Family history of CRC: not available (claimed by the author). Multicenter.	Adenoma, high grade dysplasia	Colonoscopy	15-39y: 7.2%, 40-64y: 55.5%, 65+: 37.3% 53% male	NR NR	0/319 (0)
Lecleire, 2014, 25083288, France, Non-industry	NRCS (Retrospective)	Group 1 patients: acute diverticulitis, underwent colonoscopy within 6 months following the acute episode. Group 2 patients: sex and age matched with a familial history of colorectal adenoma or neoplasia. Group 2 patients had a family history of colorectal adenoma or neoplasia. Multicenter.	Adenoma, high grade dysplasia	Colonoscopy	60.9 (12.6) 41% male	NR 10.0%/90.0%	2/404 (0.5%)

Author, Year, PMID, Country, Funding	Design	Population Diverticulitis Details Family Hx CRC Setting	Outcome	Arm	Age Sex	Age ≥50, % Complicated/ Uncomplicated diverticulitis %	n/N (%)
Meireles, 2015, 26378691, Portugal, NR	Single group (Retrospective)	Subjected to endoscopy following the primary episode of diverticulitis. Family history of CRC: not reported. Single center.	Adenoma, high grade dysplasia	Colonoscopy	64.4 (13.5) [range 23, 103] 50% male	NR 28.8%/81.2%	28/427 (6.6%)
Sallinen, 2014, 24178863, Finland, NR	NRCS (Retrospective)	Clinically and CT diagnosed acute diverticulitis. Family history of CRC: not reported. Single center.	Adenoma, high grade dysplasia	Colonoscopy	58.5 (13.9) 38% male	NR NR	4/394 (1.0%)
Suhardja, 2017, 28035461, Australia, NR	Single group (Retrospective)	Diagnosed with acute colonic diverticulitis on CT scan and received follow-up colonoscopy. Family history of CRC: not reported. Single center.	Adenoma, moderate-/high-grade dysplasia	Colonoscopy	59.3 46% male	NR 27.4%/72.6%	8/270 (3.0%)
Lau, 2011, 21904141, Australia, NR	NRCS (Retrospective)	Diverticulitis confirmed by CT and had a follow up colonoscopy within 1 year from the date of CT scan. Family history of CRC: not available (claimed by the author). Multicenter.	Moderately differentiated adenocarcinoma	Colonoscopy	15-39y: 7.2%, 40-64y: 55.5%, 65+: 37.3% 53% male	NR NR	1/319 (0.3%)
Daniels, 2015, 25472747, Netherlands, Non-industry	NRCS (Retrospective)	Primary colonoscopy screening population: randomly invited for primary colonoscopy screening and 50-75 years. Uncomplicated Diverticulitis Population: adult, CT proven uncomplicated left sided acute diverticulitis, participating in DIABOLO trial, having follow up colonoscopy within 6 months. Family history of CRC: 9.5% among diverticulitis patients and 15.3% among screening individuals. Multicenter.	Serrated polyp	Colonoscopy	Median 57 [range 49, 65] 48% male	NR NR	53/401 (13.2%)
Seoane Urgorri, 2018, 29900742, Spain, NR	Single group (Retrospective)	Colonoscopy performed after CT-confirmed diagnosis of acute diverticulitis. Family history of CRC: not reported. Single center.	Serrated polyp	Colonoscopy	59 (15) 48% male	NR 27.0%/73.0%	2/216 (0.9%)

Abbreviations: CRC = colorectal cancer, CT = computed tomography, Hx = history, NR = not reported, NRCS = nonrandomized controlled study, OR = odds ratio, RCT = randomized controlled trial..

[A] No colorectal cancer was found beyond 1 year of admission.

[B] Mean age of patients who had colon cancer 68 years (range, 42 to 94).
[C] Included patients with serrated polyps among those with advanced adenoma.

Table C-3-4 KQ 3 Categorical outcomes, Subgroup Analysis: Age ≥50 vs. Age <50

Author, Year, PMID, Country, Funding	Outcome	Subgroup	n/N (%)	Effect Size between subgroups	Reported P value
Colorectal cancer					
Brar, 2013, 24105001, Canada, NR	Colorectal cancer found within a year of admission	Colonoscopy among patients age ≥50	4/158 (2.5%)	OR 5.32 (0.28, 99.9)*	
		Colonoscopy among patients age <50	0/91 (0)		
Choi, 2014, 24723071, S Korea, NR	Colorectal cancer	Colonoscopy among patients age ≥50	11/82 (13.4%)	OR 25.27 (1.46, 437)*	
		Colonoscopy among patients age <50	0/78 (0)		
Horesh, 2016, 27170283, Israel, NR	Colorectal cancer	Colonoscopy among patients age ≥50	4/215 (1.9%)	OR 1.78 (0.20, 16.2)*	
		Colonoscopy among patients age <50	1/95 (1.1%)		
Meireles, 2015, 26378691, Portugal, NR	Colorectal cancer	Colonoscopy among patients age >50	17/342 (5.0%)	OR 1.15 (0.33, 4.04)*	
		Colonoscopy among patients age <50	3/69 (4.3%)		
High-risk colonic premalignant lesions					
Andrade, 2017, 27941344, Portugal, NR	Advanced colonic neoplasia	Colonoscopy among patients age ≥50	NR	OR 8.12 (2.46, 45.1)	0.017
		Colonoscopy among patients age <50	NR		
Seoane Urgorri, 2018, 29900742, Spain, NR	Advanced colonic neoplasia	Colonoscopy among patients age >50	7.8%		0.02
		Colonoscopy among patients age <=50	0		
Choi, 2014, 24723071, S Korea, NR	Advanced colonic neoplasia	Colonoscopy among patients age ≥50	14/71 (19.7%)	OR 9.13 (1.97, 42.3)	0.005
		Colonoscopy among patients age <50	2/78 (2.6%)		
Brar, 2013, 24105001, Canada, NR	Advanced adenomas †	Colonoscopy among patients age ≥50	16/158 (10.1%)	OR 3.31 (0.94, 11.7)*	
		Colonoscopy among patients age <50	3/91 (3.3%)		
Choi, 2014, 24723071, S Korea, NR	Advanced adenomas	Colonoscopy among patients age ≥50	3/71 (4.2%)	OR 1.68 (0.27, 10.3)	
		Colonoscopy among patients age <50	2/78 (2.6%)		

* Calculated by review team.

† Included serrated adenomas.

Table C-3-5 KQ 3 Subgroup Analysis: Complicated vs. Uncomplicated Diverticulitis

Author, Year, PMID, Country, Funding	Outcome	Subgroup	n/N (%)	Effect Size between subgroups	Reported P value
Colorectal cancer					
Andrade, 2017, 27941344, Portugal, NR	Colorectal cancer	Colonoscopy among patients with Hinchey ≥Ib	7/43 (16.3%)	OR 40.44 (4.83, 339)*	<0.001
		Colonoscopy among patients with Hinchey Ia	1/209 (0.5%)		
Brar, 2013, 24105001, Canada, NR	Colorectal cancer found within a year of admission	Colonoscopy among patients with complicated diverticulitis	4/74 (5.4%)	OR 22.50 (1.20, 424)*	
		Colonoscopy among patients with uncomplicated diverticulitis	0/175 (0)		
Choi, 2014, 24723071, S Korea, NR	Colorectal cancer	Colonoscopy among patients with complicated diverticulitis	3/21 (14.3%)	OR 2.50 (0.61, 10.3)	0.188
		Colonoscopy among patients with uncomplicated diverticulitis	8/128 (6.3%)		
Elmi, 2013, 23701063, USA, NR	Colorectal cancer	Colonoscopy among patients with abscess	NR	OR 4.67 (1.12, 19.4)	
		Colonoscopy among patients with no abscess	NR		
Meireles, 2015, 26378691, Portugal, NR	Colorectal cancer	Colonoscopy among patients with complicated diverticulitis	8/80 (10.0%)	OR 3.10 (1.22, 7.86)*	
		Colonoscopy among patients with uncomplicated diverticulitis	12/347 (3.5%)		
Suhardja, 2017, 28035461, Australia, NR	Colorectal cancer	Colonoscopy among patients with complicated diverticulitis	4/74 (5.4%)	OR 11.14 (1.22, 101)*	
		Colonoscopy among patients with uncomplicated diverticulitis	1/196 (0.5%)		
Seoane Urgorri, 2018, 29900742, Spain, NR	Colorectal cancer	Colonoscopy among patients with complicated diverticulitis	2/60 (3.3)	OR 13.45 (0.64, 284)*	0.07
		Colonoscopy among patients with uncomplicated diverticulitis	0/156 (0)		

Author, Year, PMID, Country, Funding	Outcome	Subgroup	n/N (%)	Effect Size between subgroups	Reported P value
Alcantar, 2019, 31720142, USA, NR	Colorectal cancer	Colonoscopy among patients with complicated diverticulitis	0/25 (0)		
		Colonoscopy among patients with uncomplicated diverticulitis	0/86 (0)		
High-risk colonic premalignant lesions					
Andrade, 2017, 27941344, Portugal, NR	Advanced adenoma	Colonoscopy among patients with Hinchey ≥Ib	2/43 (4.7%)	OR 0.88 (0.19, 4.11)*	0.74
		Colonoscopy among patients with Hinchey Ia	11/209 (5.3%)		
Choi, 2014, 24723071, S Korea, NR	Advanced adenoma	Colonoscopy among patients with complicated diverticulitis	1/21 (4.8%)	OR 1.55 (0.16, 14.6)*	0.537
		Colonoscopy among patients with uncomplicated diverticulitis	4/128 (3.1%)		
Seoane Urgorri, 2018, 29900742, Spain, NR	Advanced adenoma	Colonoscopy among patients with complicated diverticulitis	5/60 (8.6%)	OR 2.75 (0.77, 9.85)*	0.1
		Colonoscopy among patients with uncomplicated diverticulitis	5/156 (3.2%)		
Suhardja, 2017, 28035461, Australia, NR	Advanced adenoma	Colonoscopy among patients with complicated diverticulitis	4/74 (5.4%)	OR 2.74 (0.67, 11.3)*	
		Colonoscopy among patients with uncomplicated diverticulitis	4/196 (2.0%)		
Andrade, 2017, 27941344, Portugal, NR	Advanced colonic neoplasia	Colonoscopy among patients with Hinchey ≥Ib	9/43 (20.9%)	OR 3.37 (1.55, 13.5)	0.035
		Colonoscopy among patients with Hinchey Ia	12/209 (5.7%)		
Brar, 2013, 24105001, Canada, NR	Advanced colonic neoplasia	Abscess	14/74 (18.9%)	OR 4.15 (1.68, 10.3)*	0.002
		No abscess	9/175 (5.1%)		
Choi, 2014, 24723071, S Korea, NR	Advanced colonic neoplasia	Colonoscopy among patients with complicated diverticulitis	4/21 (19.0%)	OR 3.53 (0.96, 13.0)*	0.245
		Colonoscopy among patients with uncomplicated diverticulitis	12/128 (9.4%)		

Author, Year, PMID, Country, Funding	Outcome	Subgroup	n/N (%)	Effect Size between subgroups	Reported P value
Seoane Urgorri, 2018, 29900742, Spain, NR	Advanced colonic neoplasia	Colonoscopy among patients with complicated diverticulitis	7/60 (11.7%)	OR 3.99 (1.21, 13.1)*	0.02
		Colonoscopy among patients with uncomplicated diverticulitis	5/156 (3.2%)		
Meireles, 2015, 26378691, Portugal, NR	Adenoma, high grade dysplasia	Colonoscopy among patients with complicated diverticulitis	9/80 (11.3%)	OR 2.19 (0.95, 5.04)*	
		Colonoscopy among patients with uncomplicated diverticulitis	19/347 (5.5%)		
Suhardja, 2017, 28035461, Australia, NR	Adenoma, moderate-/high-grade dysplasia	Colonoscopy among patients with complicated diverticulitis	4/74 (5.4%)	OR 2.74 (0.67, 11.3)*	
		Colonoscopy among patients with uncomplicated diverticulitis	4/196 (2.0%)		
Suhardja, 2017, 28035461, Australia, NR	Higher risk adenomas	Colonoscopy among patients with complicated diverticulitis	8/74 (10.8%)	OR 4.63 (1.46, 14.7)*	
		Colonoscopy among patients with uncomplicated diverticulitis	5/196 (2.6%)		

* Calcuated by review team

Table C-3-6 KQ 3 Categorical outcomes, Subgroup Analysis: Others

Author, Year, PMID, Country, Funding	Outcome	Subgroup	n/N (%)	Effect Size between subgroups	Reported P value
Colorectal cancer					
Choi, 2014, 24723071, S Korea, NR	Colorectal cancer	Diverticulitis on the left side of colon	2/23 (8.7%)	OR 1.24 (0.25, 6.13)*	0.679
		Diverticulitis on the right side of colon	9/126 (7.1%)		
Soh, 2018, 29663068, Singapore, NR	Colorectal cancer	Diverticulitis on the left side of colon	2/54 (3.7%)	OR 3.38 (0.47, 24.6)*	
		Diverticulitis on the right side of colon	2/278 (1.1)		
Elmi, 2013, 23701063, USA, NR	Colorectal cancer	Colonoscopy among female patients	7/235 (3.0%)	OR 2.53 (0.52, 12.5)*	0.041
		Colonoscopy among male patients	2/167 (1.2%)		
Choi, 2014, 24723071, S Korea, NR	Colorectal cancer	Colonoscopy among female patients	NR	OR 1.08 (0.35, 3.34)*	

Author, Year, PMID, Country, Funding	Outcome	Subgroup	n/N (%)	Effect Size between subgroups	Reported P value
		Colonoscopy among male patients	NR		
Ramphal, 2018, 29945147, Netherlands, NR	Colorectal cancer	Patients with alarm symptoms	9/205 (4.4%)	OR 20.2 (2.54, 160)*	0.0002
		Patients with no alarm symptoms	1/440 (0.2%)		
High-risk colonic premalignant lesions					
Choi, 2014, 24723071, S Korea, NR	Advanced adenoma	Diverticulitis on the left side of colon	1/23 (4.3%)	OR 1.39 (0.15, 13.0)*	0.052
		Diverticulitis on the right side of colon	4/126 (3.2%)		
Choi, 2014, 24723071, S Korea, NR	Advanced colonic neoplasia	Diverticulitis on the left side of colon	3/23 (13.0%)	OR 1.30 (0.34, 4.99)*	0.715
		Diverticulitis on the right side of colon	13/126 (10.3%)		
Brar, 2013, 24105001, Canada, NR	Advanced colonic neoplasia	Anemia	NR	OR 0.78 (0.24, 2.57)	0.69
		No anemia	NR		
Brar, 2013, 24105001, Canada, NR	Advanced colonic neoplasia	Previous attack of diverticulitis	NR	OR 2.28, (0.76, 7.46)	0.14
		No previous attack of diverticulitis	NR		

* Calculated by review team.

Table C-3-7 KQ 3, Colonoscopy Tolerance, Feasibility, and Completion of Procedure; Technical Adequacy

Author, Year, PMID, Country, Funding	Design	Outcome	Arm/Subgroup	n/N (%)	Effect Size	Reported P value
Procedural complication						
Abdulazeez, 2020, 32820657, UK NR	NRCS	Procedural complication	Colonoscopy	0/120 (0%)	N/A	
			Flexible sigmoidoscopy	0/120 (0%)		
Lahat, 2007, 17554647, Israel, NR	RCT	Procedural complication	Colonoscopy (late, 6 weeks later)	0/41 (0)		
			Colonoscopy (early; in-hospital colonoscopy)	0/45 (0)		
Lau, 2011, 21904141, Australia, NR	NRCS (Retrospective)	Perforation	Colonoscopy	0/319 (0)		

Author, Year, PMID, Country, Funding	Design	Outcome	Arm/Subgroup	n/N (%)	Effect Size	Reported P value
O'Donohoe, 2019, 31882879, United Kingdom, NR	Single group (Retrospective)	Procedural complication	Colonoscopy	0/204 (0)		
Failed/incomplete procedure						
Lahat, 2007, 17554647, Israel, NR	RCT	Failed/incomplete procedure	Colonoscopy (late, 6 weeks later)	3/41 (7.3%)	OR 0.37 (0.09, 1.48)*	NS
			Colonoscopy (early; in-hospital colonoscopy)	8/45 (17.8%)		
Abdulazeez, 2020, 32820657, UK NR	NRCS	Procedural complication	Colonoscopy	5/120 (4.2%)	OR 1.70 (0.40, 7.26)*	NR
			Flexible sigmoidoscopy	3/120 (2.5%)		
Andrade, 2017, 27941344, Portugal, NR	Single group (Retrospective)	Failed/incomplete procedure	Colonoscopy	9/261 (3.4%)		
Suhardja, 2017, 28035461, Australia, NR	Single group (Retrospective)	Failed/incomplete procedure	Colonoscopy (all)	10/270 (3.7%)		
			Colonoscopy among patients with complicated diverticulitis	2/74 (2.7%)	OR 9.65 (0.14, 3.15)*	
			Colonoscopy among patients with uncomplicated diverticulitis	8/196 (4.1%)		
No show for the colonoscopy						
Lahat, 2007, 17554647, Israel, NR	RCT	No show for the colonoscopy	Colonoscopy (late, 6 weeks later)	10/41 (24.4%)	OR 4.52 (1.15, 17.8)*	0.033
			Colonoscopy (early; in-hospital colonoscopy)	3/45 (6.7%)		
Lahat, 2007, 17554647, Israel, NR	RCT	No show or incomplete exam	Colonoscopy (late, 6 weeks later)	13/41 (31.7%)	OR 1.44 (0.56, 3.70)*	
			Colonoscopy (early; in-hospital colonoscopy)	11/45 (24.4%)		

* Calculated by review team.

Nonsurgical Prevention of Recurrence (Key Questions 4a-b)

Table C-4ab-1: KQ 4ab Categorical Outcomes

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
Kvasnovsky, 2017, 28528364	No recurrence		Probiotics Symprove	All	NR (4)			HR 0.12 (0.01, 0.97)	
			Placebo	All	NR (32)				
Parente, 2013, 23754545	Recurrence of diverticulitis	2 yr	5-ASA	All	6/45 (13.3)			OR 0.40 (0.14, 1.17)	>0.05
			Placebo	All	13/47 (27.7)				
Lanas, 2013, 23092785	Recurrence of diverticulitis		Pharm Rifaximin	All	8/77 (10.4)	OR 0.31* (0.11, 0.86)	0.025		
			Placebo	All	17/88 (19.3)				
Lanas, 2013, 23092785	Hospitalization (or re-hospitalization) for diverticulitis		Pharm Rifaximin	All	2/77 (3)			OR 0.36 (0.07, 1.86)	
			Placebo	All	6/88 (7)				
Tursi, 2002, 12236485	Mortality - All-cause	12 mo	Rifaximin	All	1/109 (0.9)			OR 1.00 (0.06, 16.19)	
			5-ASA + Rifaximin	All	1/109 (0.9)				
Tursi, 2002, 12236485	Recurrence of diverticulitis	12 mo	5-ASA + Rifaximin	All	3/109 (2.75)			OR 0.13 (0.04, 0.44)	<0.01
			Rifaximin	All	20/109 (17.98)				
Tursi, 2002, 12236485	Resolution of diverticulitis symptoms	3 mo	5-ASA + Rifaximin	All	44/109 (40.36)			OR 3.21 (1.72, 5.99)	<0.005
			Rifaximin	All	19/109 (17.43)				
Tursi, 2002, 12236485	Resolution of diverticulitis symptoms	6 mo	5-ASA + Rifaximin	All	68/109 (62.96)			OR 4.17 (2.36, 7.37)	<0.001
			Rifaximin	All	31/109 (29.80)				
Tursi, 2002, 12236485	Resolution of diverticulitis symptoms	9 mo	5-ASA + Rifaximin	All	79/109 (73.83)			OR 4.92 (2.77, 8.75)	<0.0001

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
			Rifaximin	All	38/109 (39.27)				
Tursi, 2002, 12236485	Resolution of diverticulitis symptoms	12 mo	5-ASA + Rifaximin	All	89/109 (85.57)			OR 6.57 (3.54, 12.2)	<0.0005
			Rifaximin	All	44/109 (49.43)				
Tursi, 2002, 12236485	Return to normal bowel function	3 mo	5-ASA + Rifaximin	All	42/109 (38.53)			OR 2.97 (1.59, 5.56)	<0.005
			Rifaximin	All	19/109 (17.43)				
Tursi, 2002, 12236485	Return to normal bowel function	6 mo	5-ASA + Rifaximin	All	57/109 (52.77)			OR 2.52 (1.45, 4.40)	<0.001
			Rifaximin	All	33/109 (31.73)				
Tursi, 2002, 12236485	Return to normal bowel function	9 mo	5-ASA + Rifaximin	All	71/109 (66.35)			OR 2.56 (1.48, 4.42)	<0.001
			Rifaximin	All	46/109 (47.42)				
Tursi, 2002, 12236485	Return to normal bowel function	12 mo	5-ASA + Rifaximin	All	82/109 (78.85)			OR 3.21 (1.81, 5.70)	<0.001
			Rifaximin	All	53/109 (59.55)				
Tursi, 2007, 17390144	Recurrence of diverticulitis	12 mo	5-ASA + Probiotic	All	3/15 (20.0)			OR 0.38 (0.07, 1.92)	
			Probiotics	All	6/15 (46.7)				
Raskin, 2014, 25038431, PREVENT1	No recurrence	104 wk	5-ASA (1.2 g/d)	All	89/143 (62.2)		0.780 (vs. placebo)	OR 0.90 (0.56, 1.46)	
			5-ASA (2.4 g/d)	All	90/143 (62.9)		0.741 (vs. placebo)	OR 0.93 (0.58, 1.50)	
			5-ASA (4.8 g/d)	All	79/150 (52.7)		0.047 (vs. placebo)	OR 0.61 (0.38, 0.97)	
			Placebo	All	95/147 (64.6)				
Raskin, 2014, 25038431, PREVENT2	Without recurrence	104 wk	5-ASA (1.2 g/d)	All	93/148 (62.8)		0.368 (vs. placebo)	OR 0.81 (0.50, 1.32)	
			5-ASA (2.4 g/d)	All	87/147 (59.2)		0.159 (vs. placebo)	OR 0.69 (0.43, 1.12)	

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
			5-ASA (4.8 g/d)	All	103/149 (69.1)		0.778 (vs. placebo)	OR 1.07 (0.65, 1.76)	
			Placebo	All	96/142 (67.7)				
Mizuki, 2019, 31043657	Recurrence of diverticulitis		Burdock tea	All	5/47 (10.6)			OR 0.26 (0.08, 0.78)	0.013
			No intervention (non-placebo)	All	14/44 (31.8)				
Kruis, 2017, 28543263, SAG-37	Without recurrence	48 wk	5-ASA (3.0 g/d)	All	112/165 (67.9)			OR 0.73 (0.45, 1.17)	0.226
			Placebo	All	125/168 (74.4)				
Kruis, 2017, 28543263, SAG-37	Without recurrence	48 wk	5-ASA (3.0 g/d)	1 episode	61/92 (66.3)			OR 0.55 (0.29, 1.07)	
			Placebo	1 episode	71/91 (78)				
Kruis, 2017, 28543263, SAG-37	Without recurrence	48 wk	5-ASA (3.0 g/d)	>1 episode	51/73 (69.9)			OR 0.94 (0.47, 1.91)	
			Placebo	>1 episode	54/76 (71.1)				
Kruis, 2017, 28543263, SAG-37	Recurrence of diverticulitis	48 wk	5-ASA (3.0 g/d)	All	31/165 (18.8)			HR 0.60 (0.34, 1.05)	
			Placebo	All	20/168 (11.9)				
Kruis, 2017, 28543263, SAG-51	Without recurrence	48 wk	Pharm 5-ASA (1.5 g/d)	All	40/87 (46)			OR 0.62 (0.33, 1.13) vs. placebo	
			Pharm 5-ASA (3.0 g/d)	All	39/75 (52)			OR 0.78 (0.42, 1.48) vs. placebo	
			Placebo	All	47/81 (58)				
Kruis, 2017, 28543263, SAG-51	Without recurrence	96 wk	Pharm 5-ASA (1.5 g/d)	All	4/58 (6.9)			OR 0.25 (0.07, 0.82) vs. placebo	

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
			Pharm 5-ASA (3.0 g/d)	All	5/51 (9.8)			OR 0.36 (0.12, 1.12) vs. placebo	
			Placebo	All	12/52 (23.1)				
Kruis, 2017, 28543263, SAG-51	Without recurrence	48 wk	Pharm 5-ASA (1.5 g/d)	1 episode	26/47 (55.3)			OR 0.80 (0.33, 1.99) vs. placebo OR 0.80 (0.31, 2.07) vs. placebo	
			Pharm 5-ASA (3.0 g/d)	1 episode	21/38 (55.3)				
			Placebo	1 episode	20/33 (60.6)				
Kruis, 2017, 28543263, SAG-51	Without recurrence	48 wk	Pharm 5-ASA (1.5 g/d)	>1 episode	14/40 (35)			OR 0.42 (0.18, 0.99) vs. placebo OR 0.74 (0.31, 1.74) vs. placebo	
			Pharm 5-ASA (3.0 g/d)	>1 episode	18/37 (48.6)				
			Placebo	>1 episode	27/48 (56.3)				
Kruis, 2017, 28543263, SAG-51	Recurrence of diverticulitis	48 wk	Pharm 5-ASA (1.5 g/d)	All	15/87 (17.2)			OR 0.78 (0.36, 1.70) vs. placebo OR 0.94 (0.43, 2.05) vs. placebo	
			Pharm 5-ASA (3.0 g/d)	All	15/75 (20)				
			Placebo	All	17/81 (21)				
Stollman, 2013, 23426454, DIVA	Recurrence of diverticulitis	52 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	10/27 (37)			OR 1.31 (0.43, 3.96) vs. placebo OR	
			5-ASA (2.4 g/d)	All	9/32 (28.1)			OR 0.87 (0.29, 2.62) vs. placebo	
			Placebo	All	9/29 (31)				

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
Stollman, 2013, 23426454, DIVA	Surgery for diverticulitis	52 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	0/36 (0)				
			5-ASA (2.4 g/d)	All	2/40 (5)				
			Placebo	All	1/41 (2.4)				
Stollman, 2013, 23426454, DIVA	GSS response (0-1 on all 10 components of GSS)	52 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	29.2% (N<27)				
			5-ASA (2.4 g/d)	All	66.7% (N<32)				
			Placebo	All	50% (N<29)				
Stollman, 2013, 23426454, DIVA	Complete GSS response (0 on all components)	52 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	8.3% (N<27)				0.0452 (all)
			5-ASA (2.4 g/d)	All	40.7% (N<32)				
			Placebo	All	18.2% (N<29)				
Festa, 2017, 28387885	Recurrence of diverticulitis	15 mo	5-ASA	All	14/52 (26.9)	HR 0.27 (0.10, 0.72)			
			Rifaximin	All	7/72 (9.7)				
Festa, 2017, 28387885	Surgery for diverticulitis, including colostomy	15 mo	5-ASA	All	2/52 (4)				
			Rifaximin	All	2/72 (3)				

* Adjusted for age, sex, duration and localization of illness, time from last episode, and center recruitment rate.

Table C-4ab-2: KQ 4ab Continuous Outcomes

Study, Year, PMID	Outcome	Time	Arm	Subgroup	N	Result	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
Parente, 2013, 23754545	Physical condition*	2 yr	5-ASA	All	45	Mean 5.4 SD 2.7			−2.9 (−5.4, −0.4)	0.022
			Placebo	All	47	Mean 8.3 SD 5.7				
Parente, 2013, 23754545	Time to recurrence (days)	2 yr	5-ASA	All	45	Mean 219 SD 180			−151 (−366, 65)	0.17
			Placebo	All	47	Mean 369.8 SD 226.9				
Mizuki, 2019, 31043657	Acute colonic diverticulitis-free time (months)		Burdock tea	All	44	Mean 59.3			14.2 (3.1, 25.3)	0.012
			No intervention (non-placebo)	All	44	Mean 45.1				
Kruis, 2017, 28543263, SAG-51	Time to recurrence (days)	48 wk	Pharm 5-ASA (1.5 g/d)	All	NR	Mean 116 SD 134			HR 0.74 (0.38, 1.43) vs. placebo	0.369
			Pharm 5-ASA (3.0 g/d)	All	NR	Mean 191 SD 125			HR 1.02 (0.53, 1.94) vs. placebo	0.957
			Placebo	All	NR	Mean 147 SD 162				
Stollman, 2013, 23426454, DIVA	Time to recurrence (days)	52 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	27	Mean 280.7				
			5-ASA (2.4 g/d)	All	32	Mean 308.7				
			Placebo	All	29	Mean 100.1				
Stollman, 2013, 23426454, DIVA	Global symptom score (GSS), median or mean (SD)	Baseline 52 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	≤27	0: 19.4 52: 4.4				NS (vs. placebo)
			5-ASA (2.4 g/d)	All	≤32	0: 22.0 (8.6) 52: 1.0				NS (vs. placebo)
			Placebo	All	≤29	0: 23.5 (9.1) 52: 5.0				

CI = confidence interval, NR = not reported, OR = odds ratio, PMID = PubMed identifiery

Table C-4ab-3: KQ 4ab Adverse Events

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
Parente, 2013, 23754545	Adverse event – any	2 yr	5-ASA	All	6/45 (13.3)			OR 2.26 (0.53, 9.63)	
			Placebo	All	3/47 (6.4)				
Lanas, 2013, 23092785	Adverse event – any		Pharm Rifaximin	All	17/77 (22.1)			OR 1.63 (0.74, 3.63)	0.225
			Placebo	All	13/88 (14.8)				
Raskin, 2014, 25038431, PREVENT1	Adverse event – any ≥1 TEAE	104 wk	5-ASA (1.2 g/d)	All	109/143 (76.2)			OR 1.00 (0.58, 1.72) vs. placebo	
			5-ASA (2.4 g/d)	All	106/143 (74.1)			OR 0.90 (0.53, 1.53) vs. placebo	
			5-ASA (4.8 g/d)	All	101/150 (67.3)			OR 0.64 (0.39, 1.07) vs. placebo	
			Placebo	All	112/147 (76.2)				
Raskin, 2014, 25038431, PREVENT2	Adverse event – any ≥1 TEAE	104 wk	5-ASA (1.2 g/d)	All	108/148 (73)			OR 0.95 (0.56, 1.60) vs. placebo	
			5-ASA (2.4 g/d)	All	111/147 (75.5)			OR 1.09 (0.64, 1.85) vs. placebo	
			5-ASA (4.8 g/d)	All	110/149 (73.8)			OR 0.99 (0.59, 1.68) vs. placebo	
			Placebo	All	105/142 (73.9)				
Kruis, 2017, 28543263, SAG-37	Adverse event – Any	48 wk	5-ASA (3.0 g/d)	All	327/387 (85)			OR 1.45 (0.98, 2.16)	
			Placebo	All	225/285 (79)				
Festa, 2017, 28387885	Adverse event - any	15 mo	5-ASA	All	1/52 (2)				
			Rifaximin	All	0/72 (0)				
Silva Sanchez, 2014	Adverse event – any (TEAE)		5-ASA (4.8 g/d)	All	211/299 (71)				
Parente, 2013, 23754545	AE - Serious	2 yr	5-ASA	All	4/45 (8.9)			OR 2.20 (0.38, 12.62)	
			Placebo	All	2/47 (4.3)				

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
Raskin, 2014, 25038431, PREVENT1	AE – Serious	104 wk	5-ASA (1.2 g/d)	All	16/143 (11.19)			OR 1.03 (0.49, 2.15) vs. placebo	
			5-ASA (2.4 g/d)	All	15/143 (10.49)			OR 0.96 (0.46, 2.02) vs. placebo	
			5-ASA (4.8 g/d)	All	18/150 (12)			OR 1.12 (0.55, 2.28) vs. placebo	
			Placebo	All	16/147 (10.9)				
Raskin, 2014, 25038431, PREVENT2	AE – Serious	104 wk	5-ASA (1.2 g/d)	All	(8.1)				
			5-ASA (2.4 g/d)	All					
			5-ASA (4.8 g/d)	All					
			Placebo	All	15/142 (10.56)				
Kruis, 2017, 28543263, SAG-37	AE – Serious	48 wk	5-ASA (3.0 g/d)	All	55/387 (14)			OR 1.46 (0.91, 2.36)	
			Placebo	All	29/285 (10)				
Parente, 2013, 23754545	AE - Severe	2 yr	5-ASA	All	8/45 (17.8)			OR 0.91 (0.32, 2.62)	
			Placebo	All	9/47 (19.2)				
Parente, 2013, 23754545	AE – Leading to discontinuation	2 yr	5-ASA	All	8/45 (17.8)			OR 2.32 (0.65, 8.34)	
			Placebo	All	4/47 (8.5)				
Kruis, 2017, 28543263, SAG-37	AE – Leading to discontinuation	48 wk	5-ASA (3.0 g/d)	All	97/387 (25)			OR 1.53 (1.05, 2.24)	
			Placebo	All	51/285 (18)				
Raskin, 2014, 25038431, PREVENT1	AE – Sepsis (CD IV)	104 wk	5-ASA (1.2 g/d)	All	1/143 (0.7)				
			5-ASA (2.4 g/d)	All	0/143 (0)				

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
			5-ASA (4.8 g/d)	All	1/150 (0.67)				
			Placebo	All	0/147 (0)				
Raskin, 2014, 25038431, PREVENT1	AE – Major cardiac event (CD IV) Acute MI	104 wk	5-ASA (1.2 g/d)	All	1/143 (0.70)				
			5-ASA (2.4 g/d)	All	0/143 (0)				
			5-ASA (4.8 g/d)	All	0/150 (0)				
			Placebo	All	2/147 (1.36)				
Raskin, 2014, 25038431, PREVENT1	AE – Infection requiring Abx (CD II) UTI	104 wk	5-ASA (1.2 g/d)	All	14/143 (9.8)			OR 0.83 (0.39, 1.75) vs. placebo	
			5-ASA (2.4 g/d)	All	12/143 (8.4)			OR 0.70 (0.32, 1.52) vs. placebo	
			5-ASA (4.8 g/d)	All	8/150 (5.3)			OR 0.43 (0.18, 1.03) vs. placebo	
			Placebo	All	17/147 (11.6)				
Raskin, 2014, 25038431, PREVENT2	AE – Infection requiring Abx (CD II) UTI	104 wk	5-ASA (1.2 g/d)	All	11/148 (7.4)			OR 1.55 (0.58, 4.11) vs. placebo	
			5-ASA (2.4 g/d)	All	14/147 (9.5)			OR 2.03 (0.79, 5.19) vs. placebo	
			5-ASA (4.8 g/d)	All	10/149 (6.7)			OR 1.39 (0.51, 3.75) vs. placebo	
			Placebo	All	7/142 (4.9)				
Stollman, 2013, 23426454, DIVA	AE – Serious	12 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	0/36 (0)			OR 0.67 (0.11, 4.22) combined vs. placebo	
			5-ASA (2.4 g/d)	All	2/40 (5)				
			Placebo	All	3/41 (7.3)				
Stollman, 2013, 23426454, DIVA	AE – Infection requiring Abx (CD II) UTI	12 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	1/36 (2.8)				
			5-ASA (2.4 g/d)	All	1/40 (2.5)				
			Placebo	All	0/41 (0)				

Study, Year, PMID	Outcome	Time	Arm	Subgroup	n/N (%)	Effect Size (95% CI), Adjusted	P value, Adjusted	Effect Size (95% CI), Unadjusted	P value, Unadjusted
Stollman, 2013, 23426454, DIVA	Adverse event - headache	12 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	1/36 (2.8)				
			5-ASA (2.4 g/d)	All	0/40 (0)				
			Placebo	All	0/41 (0)				
Stollman, 2013, 23426454, DIVA	AE – Leading to discontinuation	12 wk	5-ASA (2.4 g/d) + probiotics (1/day)	All	1/36 (2.8)			OR 0.36 (0.04, 3.64) vs. placebo	
			5-ASA (2.4 g/d)	All	5/40 (12.5)			OR 1.81 (0.40, 8.14) vs. placebo	
			Placebo	All	3/41 (7.3)				
Silva Sanchez, 2014	AE - Infection requiring Abx (CD II) UTI		5-ASA (4.8 g/d)	All	18/299 (6)				
Silva Sanchez, 2014	Adverse event - headache		5-ASA (4.8 g/d)	All	27/299 (9)				

CI = confidence interval, NR = not reported, OR = odds ratio, PMID = PubMed identifier.

Elective Surgery (Key Question 4c)

Table C-4c-1. KQ 4c Treatment Comparisons, Categorical Outcomes

Study Year PMID Country Funding	Design	Population Diverticulitis Details Setting	Outcome	Followup Time	Arm	Arm Details	Age Sex	Severity Prior Episodes*	n/N (%)	Effect Size	Reported P value
You, 2018, 29683483, USA Industry	RCT	1 prior episode complicated diverticulitis with successful medical management Single center	Diverticulitis recurrence	3 y	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	Abscess 58% Median size 3.7 cm (IQR 2.4, 5·75) Extraluminal air 100%	2/26 (8%)	OR 0.18 (0.04, 0.80)	0.009 (Bonferroni adjustment)
					No treatment	Medical observation	55.2 (13.1) 63% male	Abscess 42% Median size 3.8 cm (IQR (2·15, 6·1) Extraluminal air 100%	26/81 (32%)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Diverticulitis recurrence	5 y	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	6/53 (11)	0.3 (0.1, 0.8)	
					No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)	17/56 (30)		

Study Year PMID Country Funding	Design	Population Diverticulitis Details Setting	Outcome	Followup Time	Arm	Arm Details	Age Sex	Severity Prior Episodes*	n/N (%)	Effect Size	Reported P value
Aquina, 2019, 30335195, USA	NRCS (retrospective)	With acute diverticular abscess	Diverticulitis recurrence	5 y	Elective surgery	Colectomy	Median 56 (IQR 47, 66) 51.8% male	At least 1 prior episode, 16.3	70/1660 (4.2)	0.1 (0.1, 0.2)	<0.001
					No intervention	Nonoperative management	Median 58 (IQR 47, 72) 46.3% male	At least 1 prior episode, 10.1	1340/5412 (24.8)		
You, 2018, 29683483, USA Industry	RCT	1 prior episode complicated diverticulitis with successful medical management. Single center	Mortality	3 y	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	Abscess 58% Median size 3.7 cm (IQR 2.4, 5·75) Extraluminal air 100%	0/26 (0%)		
					No treatment	Medical observation	55.2 (13.1) 63% male	Abscess 42% Median size 3.8 cm (IQR (2·15, 6·1) Extraluminal air 100%	0/81 (0%)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Mortality	5 y	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	0/53 (0)	0.5 (0, 15.6)	
					No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)	1/56 (1.8)		

Study Year PMID Country Funding	Design	Population Diverticulitis Details Setting	Outcome	Followup Time	Arm	Arm Details	Age Sex	Severity Prior Episodes*	n/N (%)	Effect Size	Reported P value
Aquina, 2019, 30335195, USA NR	NRCS (retrospective)	With acute diverticular abscess	Mortality – diverticulitis related	30 d	Elective surgery	Colectomy	Median 56 (IQR 47, 66) 51.8% male	At least 1 prior episode, 16.3	3/1660 (0.2)	0.1 (0, 0.3)	
					No intervention	Nonoperative management	Median 58 (IQR 47, 72 46.3% male	At least 1 prior episode, 10.1	104/5412 (1.9)		

LCUD = left colon uncomplicated diverticulitis, OR = odds ratio, PMID = PubMed identifier, RCT = randomized controlled trial.

* Median (range) data in square brackets; otherwise mean (SD)

Table C-4c-2. KQ 4c Treatment Comparisons, Continuous Outcomes

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
You, 2018, 29683483, USA Industry	RCT	1 prior episode complicated diverticulitis with successful medical management. Single center	Elective surgery	53.3 (13.5) 54% male	Abscess median 3.8 (range 3.8-7.7); extraluminal air 100	Length of hospital stay	30 d	26	Median 5.5 d, IQR 4, 8.5			0.903
			No treatment	55.2 (13.1) 63% male	Abscess median 1 (range 1-1.5); extraluminal air 100			81	Median 5 d, IQR 4, 8			

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
Aquina, 2019, 30335195, USA Not reported	NRCS (retrospective)	Mortality – diverticulitis related	Elective surgery	Median 56 (IQR 47, 66) 51.8 % male	At least 1 prior episode, 16.3	Length of hospital stay	30 d	1660	8.0 (7.8)	3.4 (2.95, 3.85)		<0.001
			No intervention	Median 58 (IQR 47, 72) 46.3 % male	At least 1 prior episode, 10.1			5412	4.6 (18.5)			
You, 2018, 29683483, USA Industry	RCT	1 prior episode complicated diverticulitis with successful medical management. Single center	Elective surgery	53.3 (13.5) 54% male	Abscess median 3.8 (range 3.8-7.7); extraluminal air 100	Time to recurrence	3 y	26	Median 11 m, IQR 8, 14			0·015
			No treatment	55.2 (13.1) 63% male	Abscess median 1 (range 1-1.5); extraluminal air 100			81	Median 7 m, IQR 3.25, 15			

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Elective surgery	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	Quality of life GIQLI	Baseline 6 m 5 y	53	92.6 (22.8) 114.4 (22.3) 118.2 (21.0)	6m 13.6 (5.2, 22) 5y 9.3 (1.3, 17.3)		6 m 0.0001 favors elective surgery 5 y 0.018 favors elective surgery
			No intervention	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)			56	92.2 (21.3) 100.4 (22.7) 108.5 (20.0)			

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Elective surgery	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	Quality of life SF-36 mental	Baseline 6 m 5 y	53	41.6 (14.5) 47.7 (12.4) 50.7 (9.4)	6m 4.1 (-0.4, 8.6) 5y 6.4 (2.2, 10.6)		6 m 0.263 favors elective surgery 5 y 0.010 favors elective surgery
			No intervention	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)			56	43.3 (9.5) 45.3 (10.3) 46.0 (9.2)			

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Elective surgery	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	Quality of life SF-36 physical	Baseline 6 m 5 y	53	37.0 (7.1) 43.5 (8.8) 47.6 (9.9)	6m 3.9 (1.1, 6.7) 5y 4.9 (1.5, 8.3)		6 m 0.016 favors elective surgery 5 y 0.030 favors elective surgery
			No intervention	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)			56	36.9 (6.7) 39.5 (7.0) 42.6 (10.5)			

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Elective surgery	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	Quality of life EQ-5D	Baseline 6 m 5 y	53	0.69 (0.21) 0.84 (0.20) 0.85 (0.18)	6m 0.2 (0.1, 0.2) 5y 0.2 (0.1, 0.2)		6 m 0.001 favors elective surgery 5 y 0.016 favors elective surgery
			No intervention	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)			56	0.74 (0.20) 0.73 (0.19) 0.74 (0.21)			

Study Year PMID Country	Design	Population Diverticulitis Details Setting	Arm	Age Sex	Severity Prior Episodes	Outcome	Follow up Time	N, Intervention (Control)	Results intervention (control)	Difference (95%CI)	Reported Difference (95%CI)	Reported P value
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	Ongoing abdominal complaints or frequently recurring left-sided diverticulitis after a confirmed episode of diverticulitis. Multicenter	Elective surgery	Median 54.1 (IQR 44.6-62.1) 28% male	Mean number previous episodes 3.1 (SD 1.0)	Pain (VAS, 0-10)	Baseline 6 m 5 y	53	63.3 (21.7) 23.9 (23.4) 30.5 (29.6)	6m -18.4 (-26.4, -10.4) 5y -11 (-20.1, -1.9)		6 m <0.0001 favors elective surgery 5 y 0.011 favors elective surgery
			No intervention	Median 56.5 (IQR 48.3-63.2) 43% male	Mean number previous episodes 4.1 (SD 2.0)			56	69.3 (13.6) 48.3 (22.9) 47.5 (25.1)			

CI = confidence interval, HR = hazard ratio, LCUD = left colon uncomplicated diverticulitis, NR = not reported, PMID = PubMed identifier, RCT = randomized controlled trial, SD = standard deviation.

Table C-4c-3. KQ 4c Adverse Events

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
You, 2018, 29683483, USA Industry	RCT	AE - Infection requiring Abx (CD II): Deep incisional Surgical Site Infection	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	1/26 (4%)		
			No treatment	Medical observation	55.2 (13.1) 63% male	0/81 (0%)		
You, 2018, 29683483, USA Industry	RCT	AE - Return to OR or unplanned procedure (CD III): Small bowel obstruction	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	1/26 (4%)		
			No treatment	Medical observation	55.2 (13.1) 63% male	0/81 (0%)		
You, 2018, 29683483, USA Industry	RCT	AE - Return to OR or unplanned procedure (CD III): Reoperation	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	0/26 (0%)		
			No treatment	Medical observation	55.2 (13.1) 63% male	0/81 (0%)		
You, 2018, 29683483, USA Industry	RCT	AE - Serious	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	1/26 (4%)		
			No treatment	Medical observation	55.2 (13.1) 63% male	0/81 (0%)		
You, 2018, 29683483, USA Industry	RCT	AE - Ileus	Elective surgery	Laparoscopic sigmoid colectomy	53.3 (13.5) 54% male	1/26 (4%)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
			No treatment	Medical observation	55.2 (13.1) 63% male	0/81 (0%)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	AE - Serious (SAE) Any	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	6m: 18/53 (34.0) 5 y: 37/53 (69.8)		
			No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	6m: 23/56 (41.1) 5y: 45/56 (80.4)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	AE - Infection requiring Abx (CD II) urinary tract infection	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	6m: 4/53 (7.5) 5y: 0/53 (0)		
			No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	6m: 2/56 (3.6) 5y: 1/56 (1.8)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	AE - Major pulmonary event (CD IV) Pulmonary embolism	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	6m: 0/53 (0) 5y: 2/53 (3.8)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
			No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	6m: 1/56 (1.8) 5y: 1/56 (1.8)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	AE - Return to OR or unplanned procedure (CD III) CPR in OR	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	1/53 (1.9)		
			No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	0/56 (0)		
van de Wall, 2017, 28404008, DIRECT trial, Netherlands Non-industry	RCT	AE - Return to OR or unplanned procedure (CD III) anastomotic leakage	Elective surgery	Laparoscopic sigmoidectomy,	Median 54.1 (IQR 44.6-62.1) 28% male	7/53 (13.2)		
			No intervention	Conservative management	Median 56.5 (IQR 48.3-63.2) 43% male	0/56 (0)		
Aquina, 2019, 30335195, USA Not reported	NRCS (retrospective)	AE - Stoma	Elective surgery	Colectomy	Median 56 (IQR 47, 66) 51.8% male	166/1660 (10.0)		<0.001

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
			No intervention	Nonoperative management	Median 58 (IQR 47, 72 46.3% male	309/5412 (5.7)		
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA Non-industry	Single group (Prospective)	AE - Infection requiring Abx (CD II) organ or space surgical site infection	Elective surgery (all)	Laparoscopic	55.7 47% male	13/576 (2.3)		
			Elective surgery (simple diverticulitis)	Laparoscopic		9/437 (2.1)		
			Elective surgery (complicated diverticulitis)	Laparoscopic		5/139 (3.6)		
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA Non-industry	Single group (Prospective)	AE - Ileus	Elective surgery (all)	Laparoscopic	55.7 47% male	22/576 (3.8)		
			Elective surgery (simple diverticulitis)	Laparoscopic		14/437 (3.2)		
			Elective surgery (complicated diverticulitis)	Laparoscopic		12/139 (8.6)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA Non-industry	Single group (Prospective)	AE - Return to OR or unplanned procedure (CD III) Anastomatic leak	Elective surgery (all)	Laparoscopic	55.7 47% male	12/576 (2.1)		
			Elective surgery (simple diverticulitis)	Laparoscopic		10/437 (2.3)		
			Elective surgery (complicated diverticulitis)	Laparoscopic		2/139 (1.4)		
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA Non-industry	Single group (Prospective)	AE - Return to OR or unplanned procedure (CD III) Incisional hernia	Elective surgery (all)	Laparoscopic	55.7 47% male	10/576 (1.8)		
			Elective surgery (simple diverticulitis)	Laparoscopic		7/437 (1.6)		
			Elective surgery (complicated diverticulitis)	Laparoscopic		4/139 (2.9)		
Bhakta, 2016, 26275534, Albany Medical Center 2001-13, USA Non-industry	Single group (Prospective)	AE - Clostridioides difficile (C diff) infection	Elective surgery (all)	Laparoscopic	55.7 47% male	17/576 (3.0)		
			Elective surgery (simple diverticulitis)	Laparoscopic		13/437 (2.9)		
			Elective surgery (complicated diverticulitis)	Laparoscopic		4/139 (2.9)		
Bordeianou, 2019, 29916880, PREVENTT, USA Not reported	Single group (Prospective)	AE - Infection requiring Abx (CD II) Total Surgical Site Infection	Elective surgery (all)	Any	59.9 (12.7) 43.6% male	284/1506 (18.9)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Bordeianou, 2019, 29916880, PREVENTT, USA Not reported	Single group (Prospective)	AE - Infection requiring Abx (CD II) Organ space Surgical Site Infection	Elective surgery (all)	Any	59.9 (12.7) 43.6% male	73/1506 (4.8)		
Bordeianou, 2019, 29916880, PREVENTT, USA Not reported	Single group (Prospective)	AE - Infection requiring Abx (CD II) Deep Surgical Site Infection	Elective surgery (all)	Any	59.9 (12.7) 43.6% male	13/1506 (0.9)		
Bordeianou, 2019, 29916880, PREVENTT, USA Not reported	Single group (Prospective)	AE - Infection requiring Abx (CD II) Superficial Surgical Site Infection	Elective surgery (all)	Any	59.9 (12.7) 43.6% male	224/1506 (14.9)		
Silva-Velazco, 2016, 26541732, USA Non-industry	Single group (Prospective)	AE - 30-day mortality	Elective surgery (all)	Laparoscopic	55 (12) 52% male	2/1059 (0.19)		
Silva-Velazco, 2016, 26541732, USA Non-industry	Single group (Prospective)	AE - Unplanned (re)hospitalization 30 d rehospitalization	Elective surgery (all)	Laparoscopic	55 (12) 52% male	120/1059 (11)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Silva-Velazco, 2016, 26541732, USA Non-industry	Single group (Prospective)	AE - Return to OR or unplanned procedure postoperative anastomotic leak and/or abdomino-pelvic abscess	Elective surgery (all)	Laparoscopic	55 (12) 52% male	39/1059 (3.7)		
			Elective surgery (BMI <30)	Laparoscopic	55 (12) 52% male		Ref	
			Elective surgery (BMI 30-35)	Laparoscopic	55 (12) 52% male		OR 1.33 (95%CI 0.69, 2.55)	P=0.39
			Elective surgery (BMI ≥ 35)	Laparoscopic	55 (12) 52% male		OR 2.30 (95%CI 1.16, 4.55)	P=0.017
			Elective surgery (Uncomplicated diverticulitis)	Laparoscopic	55 (12) 52% male		Ref	
			Elective surgery (Complicated diverticulitis)	Laparoscopic	55 (12) 52% male		OR 2.37 (95%CI 1.36, 4.11)	P=0.002

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Silva-Velazco, 2016, 26541732, USA Non-industry	Single group (Prospective)	AE - Serious (SAE) clinical anastomotic leak, abdominal and/or pelvic abscess, postoperative bleeding, DVT, dehydration, ileus, mechanical small bowel obstruction, small bowel leak, stoma complications, Clostridium difficile, sepsis, wound infection, wound dehiscence, urinary, renal, cardiovascular and other respiratory morbidity.	Elective surgery (all)	Laparoscopic	55 (12) 52% male	296/1059 (28)		
			Elective surgery (BMI <30)	Laparoscopic	55 (12) 52% male		Ref	
			Elective surgery (BMI 30-35)	Laparoscopic	55 (12) 52% male		OR 1.31 (95%CI 0.93, 1.84)	P=0.12
			Elective surgery (BMI ≥ 35)	Laparoscopic	55 (12) 52% male		1.05 (95%CI 0.68, 1.60)	P=0.84
			Elective surgery (Uncomplicated diverticulitis)	Laparoscopic	55 (12) 52% male		Ref	
			Elective surgery (Complicated diverticulitis)	Laparoscopic	55 (12) 52% male		OR 1.32 (95%CI 0.96, 1.82)	P=0.08

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Simianu, 2015, 25773308, Surgical Care and Outcomes Assessment Program (SCOAP), USA Non-industry	Single group (Prospective)	AE - Serious (SAE) In-hospital complications, including cardiac, pulmonary, renal, infectious, or other, requiring nonoperative intervention	Elective surgery	Laparoscopic	57.8 (12.7) 47% male	139/1790 (7.8)		
Simianu, 2015, 25773308, Surgical Care and Outcomes Assessment Program (SCOAP), USA Non-industry	Single group (Prospective)	AE - Return to OR or unplanned procedure (CD III) composite adverse events (CAE), including cardiac, pulmonary, renal, infectious, or other complications requiring nonoperative intervention + reoperative interventions and in-hospital deaths	Elective surgery	Laparoscopic	57.8 (12.7) 47% male	210/1790 (11.7)		
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	AE – 30-day mortality	Elective surgery (all)	Laparoscopic	63 [Range 23, 91] 42% male	2/846 (0.2)		
			Elective surgery (age <60)	Laparoscopic		0/358 (0)		
			Elective surgery (age 60-69)	Laparoscopic		0/277 (0)		
			Elective surgery (age >69)	Laparoscopic		2/211 (1)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	AE - Return to OR or unplanned procedure Anastomosis	Elective surgery (all)	Laparoscopic	63 [Range 23, 91 42% male	17/846 (2)		P-value across age groups 0.605
			Elective surgery (age <60)	Laparoscopic		6/358 (1.7)		
			Elective surgery (age 60-69)	Laparoscopic		5/277 (1.8)		
			Elective surgery (age >69)	Laparoscopic		6/211 (2.8)		
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	AE - Return to OR or unplanned procedure hemorrhage requiring revision	Elective surgery (all)	Laparoscopic	63 [Range 23, 91] 42% male	7/846 (0.8)		P-value across age groups 0.042
			Elective surgery (age <60)	Laparoscopic		6/358 (1.7)		
			Elective surgery (age 60-69)	Laparoscopic		1/277 (0.4)		
			Elective surgery (age >69)	Laparoscopic		0/211 (0)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	AE – Ileus Paralytic Ileus	Elective surgery (all)	Laparoscopic	63 [Range 23, 91] 42% male	5/846 (0.6)		P-value across age groups 0.155
			Elective surgery (age <60)	Laparoscopic		0/358 (0)		
			Elective surgery (age 60-69)	Laparoscopic		3/277 (1.1)		
			Elective surgery (age >69)	Laparoscopic		2/211 (1)		
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	AE - Ileus	Elective surgery (all)	Laparoscopic	63 [Range 23, 91] 42% male	2/846 (0.2)		P-value across age groups 0.05
			Elective surgery (age <60)	Laparoscopic		0/358 (0)		
			Elective surgery (age 60-69)			0/277 (0)		
			Elective surgery (age >69)	Laparoscopic		2/211 (1)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	Hospitalization for diverticulitis 30-day readmission	Elective surgery (all)	Laparoscopic	63 [Range 23, 91] 42% male	33/846 (3.9)		P-value across age groups 0.81
			Elective surgery (age <60)	Laparoscopic		15/358 (4.2)		
			Elective surgery (age 60-69)	Laparoscopic		9/277 (3.3)		
			Elective surgery (age >69)	Laparoscopic		9/211 (4.3)		
Tsilimparis, 2010, 20812161, Fast-track Kolon II, Germany Not reported	Single group (Prospective)	AE - Bleed requiring transfusion (CD II)	Elective surgery (all)	Laparoscopic	63 [Range 23, 91] 42% male	6/846 (0.7)		P-value across age groups 0.06
			Elective surgery (age <60)	Laparoscopic		2/358 (0.6)		
			Elective surgery (age 60-69)	Laparoscopic		0/277 (0)		
			Elective surgery (age >69)	Laparoscopic		4/211 (1.9)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE – 30-day mortality	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	2/564 (0.4)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	0/66 (0)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	0/54 (0)		
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE - Acute Renal Failure	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	5/564 (0.9)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	0/66 (0)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	0/54 (0)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE - Bleed requiring transfusion	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	28/564 (5)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	1/66 (1.5)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	0/54 (0)		
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE - Infection requiring Abx Urinary tract infection	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	12/564 (2)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	1/66 (1.5)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	1/54 (2)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE - Major cardiac event atrial fibrillation or myocardial infarction	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	9/564 (1.6)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	2/66 (3)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	2/54 (3.7)		
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE - Major pulmonary event respiratory failure or pulmonary embolus or deep venous thrombosis	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	8/564 (1.4)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	0/66 (0)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	0/54 (0)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE - Return to OR or unplanned procedure anastomotic leakage	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	8/564 (1.4)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	0/66 (0)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	1/54 (2)		
Boostrom, 2012, 22696233, Mayo Clinic, Rochester, USA Not reported	Single group (Retrospective)	AE – Stroke Ischemic stroke	Elective surgery (Acute resolving uncomplicated diverticulitis)	Sigmoidectomy	Median 63 45% male	2/564 (0.4)		
			Elective surgery (Chronic/ smoldering uncomplicated diverticulitis)	Sigmoidectomy	Median 66 38% male	0/66 (0)		
			Elective surgery (Atypical uncomplicated diverticulitis)	Sigmoidectomy	Median 64 37% male	0/54 (0)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE – 30-day mortality	Elective surgery	Sigmoidectomy	65.7 (13.1) 45.7% male	4,413/124,421 (3.5)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Acute Renal Failure	Elective surgery	Sigmoidectomy	65.7 (13.1)	385/11192 (3.4)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - DVT	Elective surgery	Sigmoidectomy	45.7% male	18/11192 (0.2)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Infection requiring Abx Intra-abdominal abscess	Elective surgery	Sigmoidectomy	65.7 (13.1)	138/11192 (1.2)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Major pulmonary event Acute respiratory distress syndrome	Elective surgery	Sigmoidectomy	45.7% male	114/11192 (1.0)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Major pulmonary event Pneumonia	Elective surgery	Sigmoidectomy	65.7 (13.1)	1.5/11192 (166)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Return to OR or unplanned procedure Reoperation	Elective surgery	Sigmoidectomy	45.7% male	679/11192 (6.1)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Sepsis	Elective surgery	Sigmoidectomy	65.7 (13.1)	120/11192 (1.1)		
Ilyas, 2017, 27422847, Nationwide Inpatient Sample (2004-2001), USA Non-industry	Single group (Retrospective)	AE - Return to OR or unplanned procedure Anastomotic leakage	Elective surgery	Sigmoidectomy	45.7% male	929/11192 (8.3)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE – 30-day mortality	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	277/22752 (1.22)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference category	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.6 (95%CI 1.05, 2.61)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 2.8 (95%CI 2.46, 6.05)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 3.8 (95%CI 2.46, 6.05)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 10.2 (95%CI 6.49, 15.98)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 3.5 (95%CI 2.59, 4.63) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 1.2 (95%CI 0.91, 1.63) compared to no COPD	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Infection requiring Abx Infection, Seroma, Dehiscence, Nonhealing wound, or Emphysema (subcutaneous)	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	1052/22752 (4.6)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference category	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 0.9 (95%CI 0.80, 1.10)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 0.9 (95%CI 0.79, 1.12)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 0.7 (95%CI 0.56, 0.89)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 1.9 (95%CI 1.50, 2.39) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 1.4 (95%CI 1.19, 1.67) Compared to no COPD	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Acute renal failure	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	490/22752 (2.49)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference category	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.3 (95%CI 0.98, 1.63)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.7 (95%CI 1.34, 2.22)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 1.7 (95%CI 1.26, 2.25)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 4.1 (95%CI 3.22, 5.12) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 0.9 (95%CI 0.74, 1.17) compared to no COPD	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Major cardiac event Complications, Acute myocardial infarction	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	594/22752 (2.5)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.1 (95%CI 0.87, 1.45)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.4 (95%CI 1.12, 1.85)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 2.2 (95%CI 1.59, 3.09)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 1.7 (95%CI 1.28, 2.24)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 4.6 (95%CI 3.68, 5.74) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 0.9 (95%CI 0.76, 1.20) compared to no COPD	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Infection requiring Abx Respiratory tract complications, Acute bacterial pneumonia, Acute respiratory failure	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	1782/22752 (7.5)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.1 (95%CI 0.98, 1.33)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.5 (95%CI 1.32, 1.80)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 1.9 (95%CI 1.60, 2.22)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 2.8 (95%CI 2.26, 3.40)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 4.2 (95%CI 3.59, 4.85) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 2.2 (95%CI 1.94, 2.50) compared to no COPD	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE – Sepsis Postoperative SIRS, sepsis, or Septicemia	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	495/22752 (2.08)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.1 (95%CI 0.81, 1.48)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.6 (95%CI 1.23, 2.19)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 2.3 (95%CI 1.69, 3.14)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 3.5 (95%CI 2.47, 4.98)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 3.2 (95%CI 2.53, 4.35) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 1.1 (95%CI 0.82, 1.38) compared to no COPD	
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE – DVT Acute pulmonary embolism or Acute deep vein thrombosis	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	259/22752 (1.09)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.0 (95%CI 0.72, 1.46)	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.3 (95%CI 0.90, 1.83)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 2.3 (95%CI 1.69, 3.14)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 1.3 (95%CI 0.72, 2.30)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 1.6 (95%CI 1.00, 2.43) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 1.0 (95%CI 0.71, 1.42) compared to no COPD	
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Return to OR or unplanned procedure Colostomy	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	2071/22752 (9.1)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference category	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.1 (95%CI 0.98, 1.29)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.1 (95%CI 1.28, 1.68)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 2.2 (95%CI 1.92, 2.58)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 4.3 (95%CI 3.69, 5.29)	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 1.1 (95%CI 0.98, 1.25) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 1.9 (95%CI 1.68, 2.27) compared to no COPD	
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Return to OR or unplanned procedure Ileostomy	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	3006/23764 (12.7)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference category	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.3 (95%CI 1.05, 1.74)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.9 (95%CI 1.42, 2.52)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 1.4 (95%CI 1.11, 1.90)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 1.0 (95%CI 0.59, 1.61)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 1.2 (95%CI 0.88, 1.77) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 1.1 (95%CI 0.87, 1.41) compared to no COPD	

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Lidor, 2010, 20878256, USA Non-industry	Single group (Retrospective)	AE - Return to OR or unplanned procedure Ileostomy	Elective surgery (all)	Left colectomy with ileostomy	73.9 (5.9) 28.9% male	470/22752 (1.98)		
			Elective surgery (Age 65-69)	Left colectomy with ileostomy		N = 6622	reference	
			Elective surgery (Age 70-74)	Left colectomy with ileostomy		N = 6817	OR 1.0 (95%CI 0.75, 1.32)	
			Elective surgery (Age 75-79)	Left colectomy with ileostomy		N = 5336	OR 1.4 (95%CI 1.09, 1.80)	
			Elective surgery (Age 80-84)	Left colectomy with ileostomy		N = 2816	OR 1.1 (95%CI 0.82, 1.60)	
			Elective surgery (Age 85+)	Left colectomy with ileostomy		N = 1161	OR 1.1 (95%CI 0.74, 1.72)	
			Elective surgery (CHF)	Left colectomy with ileostomy		N = 1486	OR 1.5 (95%CI 1.01, 2.11) compared to no CHF	
			Elective surgery (COPD)	Left colectomy with ileostomy		N = 4116	OR 0.8 (95%CI 0.63, 1.11) compared to no COPD	
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE – 30-day mortality	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	20/9788 (0.2)		
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Major cardiac event Myocardial infarction	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	20/9788 (0.2)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Major cardiac event Cardiac arrest	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	10/9788 (0.1)		
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Major pulmonary event Pulmonary embolism	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	29/9788 (0.3)		
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Reintubation Unplanned intubation	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	49/9788 (0.5)		
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Return to OR or unplanned procedure	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	401/9788 (4.1)		
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Sepsis Septic shock	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	59/9788 (0.6)		
Moghadamyeghaneh, 2015, 26116319, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Unplanned (re)hospitalization (CD IV)	Elective surgery	Open (28%) Laparoscopic (72%)	58 (12) 45.9% male	715/9788 (7.3)		
Novitsky, 2009, 18639223, Nationwide Inpatient Sample (2001-2002), USA Non-industry	Single group (Retrospective)	Surgery for diverticulitis colostomy	Elective surgery	Left colectomy/Left colectomy with ostomy/Left colectomy with ileostomy	67.1 (13.8) 41.8% male	213/3716 (6)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Novitsky, 2009, 18639223, Nationwide Inpatient Sample (2001-2002), USA Non-industry	Single group (Retrospective)	Morbidity	Elective surgery	Left colectomy/Left colectomy with ostomy/Left colectomy with ileostomy	67.1 (13.8) 41.8% male	557/3716 (15)		
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA Not reported	Single group (Retrospective)	AE - 30-day mortality	Elective surgery	Laparoscopic approach and ostomy creation	<50 years 24.2% to 29.7%, 65+ years 2	115/29893 (0.4)		
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA Not reported	Single group (Retrospective)	AE - Sepsis	Elective surgery	Laparoscopic approach and ostomy creation	<50 years 24.2% to 29.7%, 65+ years 2	878/29893 (2.9)		
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA Not reported	Single group (Retrospective)	AE - Major cardiac event Myocardial Infarction	Elective surgery	Laparoscopic approach and ostomy creation	<50 years 24.2% to 29.7%, 65+ years 2	76/29893 (0.3)		
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA Not reported	Single group (Retrospective)	AE - Major pulmonary event Pulmonary embolism	Elective surgery	Laparoscopic approach and ostomy creation	<50 years 24.2% to 29.7%, 65+ years 2	124/29893 (0.4)		
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA Not reported	Single group (Retrospective)	AE - Reintubation	Elective surgery	Laparoscopic approach and ostomy creation	<50 years 24.2% to 29.7%, 65+ years 2	233/29893 (0.8)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Papageorge, 2016, 27120447, ACS-NSQIP 2005-13, USA Not reported	Single group (Retrospective)	AE - Major cardiac event Cardiac arrest	Elective surgery	Laparoscopic approach and ostomy creation	<50 years 24.2% to 29.7%, 65+ years 2	43/29893 (0.1)		
Perez, 2020, 32748338, New York Statewide Planning and Research Cooperative System (SPARCS), US Not reported	Single group (Retrospective)	AE - Return to OR or unplanned procedure Incisional hernia repair	Elective surgery	Open or laparoscopic sigmoid or left hemicolectomy	55.9 years 50.1% male	1 year: 129/6811 (1.9%) 3 year: 272/6811 (4.0%) 5 year: 334/6811 (4.9%)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - 30-day mortality	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	7/582 (1.2)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Return to OR or unplanned procedure anastomotic leakage	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	9/582 (1.5)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Major pulmonary event pulmonary edema	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	10/582 (1.7)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Stroke	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	3/582 (0.5)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Major cardiac event myocardial infarction	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	5/582 (0.9)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - DVT	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	4/582 (0.7)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Major pulmonary event Pulmonary embolism	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	1/582 (0.2)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Major pulmonary event pneumonia	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	26/582 (4.5)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Infection requiring Abx Urinary tract infection	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	29/582 (5.0)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Infection requiring Abx Urinary tract infection	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	5/582 (1.8)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Acute Renal Failure	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	4/582 (0.7)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Sepsis (CD IV)	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	9/582 (1.5)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE- Morbidity	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	145/582 (24.9)		
Pessaux, 2004, 14639493, French Association for Surgical Research, France Not reported	Single group (Retrospective)	AE - Infection requiring Abx Deep infection	Elective surgery	Laparotomy for colon or rectal resection for diverticulitis	<58 years 37.5%, 59-75 years 45.8%, >76 years 16.7% 46.6% male	13/582 (1.4)		
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA Not reported	Single group (Retrospective)	AE - 30-day mortality	Elective surgery	Open	59.2 46.9% male	14/3502 (0.4)		0.0004
			Elective surgery	Laparoscopic	55.6 49.1% male	38/3468 (1.1)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA Not reported	Single group (Retrospective)	AE - Bleed requiring transfusion	Elective surgery	Open	59.2 46.9% male	32/3502 (0.9)		<0.0001
				Laparoscopic	55.6 49.1% male	232/3468 (6.7)		
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA Not reported	Single group (Retrospective)	AE - Sepsis	Elective surgery	Open	59.2 46.9% male	77/3502 (2.2)	OR 0.659 (95%CI 0.48, 0.90) favors laparoscopic	<0.0001
				Laparoscopic	55.6 49.1% male	156/3468 (4.5)		
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA Not reported	Single group (Retrospective)	AE - Sepsis Septic shock	Elective surgery	Open	59.2 46.9% male	77/3502 (2.2)	OR 0.44 (95%CI 0.26, 0.76) favors laparoscopic	<0.0001
				Laparoscopic	55.6 49.1% male	156/3468 (4.5)		
Russ, 2010, 20193685, ACS-NSQIP 2005-08, USA Not reported	Single group (Retrospective)	AE - Major pulmonary event Pulmonary embolism	Elective surgery	Open	59.2 46.9% male	11/3502 (0.3)	0.49 (95%CI 0.23, 1.05) favors laparoscopic	0.039
				Laparoscopic	55.6 49.1% male	28/3468 (0.8)		
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Sepsis	Elective surgery		>65 years 31.5%	64/2444 (2.6)		
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Sepsis Septic shock	Elective surgery		>65 years 31.5%	17/2444 (0.7)		

Study Year PMID Country Funding	Design	Outcome	Arm/Subgroup	Arm/subgroup Details	Age Sex	n/N (%)	Effect Size	Reported P value
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Return to OR or unplanned procedure	Elective surgery		>65 years 31.5%	108/2444 (4.4)		
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - DVT	Elective surgery		>65 years 31.5%	12/2444 (0.5)		
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Major cardiac event Myocardial infarction	Elective surgery		>65 years 31.5%	7/2444 (0.3)		
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Infection requiring Abx Urinary tract infection	Elective surgery		>65 years 31.5%	51/2444 (2.1)		
Valizadeh, 2018, 30747633, ACS-NSQIP 2012-13, USA Not reported	Single group (Retrospective)	AE - Infection requiring Abx Pneumonia	Elective surgery		>65 years 31.5%	20/2444 (0.8)		
Varma, 2019, 30527478, California State Inpatient Database 2005-13, USA Non-industry	Single group (Retrospective)	AE - Unplanned (re)hospitalization (CD IV)	Elective surgery		55.3 years 48.4% male	~148/3533 (4.2)		
von Strauss und Torney, 2020, 32401298, Switzerland & UK Non-industry	Single group (Retrospective)	AE - 30 day mortality (post-surgical, CD V)	Elective surgery		NR	30/3511 (0.85)		
von Strauss und Torney, 2020, 32401298, Switzerland & UK Non-industry	Single group (Retrospective)	AE - Return to OR or unplanned procedure (CD III)	Elective surgery		NR	159/3511 (4.5)		

Table C-4c-4. KQ 4c Adverse Events Summary

Adverse Event (Clavien-Dindo Classification, As Applicable)	n/N (Total)	Summary Percentage (95% CI)	Range Across Studies	Evidence Base
Serious AE (composite or not otherwise specified)	544/2928	**25.1 (3.7, 57.0)**	4.0 – 69.8	**4 studies(52-55, 68, 69)**
Ostomy (either planned or unplanned, implied)	3006/23,752	12.6 (12.2, 13.1)	12.6	1 study(60 , 67)
Major pulmonary event, composite (CD IV) (Respiratory tract complications, acute bacterial pneumonia, acute respiratory failure)	1782/22,752	7.8 (7.5, 8.2)	7.8	1 study(60 , 67)
30-day readmission (CD IV)	983/14,380	7.3 (3.8, 11.8)	4.2 – 11.0	3 studies(62, 68, 72)
Reoperation, unplanned (CD III)	1236/15,367	**4.3 (2.2, 6.9)**	0 – 13.2	**8 studies (52, 59, 60, 62, 67, 69, 71, 73)**
Anastomotic leakage requiring procedure (CD III)	1077/15,367	**4.3 (2.2, 6.9)**	1.5 – 13.2	**6 studies (53-55, 57, 59, 65, 68, 70)**
Urinary tract infections requiring antibiotics (CD II)	84/3079	3.9 (1.6, 7.2)	2.1 – 7.5	3 studies(53-55, 65, 71)
Small bowel obstruction requiring procedure (CD III)	1/26	3.8 (0.5, 22.8)	3.8	1 study(52)
C diff infection	17/576	3.0 (1.8, 4.7)	3.0	1 study(57)
Acute renal failure	879/34,526	2.0 (0.7, 3.9)	0.7 – 3.4	3 studies(59, 60, 65, 67)
Pulmonary edema (CD IV)	10/582	1.7 (0.9, 3.2)	1.7	1 study(65)
Incisional hernia requiring procedure (CD III)	**139/7387**	**1.9 (1.6, 2.2)**	**1.7 – 1.9**	**2 studies(57, 64)**
Sepsis (CD IV)	**1719/82,597**	**1.6 (1.0, 2.3)**	**0.6 – 2.9**	**7 studies (59, 60, 62, 63, 65-67, 71)**
Surgical site infections requiring antibiotics (CD II)	40/3272	**1.4 (0.8, 1.9)**	0.9 – 4.0	**4 studies(52, 57, 58, 65)**
Pneumonia (CD IV)	48/14,218	1.3 (0, 4.4)	0.8 – 4.5	3 studies(59, 65, 71)
Ileus	30/2294	1.3 (0.1, 3.8)	0.2 – 4.0	3 studies(52, 57, 70)
Intra-abdominal abscess (CD IV)	138/11,192	1.2 (1.0, 1.5)	1.2	1 study(59)
Bleed requiring transfusion (CD II)	515/27,946	1.1 (0.6, 1.8)	0.7 – 2.0	3 studies(60, 66, 67, 70)
Acute respiratory distress syndrome (CD IV)	114/11,192	1.0 (0.8, 1.2)	1.0	1 study(59)

Adverse Event (Clavien-Dindo Classification, As Applicable)	n/N (Total)	Summary Percentage (95% CI)	Range Across Studies	Evidence Base
30-day mortality (CD V)	4957/199,915	**0.7 (0.3, 1.4)**	0.18 – 3.5	**10 studies (56, 59, 60, 62, 63, 65-68, 70, 73)**
Myocardial infarction (CD IV)	702/65,459	**0.7 (0.1, 1.6)**	0.2 – 2.5	**5 studies (60, 62, 63, 65, 67, 71)**
Cardiac arrest (CD IV)	160/25,205	0.6 (0, 1.7)	0.1 – 1.9	3 studies(53-55, 61, 63)
DVT	293/36,970	**0.6 (0.2, 1.1)**	0.2 – 1.1	**4 studies (59, 60, 65, 67, 71)**
Reintubation (CD IV)	282/39,681	0.6 (0.4, 0.9)	0.5 – 0.8	2 studies(62, 63)
Stroke (CD IV)	3/582	0.5 (0.2, 1.6)	0.5	1 study(65)
Pulmonary embolism (CD IV)	167/43,818	**0.3 (0.1, 0.6)**	0.2 – 3.8	**5 studies (53-55, 62, 63, 65, 66)**

Adverse events reported by at least four studies are emphasized in bold font.

Abbreviations: AE=adverse event; C diff = Clostridioides difficile; CD=Clavien-Dindo Classification; CPR = cardiopulmonary resuscitation; DVT=deep vein thrombosis; OR=operating room; SAE= serious adverse event.

TO: Clinical Guidelines Committee (CGC)

SUBJECT: Resolution 4-F19: Referred from the Board of Regent (BOR) to the Clinical Guidelines Committee (CGC) for Implementation

BACKGROUND: The BOR has referred the following resolution to the CGC for implementation over the course of the next year.

> **Resolution 4-F19. Ensuring that ACP Guidelines Incorporate the Potential Adverse Effects of Polypharmacy**
>
> **RESOLVED, that the Board of Regents advocates for and works with stakeholders and guideline developers to ensure that ACP treatment guidelines incorporate the potential adverse effects of polypharmacy and reduce the burden of medication overload.**

During the January 2021 webinar, the CGC will discuss potential strategies to implement the intent of the resolution within the next year. A report summarizing the CGC discussion and summary of any steps taken is due back to the BOR in Fall 2021.

To inform the discussion, the following documents are enclosed:

- CGC final report and recommendation on draft resolution
    - CGC email discussion re: draft resolution
- Background information on draft resolution
- BOR/BOG LeaderNet discussion on draft resolution

Clinical Guidelines Committee Report (June 2020)

The Clinical Guidelines Committee (CGC) has reviewed and discussed Resolution 4-F19 and offers the following comments in response:

Resolution 4-F19. Insuring that ACP Guidelines Consider the Potential Adverse Effects of Polypharmacy

RESOLVED, that the Board of Regents advocates for and works with stakeholders and guideline developers to insure that ACP guidelines incorporate evidence-based, patient-centered recommendations to consider the potential adverse effects of polypharmacy and reduce the burden of medication overload.

The Clinical Guidelines Committee (CGC) is supportive of the resolution's intent. We suggest specifying that the resolution applies to treatment guidelines, given that some ACP guidelines address screening or diagnosis and for which this resolution would not be relevant. Definitions of polypharmacy vary, but it is commonly defined as >5 medications daily (1), and as such, it would be difficult to operationalize each guideline to address specific drug-drug interactions in a way that would be useful to individual clinicians and patients. The CGC develops each clinical recommendation by rigorously weighing the evidence on an intervention's clinical benefits against its harms, based on a systematic review of the evidence, in addition to considering information on costs and patient values and preferences (2). The evidence on harms is derived from research studies, thus the extent to which we can make evidence-based recommendations on the adverse effects of polypharmacy is informed by the whether or not this issue is addressed by the available studies. In cases where the trial evidence does not specifically address polypharmacy, polypharmacy and medication burden are more appropriately addressed in a guideline's "Clinical Considerations" and "Multiple Comorbidities" sections, rather than the recommendations themselves. For example, ACP's 2017 guideline on pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets includes the following statements in its clinical considerations and multiple chronic conditions sections (3):

- "Many older adults may be taking various medications. Clinicians should consider treatment burden and drug interaction when deciding on treatment options."
- "Individual assessment of benefits and harms is particularly important in adults aged 60 years or older with multiple chronic conditions, several medications, or frailty."

Based on these considerations, the CGC recommends adopting the resolution with the following amendments that are intended to specify treatment guidelines in the resolution and to more clearly convey that polypharmacy and medication overload should be considered in clinical decision-making, without mandating the development of specific recommendations:

RESOLVED, that the Board of Regents advocates for and works with stakeholders and guideline developers to ~~ie~~nsure that ACP treatment guidelines ~~incorporate evidence-based, patient-centered recommendations to~~ consider the potential adverse effects of polypharmacy and ~~reduce~~ the burden of medication overload.

References

1. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230. Published 2017 Oct 10. doi:10.1186/s12877-017-0621-2

2. Qaseem A, Kansagara D, Lin JS, Mustafa RA, Wilt TJ, for the Clinical Guidelines Committee of the American College of Physicians. The Development of Clinical Guidelines and Guidance Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods. Ann Intern Med. [Epub ahead of print 11 June 2019]170:863–870. doi: 10.7326/M18-3290
3. Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA, et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. [Epub ahead of print 17 January 2017]166:430–437. doi: 10.7326/M16-1785

FINANCIAL IMPACT ESTIMATE:

_____ None (0-$999)
_____ Minimal ($1,000-$14,999)
_____ Moderate ($15,000 - $49,999)
_____ Significant ($50,000 - $99,999)
___X__ Substantial ($100,000 or more) (if an evidence review on polypharmacy is undertaken)

What percentage of these funds is unbudgeted? _100_____ %

PREVIOUS CGC DISCUSSION RELEVANT TO IMPLEMENTATION OF DRAFT RESOLUTION 4-F19

Emailed Comments from CGC Members (June 2020) regarding draft resolution 4-F19: RESOLVED, that the Board of Regents advocates for and works with stakeholders and guideline developers to insure that ACP guidelines incorporate evidence-based, patient-centered recommendations to consider the potential adverse effects of polypharmacy and reduce the burden of medication overload.	
#1	Of note we had begun to develop sections on Patients with multiple comorbidities. This has implications related to polypharmacy (we also noted this in our DM Targets guidance statement). Not sure that our response would differ but I agree that ensuring our guidelines regarding medications take into account the impact of recommending for or against a medication especially in older adults with multiple comorbidities is important. Finally, in developing our recommendations the CGC considers the generalizability of findings from studies (RCTs) that may recruit a population uniquely interested or likely to benefit from the intervention and might exclude individuals specifically taking certain meds or likely to be taking multiple medications (or with multiple comorbidities) and/or in whom medication adherence is problematic (an issue exacerbated with polypharmacy).
#2	In order to implement this, we'd have to require all systematic reviews to include a key question regarding individuals with comorbidities and polypharmacy as subgroups of special interest, and I'm suspecting that quite often we'll be forced (unfortunately) to conclude that evidence is insufficient to allow specific recommendations to be targeted to those subgroups.
#3	I do think the issue about polypharmacy and multiple co morbidities is an important one. It is very important to highlight that we are already addressing this issue although the labelling may not be explicit: • Majority of the treatment studies (RCTs and observational) we assess when reviewing evidence to support the recommendations include patients with multiple co morbidities and polypharmacy • Even if the studies do not explicitly mention poly pharmacy, I think we can make inferences about poly pharmacy based on the included patients (% with DM, % with HTN, % with CVD..etc) • If the studies included patients that are not typical of the population of interest (including for example a healthier population with less comorbidities) we will downgrade our certainty under the indirectness domain which addresses the applicability of the existing evidence to the recommendations. We may want to explicitly highlight the issue of polypharmacy under the indirectness domain moving forward. • We may also want to add a good practice statement to guidelines that typically address treatments of populations that will likely have co morbidities/ polypharmacy stating that it is important to consider interaction of the suggested/recommended treatment with other medications that the patients are likely to be on. We may also highlight the common ones in a table. • For us to address the issue of comorbidities/polypharmacy in more details that will require separate resources to support reviews about: - patients values - burden of treatment and if this evidence is missing in the literature (which is often missing) then we need to have the capacity to generate primary evidence which will require running patients focus groups. - potential interaction with other medications. I honestly do not see that completing these detailed reviews will be a good return on investment. So I think the points above will be sufficient from the CGC point of view.

#4	I think with the rephrasing of the resolution the word “reduce” could be eliminated. I also think that “ensure” is more appropriate than “insure." Thus change "insure that ACP treatment guidelines consider the potential adverse effects of polypharmacy and reduce the burden of medication overload” to “ensure that ACP treatment guidelines consider the potential adverse effects of polypharmacy and the burden of medication overload.” I
#5	I do like the idea of routinely addressing, if applicable, the implications for polypharmacy in the persons with multiple comorbidities section and seeing what we can reasonably extrapolate from the included evidence, as well as the addition of a good practice statement (as Reem suggests) for patients who are at higher risk for polypharmacy.
#6	I agree we should think carefully about how to implement the resolution, and would caution us against proscribing something too detailed or fancy at this point. One low-hanging-fruit way of incorporating this concept routinely into CGC decision making would be to include the concept of "burden" in the Evidence to decision table framework - I think it is already there actually, and is kind of considered alongside cost. Of note, the concept of burden might be related to polypharmacy (ie - just taking too many pills), but it might also be related to any monitoring/testing that might be associated with a given treatment. Drug interactions related to the addition of a given med are related to polypharmacy, but seems a bit different from the concept of "burden" - it seems more closely related to the concept of harms. Cynthia Boyd, Linda Humphrey, I and others had spent some time writing up a practical approach to presenting data to inform the multimorbidity section a few years back. I can't find it off hand. I don't think we ever really implemented that beyond one or two guidelines. The example cited in the resolution is the hypertension guideline. That one was somewhat unique in the sense that pill burden was an actual outcome reported in the evidence review (it was feasible to do so because a number of studies reported that outcome). I think finding that type of outcome will be the exception rather than the rule.
#7	I agree…we don’t want to try and get fancy (I don’t think the literature would support it) and likely a low yield pursuit.
#8	This is an important consideration, and can be commented on within the practice statement recommendations, in my mind similar to the more simplified way of making reader aware of cost differences without going into a major cost analysis. I think the concept is intuitive to clinicians in most situations, but we have to be cognizant of recognizing and addressing to highlight the concept consistently. I am sure there will be a difference in how closely we study/highlight this depending on the topic. The htn example is a great one, where it is directly relevant and recommended combinations are well-studied. But in most situations, if we get too into the weeds, despite the time and cost investment, I don’t think it will change the overall take home message for the reader.
#9	Polypharmacy is a very important issue. I have heard so many stories of friends/ colleagues who during the course of caregiving for elderly family or friends realized many medicines were bringing actual harm to their loved ones and were able to eliminate most if not all through healthy diet and lifestyle changes. Quality of life improved. Can't say enough about benefits of medication management and opportunities made available for healthier lives and livelihoods

94

Background Information

Resolution 4-F19. Insuring that ACP Guidelines Consider the Potential Adverse Effects of Polypharmacy

RESOLVED, that the Board of Regents advocates for and works with stakeholders and guideline developers to insure that ACP guidelines incorporate evidence-based, patient-centered recommendations to consider the potential adverse effects of polypharmacy and reduce the burden of medication overload.

---

1. PREVIOUS RELATED RESOLUTIONS:

2-F17. Developing ACP Policy for Appropriate Use of Step Therapy, RESOLVED, that the Board of Regents develops policy for appropriate use of step therapy and defines medically justifiable exemptions.

At the October 2017 Business Meeting, the BOG recommended that the BOR adopt Resolution 2-F17 as amended. At its November 2017 meeting, the BOR voted to adopt and refer the 1st resolved clause to the Medical Practice and Quality Committee for implementation, and did not adopt the 2nd resolved clause

At their February 2018 webinar, the Medical Practice and Quality Committee (MPQC) discussed and approved the development of a policy paper regarding appropriate use of step therapy. Committee members suggested the paper balance the competing needs of patient safety, administrative burdens, and keeping costs down, as well as incorporate elements of related Resolutions 3-F17, Updating ACP Policy on Drug Formularies and Pharmacy Benefit Managers, and 4-F17, Developing ACP Policy to Address the Problem of Non-medical Switching of Medications by Insurance Companies and Pharmacy Benefit Managers, once they are referred by the BOR for implementation. College staff will begin development of this policy paper this fall, with a plan for it to be completed and released in 2019.

2. DIVISION/DEPARTMENT BACKGROUND SUMMARY:

Executive Office: Clinical Policy

The Clinical Guidelines Committee (CGC) follows a rigorous process and methodology to identify and assess potential outcomes, including harms, of a given intervention and includes input from the CGC Public Panel. The CGC, with input from a technical expert panel, drafts or revises the initial key questions and determines the population, interventions, comparators, and outcomes of interest, including both benefits and harms (1). Harms vary by a clinical condition or intervention, as will the rating and availability of evidence on each outcome. Polypharmacy and medication burden is an important area that CGC considers when developing its recommendations. We highlighted this issue in our recent guidelines such as treatment of hypertension or management of diabetes (2, 3)

References

1. Qaseem A, Kansagara D, Lin JS, Mustafa RA, Wilt TJ, for the Clinical Guidelines Committee of the American College of Physicians. The Development of Clinical Guidelines and Guidance Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods. Ann Intern Med. [Epub ahead of print 11 June 2019]170:863–870. doi: 10.7326/M18-3290

2. Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA, et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. [Epub ahead of print 17 January 2017]166:430–437. doi: 10.7326/M16-1785
3. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA, et al. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med. [Epub ahead of print 6 March 2018]168:569–576. doi: 10.7326/M17-0939

3. FINANCIAL IMPACT ESTIMATE:

_X___ None (0-$999)
_____ Minimal ($1,000-$14,999)
_____ Moderate ($15,000 - $49,999)
_____ Significant ($50,000 - $99,999)
___X_ Substantial ($100,000 or more) (if an evidence review is undertaken)

What percentage of these funds is unbudgeted? _100_____ %

ACP LeaderNet Comments on Draft Resolution

Resolution 4-F19. Insuring that ACP Guidelines Consider the Potential Adverse Effects of Polypharmacy

(Sponsor: BOG Class of 2021)

WHEREAS, polypharmacy is often considered to be five or more medications per patient; and

WHEREAS, polypharmacy may include prescription medications, over-the-counter drugs and supplements that were either never necessary, indicated but not beneficial, or no longer necessary; and

WHEREAS, polypharmacy is a public health problem that may affect as many as two-thirds of adults over the age of 65 years; and

WHEREAS, polypharmacy increases the risk of drug-drug interactions, adverse drug events, preventable hospitalizations, and mortality; and

WHEREAS, polypharmacy increases the risk of non-adherence to medications that are necessary and high-value; and

WHEREAS, polypharmacy is associated with high costs to patients and health care delivery systems; and

WHEREAS, many current clinical guidelines emphasize "step therapy" and escalation of dosage to achieve therapeutic goals, insufficient attention is paid to "step down" therapy to taper or deprescribe medications that were not beneficial or no longer provide benefit; and

WHEREAS, current American College of Physician policies and guidelines recognize polypharmacy as a harm that might be mitigated by implementation of shared decision-making and patient-centered medical homes, current ACP policy does not treat polypharmacy as an outcome for intervention by itself; and

WHEREAS, some ACP guidelines suggest consideration of "deintensifying pharmacologic therapy," there are others that do not address the potential risks associated with polypharmacy; therefore be it

RESOLVED, that the Board of Regents advocates for and works with stakeholders and guideline developers to insure that ACP guidelines incorporate evidence-based, patient-centered recommendations to consider the potential adverse effects of polypharmacy and reduce the burden of medication overload.

References:

https://lowninstitute.org/wp-content/uploads/2019/04/medication-overload-lown-web.pdf
Medication Overload: America's Other Drug Problem
lowninstitute.org

Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Non pregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med. 2018 Apr 17;168(8):569-576. doi: 10.7326/M17-0939. Epub 2018 Mar 6. PMID: 29507945

Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017 Apr 4;166(7):514-530. doi: 10.7326/M16-2367. Epub 2017 Feb 14. PMID: 2819278

Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016 Jul 19;165(2):125-33. doi: 10.7326/M15-2175. Epub 2016 May 3. PMID: 27136449

Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians.

Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher VersusLower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017 Mar 21;166(6):430-437. doi: 10.7326/M16-1785. Epub 2017 Jan 17. PMID: 28135725

patient-centered_physician-guided_care_for_chronically_ill_2004 (https://www.acponline.org/cgi-bin/policy-library)

medicare_reform_patient_centered_medical_home_2007 (https://www.acponline.org/cgi-bin/policy-library)

acp_response_to_sfc_chronic_care_policies_2015 (https://www.acponline.org/cgi-bin/policy-library)

ACP Policies and Recommendations | Advocacy | ACP

www.acponline.org

patient_safety_in_the_office_based_practice_setting_2017 (https://www.acponline.org/cgi-bin/policy-library)

ACP Policies and Recommendations | Advocacy | ACP

www.acponline.org

Linsky A, Simon SR, Stolzmann K, Meterko M. Patient attitudes and experiences that predict medication discontinuation in the Veterans Health Administration. J Am Pharm Assoc (2003). 2018 Jan - Feb;58(1):13-20. doi: 10.1016/j.japh.2017.10.012. Epub 2017 Nov 16. PMID: 29154017

Linsky A, Meterko M, Bokhour BG, Stolzmann K, Simon SR. Deprescribing in the context of multiple providers: understanding patient preferences. Am J Manag Care. 2019 Apr;25(4):192-198. PMID: 30986016

Jonathan Shammash, Governor, New Jersey (NJN) replied on August 8, 2019 - 9:44pm | Disclosures

I support the resolution, though unsure if it would be practical to implement.

> *Mark Noah, Governor, California Southern 1 (CAS1) replied on September 19, 2019 - 5:34pm | Disclosures*
>
> The Southern California Region 1 Governor's Advisory Council supports this resolution, but is not sure how it would be implemented.

Andrew Dunn, Former Governor, New York (NYD1) replied on August 15, 2019 - 9:59am

I agree with the resolution in concept but as others have suggested may be hard to implement as a standard part of every ACP guideline. Having seen the process in action, each potential recommendation for a medication is considered based on the evidence of the benefits and harms of the medication, which would include harms noted in trials that may in part be related to polypharmacy. Wording could be revised to ensure polypharmacy is considered for all guidelines without requiring incorporation in every instance.

> *Noel Deep, Governor, Wisconsin (WI) replied on September 21, 2019 - 11:17pm | Disclosures*
>
> I agree.
>
> *Mangla Gulati, Governor, Maryland (MD) replied on September 22, 2019 - 1:30pm | Disclosures*
>
> I agree.

Myriam Allende-Vigo, Governor, Puerto Rico (PR) replied on September 2, 2019 - 9:43am | Disclosures

I support in principle the resolution, do not support as written. Most of my patients are on polypharmacy just for concurrent medical conditions, let alone OTC and/or supplements. It would be

very hard for ACP to make a recommendation specific and tailored to individual cases, nor address it in guidelines. I see it more like a partnership between all health care providers and pharmacists in communication with patients in order to avoid ASE, duplication of medications and use of unnecessary meds. Probably this is a re affirmation of current policy.

Ashesh Patel, Governor, District of Columbia (DC) replied on September 23, 2019 - 8:10pm | Disclosures

I agree.

Peter Basch, BOR Member, District of Columbia (DC) replied on September 2, 2019 - 12:44pm | Disclosures

I think I understand the intent of resolution - which I believe is that most guidelines look at treatment for a problem or circumstance, and may end up recommending 3 or more drugs for one condition (for example, to meet a BP target or an A1C target). Failure to follow a guideline could result in lower quality scores in process or intermediate outcomes measures, and perhaps even a malpractice suit (should the patient suffer an untoward event).

Guidelines may include comments about shared-decision making, and quality measures sometimes refer to reasons that can be used (and thus count as exclusions) such as medical reasons and patient reasons (i.e., adverse reaction or patient decline).

This may actually be less difficult to implement than we think (or it may be impossible). I would suggest referring it to the Guidelines Committee for their sage advice

Mangla Gulati, Governor, Maryland (MD) replied on September 22, 2019 - 1:30pm | Disclosures

I agree.

Marianne Parshley, Governor, Oregon (OR) replied on September 23, 2019 - 1:23pm | Disclosures

I agree.

Marianne Parshley, Governor, Oregon (OR) replied on September 23, 2019 - 1:23pm | Disclosures

I agree.

Douglas DeLong, BOR Member, New York (NYHV) replied on September 3, 2019 - 3:37pm | Disclosures

as a quasi-geriatrician, one who thinks "drugs!" as the likely culprit in almost any clinical situation, and one who spends a significant portion of every medical encounter "reconciling" or pruning medication lists, I am clearly in favor of addressing polypharmacy. But I agree with others on this one that either reaffirmation or aspirational only.

Noel Deep, Governor, Wisconsin (WI) replied on September 21, 2019 - 11:18pm | Disclosures

I agree.

Samuel Thigpen, Governor, Mississippi (MS) replied on September 18, 2019 - 11:17pm | Disclosures

The Mississippi Council supports this resolution.

Charles Hamori, Governor, California Southern 3 (CAS3) replied on September 19, 2019 - 7:03pm | Disclosures

SoCal Region 3 strongly supports this. We often have EMR alerts about drug-drug interactions, but rarely are there alerts about guideline-guideline interactions. The intent of the resolution is to make sure that drafters of guidelines explicitly state how theirs will interact with others.

Tiffany Leung, Chair-elect, CECP, No Chapter (OTH) replied on September 24, 2019 - 10:38am | Disclosures

As an individual, I support in principle the importance of noting how guidelines interact. However, based on my past experience in informatics fellowship examining clinical practice guidelines and their utility in cases of multimorbidity, this is incredibly computationally complex to represent and then resolve interactions between guideline-guideline interactions, for purposes of computerized decision support systems. Easy to ask (and logical from our medical expert viewpoints) but hard to do. From a knowledge expertise standpoint in evidence reviews when CPGs are made, it would also

seem very difficult to encompass all possible polypharmacy and guideline interactions even in narrative form; even if there is a prioritization based on commonest comorbidities, this still presents a challenge. I don't disagree that it is still an important problem though, as any individual clinician is hard pressed to remember and recall all of those interactions, too.

James Graumlich, Governor, Illinois Southern (ILS) replied on September 21, 2019 - 6:27pm | Disclosures
Illinois Health and Public Policy Committee supports the intent of the resolution but shares the concerns aforementioned about implementation.

Noel Deep, Governor, Wisconsin (WI) replied on September 21, 2019 - 11:22pm | Disclosures
Agree with the intent of the resolution, but do not believe it can be implemented.

David Hilden, Governor, Minnesota (MN) replied on September 22, 2019 - 9:49pm | Disclosures
It's hard to not support efforts against polypharmancy and our MN HPPC members support the resolution. Speaking for myself, I agree with Dr. Lenchus in asking whether a resolution is the best vehicle for this. In the end, though, we support the resolution.

Elisa Choi, Governor, Massachusetts (MA) replied on September 24, 2019 - 4:41am | Disclosures
Our Chapter and Council agrees with this resolution. In addition, on member also added the following: "I think this should be a billable service including the conversation on the phone with the patient's other prescriber. I'm thinking of the interactions here between opioids, benzos, gabapentinoids, z-drugs etc which dramatically increases risk but when you are not the prescriber what can you do?"

Marianne Parshley, Governor, Oregon (OR) replied on September 23, 2019 - 1:33pm | Disclosures
My council generally supported the intent behind the resolution (address polypharmacy) but share the concerns about. However, one of my council, who served on the guidelines committee, strongly supported it despite also noting that the CGC already does some of this and suggested we co-sponsor it if it were reworded more clearly (not specific wording offered).

Most expressed not only concern about addressing polypharmacy in a more positive proactive way, (sometimes is addressed in a judgemental way according to some stories) and expressed the need for better education about de-prescribing and de-escalating medication, though they were not certain this resolution was the vehicle. I, personally, would hope ACP could help facilitate teaching these skills across the spectrum of GIM docs from learner to late career.

Ashesh Patel, Governor, District of Columbia (DC) replied on September 23, 2019 - 8:12pm | Disclosures
DC council supports but one member made a very good point that sometimes polypharmacy is unavoidable simply to treat co-existing conditions. I agree with the comments by Puerto Rico.

Tiffany Leung, Chair-elect, CECP, No Chapter (OTH) replied on September 24, 2019 - 10:33am | Disclosures
Most of CECP agrees with the importance of emphasizing consideration of polypharmacy in developing ACP guidelines, but also noted that spending significant resources on an evidence review wouldn't be necessary. CECP questioned if this represents a reaffirmation of an existing ACP policy. We also discussed that if this is reaffirmation, then presumably there is not a significant cost associated with this resolution (background materials note a $10k price tag for evidence review, which CECP felt was costly).

Mary Beth Poston, Governor, South Carolina (SC) replied on September 24, 2019 - 11:19am | Disclosures
The South Carolina Governor's Council supports this resolution.

Systematic Review Protocol

Project Title:

Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder

An Update of the 2014 Comparative Effectiveness Review

December 2020

Version 3.0

ACP Medical Officer: Itziar Etxeandia-Ikobaltzeta, PharmD, PhD

Project Lead Investigator: Gerald Gartlehner, MD, MPH

Project Staff:

Gernot Wagner, MD, Co-Investigator

Lisa Affengruber, MSc, Co-Investigator

Andreea Dobrescu, MD, PhD, Co-Investigator

Ana Toromanova, Co-Investigator

Irma Klerings, Information Specialist

Petra Wellemsen, Project Coordinator

Christoph Pieh, MD, Clinical Expert

Emma Persad, Student Assistant

PROSPERO Registration Number: TBD

Background and Objectives

Depressive disorders can be serious, disabling illnesses. Major depressive disorder (MDD),[1] defined as the presence of depressed mood or loss of interest or pleasure, along with at least four additional MDD diagnosis criteria or symptoms for a duration of at least 2 weeks, [1] is the most prevalent and disabling, affecting more than 16 percent of U.S. adults (lifetime).[2] Mortality rates attributable to MDD and other depressive illnesses are high; approximately 4 percent of adults with a mood disorder commit suicide, and about two-thirds of suicides are preceded by depression.[3] In any given year, nearly 7 percent of the U.S. adult population experiences an episode of MDD that warrants treatment.[2]

Most patients receiving care obtain treatment in primary care settings,[4] where second-generation antidepressants (SGAs) are the most commonly prescribed treatments.[5] Other first line treatment options include psychotherapies or complementary and alternative treatments such as St. John's Wort, acupuncture, Yoga, and others. Following initial treatment, however, only about 30 percent of patients will experience symptom remission.[6,7] Second-step treatments can include switching antidepressants or augmenting with a second medication. A second treatment attempt produces similar rates of improvement as the first treatment attempt.[8] This Systematic Review will focus on the initial two treatment attempts for depressive illness.

1. As an initial treatment choice, how effective are SGAs compared with nonpharmacologic interventions?
2. For patients whose depression did not achieve remission following initial treatment with an SGA, what is the comparative effectiveness of alternative pharmacologic and nonpharmacologic options? These options include adding a pharmacologic or nonpharmacologic treatment to the initial medication choice (which we refer to as augmentation or switching to a different SGA or to a nonpharmacologic treatment).

Key Questions

The following key questions will guide our systematic review:

KQ 1: In adult patients with MDD who are undergoing an initial treatment attempt, what are the comparative benefits and harms of SGAs and non-pharmacologic treatments?

KQ 1a: Do treatment benefits and harms vary by MDD severity?

KQ 1b: Do treatment benefits and harms vary by:

- subgroups of patients with MDD defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy, or somatization)
- demographic characteristics (age, sex, race, or ethnicity)?

KQ 2: In adult patients with MDD who did not achieve remission following an initial adequate trial with one SGA, what are the benefits and harms of second-step therapies?

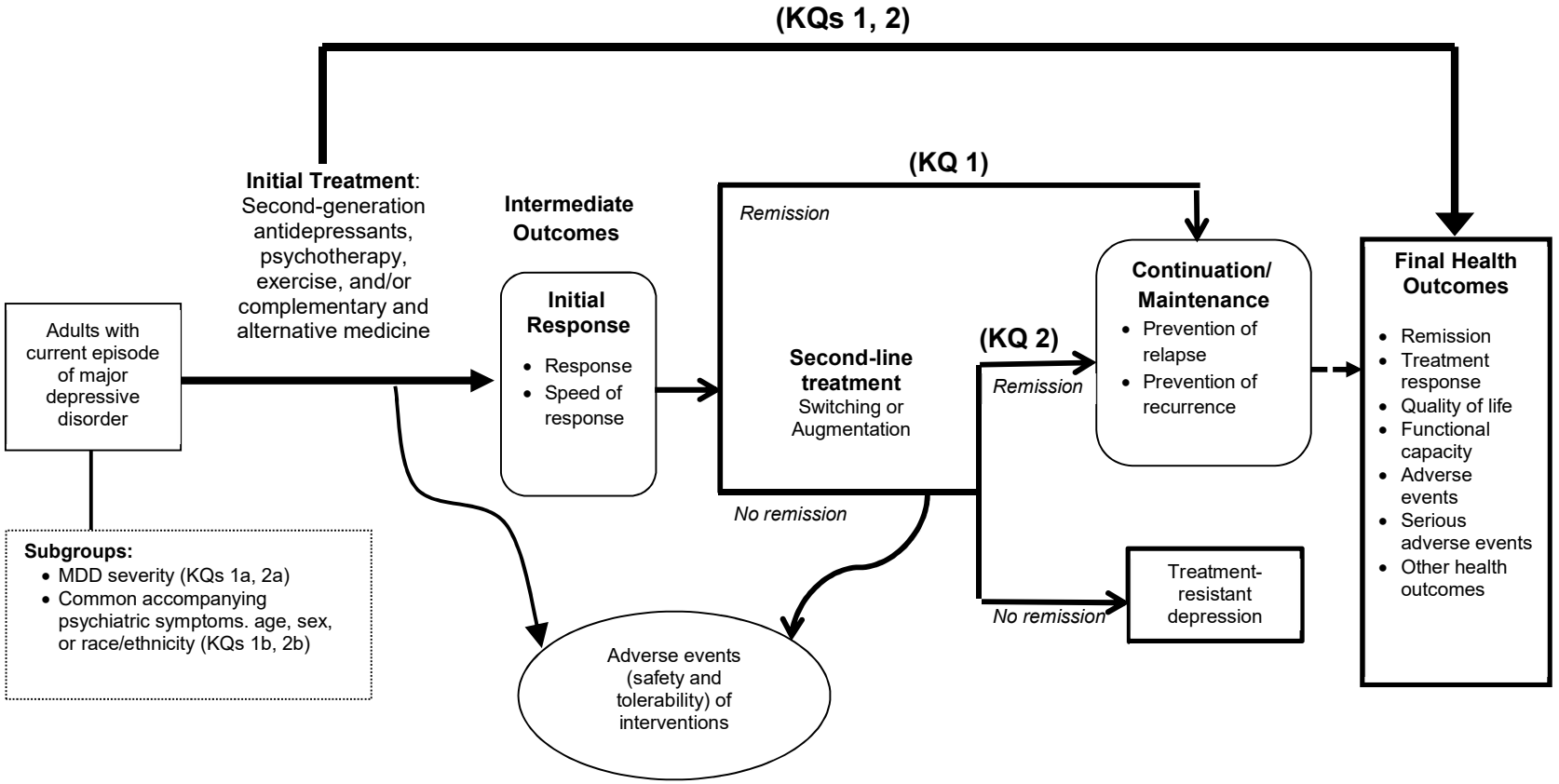
KQ 2a: Does treatment effectiveness vary by MDD severity?

KQ 2b. Do the benefits and risks of harms of these treatment options differ by

- subgroups of patients with MDD defined by common accompanying psychiatric symptoms (coexisting anxiety, insomnia, low energy, or somatization)
- demographic characteristics (age, sex, race, or ethnicity)?

Analytic Framework

Figure 1. Analytic Framework for Treatment of Major Depressive Disorder



KQ = Key Question; MDD = major depressive disorder; SGA = second-generation antidepressant

Methods

Study eligibility criteria

We specified our inclusion and exclusion criteria based on the population, intervention, comparators, outcomes, timing, and settings (PICOTS) in Table 1. We will exclude study designs without control groups to ensure that our pool of included studies can inform the causal link between the intervention and outcomes.

Table 2. Inclusion/exclusion criteria

	Criteria		
Category		**Inclusion**	**Exclusion**
Population	KQ 1 or KQ 2	Adult (18 years or older) outpatients of all races and ethnicities with MDD during either an initial treatment attempt or a second treatment attempt in patients who did not remit following an initial adequate trial with an SGA	• Children under age 18 • Patients with perinatal depression, seasonal affective disorder, psychotic depression, or treatment-resistant depression (i.e., two or more treatment failures)
	KQ 1a, 2a KQ 1b, 2b	**Subgroups of interest are based on:** • MDD severity • Common accompanying psychiatric symptoms, (anxiety, insomnia, low energy, somatization), •age, sex, and race or ethnicity	
Interventions		Pharmacological treatments: **Second-generation antidepressants:**[a] Bupropion, Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Levomilnacipran, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Trazodone, Venlafaxine, Vilazodone, Vortioxetine **For combination with or augmentation of SGA:** **Other pharmacotherapies (i.e. non-SGA medication)** • Atypical antipsychotics (aripiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) • Psychostimulants (amphetamine, dextroamphetamine, armodafinil, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methyphenidate, modafinil) • Buspirone • Levothyroxine (T4) • Triiodothyronine (T3) • Lithium • Pindolol	• First-generation antidepressants • Any other interventions not defined in the PICOTS criteria

Table 2. Inclusion/exclusion criteria (ongoing)

		Criteria	
Category		**Inclusion**	**Exclusion**
		Nonpharmacological treatments: **Common depression-focused psychotherapies** (includes all therapies listed in the Cochrane classification of psychological treatments; see Appendix): • Behavioral therapies/behavior modification • Cognitive behavioral therapies • Integrative therapies (e.g., interpersonal therapy) • Psychodynamic therapies • Third-wave cognitive behavioral therapies **Complementary and alternative medicines** • Acupuncture • Meditation (e.g., mindfulness-based stress reduction) • Omega-3 fatty acids • S-adenosyl-L-methionine (SAMe) • St. John's wort (Hypericum perforatum) • Yoga **Exercise:** • Any formal exercise program	
Control interventions and comparisons	KQ 1, KQ 2	**For all populations of interest: SGAs** • SGAs vs. psychotherapies • SGAs vs. CAM • SGAs vs. exercise • SGAs vs. SGA + psychotherapies • SGAs vs. SGA + CAM • SGAs vs. SGA + exercise • SGAs vs. combinations of eligible interventions We are interested in direct comparisons of eligible interventions with SGAs as single interventions.	
	KQ 2,	**In addition, for populations who did not have remission following an initial adequate trial with an SGA** • SGA switch[b] vs. SGA switch[b] • SGA switch[b] vs. SGA augmentation[c] • SGA switch[b] vs. nonpharmacological treatment • SGA augmentation[c] vs. SGA augmentation[c] • SGA augmentation[c] vs. nonpharmacological treatment	
Outcomes		**Benefits** • Response to treatment, • Remission, • Speed of response, speed of remission, • Relapse, quality of life, functional capacity, reduction of suicidal ideas or behaviors, • Reduction of hospitalization **Harms** • Overall adverse events, • Withdrawals because of adverse events, • Serious adverse events, • Specific adverse events (including hyponatremia, seizures, suicidal ideas or behaviors, hepatotoxicity,	• Studies that do not include at least one of the outcomes listed under the inclusion criteria

	Criteria	
Category	**Inclusion**	**Exclusion**
	weight gain, gastrointestinal symptoms, sexual side effects, and others), • Withdrawals because of specific adverse events, • Or drug interactions (pharmacological and complementary and alternative treatments)	
Timing of intervention	No limitations	NA
Geography	No limitations	NA
Settings	• Primary, secondary, and tertiary care outpatient settings	• Inpatient settings
Publication language	• English	• All other languages
Study design	Original research **For efficacy/effectiveness** • RCTs **In addition for harms** • Nonrandomized controlled trials • Prospective controlled cohort studies • Retrospective controlled cohort studies • Case-control studies • Nonrandomized studies must have a minimum sample size of 500 participants	• Case series • Case reports • Nonsystematic reviews • Studies without a control group • Nonrandomized studies with fewer than 500 participants • Systematic reviews and meta-analyses(will be used for searches of reference lists) • Post-hoc analyses • Pooled data analyses
Publication type	Any publication reporting primary data	Publications not reporting primary data

MDD = major depressive disorder; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial; SGA=second-generation antidepressant; SR = Systematic Review.

a SGAs approved for treatment of MDD by the Food and Drug Administration.

b Switching to another SGA.

c Augmenting with a second SGA, an additional non-SGA medication, or a nonpharmacological treatment.

Literature Search

An experienced information specialist will assess the search strategies of the original review. If necessary, the search will be modified to improve the balance of sensitivity and precision and to take into account any changes in inclusion criteria. We will search MEDLINE (Ovid), the Cochrane Library (Wiley), EMBASE (Elsevier), AMED (Allied and Complementary Medicine Database) (Ovid) and PsycINFO (Ebsco). We will use a combination of free text and controlled vocabulary (e.g., MeSH) in the search strategies. The search period will go back to January 2014 and we will limit the searches to English -language and human-only studies. We will conduct quality checks to ensure that the searches identify known studies. If we do not identify the known studies, we will revise and rerun our searches.

In addition, we will search the "gray literature" for unpublished studies relevant to this review following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for these steps.[9,10] We will include studies that meet all the inclusion criteria and contain enough methodological information to enable us to assess risk of bias. We will also search ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP).

In addition, in an attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed.

We will conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. We will investigate any literature that the peer reviewers suggest and, if appropriate, will incorporate additional studies into the final review. The appropriateness of those studies will be determined using the methods described above.

Screening of the Literature and Data Abstraction

Two trained research team members will independently review all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® bibliographic database (Clarivate Analytics).

We will retrieve and review the full text of all titles included during the title/abstract review phase. Two trained team members will independently review each full-text article for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and

consensus or by consulting a third member of the review team. All results will be tracked in an EndNote® database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract important information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. A second member of the team will review all data abstractions for completeness and accuracy.

Assessment of Risk of Bias of Individual Studies

To assess the risk of bias of studies, we will use predefined criteria based on available guidance. For randomized controlled trials, we will use the Cochrane Risk of Bias Tool 2.0.[11] For non-randomized studies, we will use ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions)[12]. A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. We will consider the risk of bias for each relevant outcome of a study.

Two independent reviewers will assess the risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

Data Synthesis and Analyses

If we find three or more similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. For all analyses, we will use random-effects models to estimate pooled or comparative effects.

To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.[13] We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the chi^2- statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for I^2). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects. We will also examine potential sources of

heterogeneity using sensitivity analysis or analysis of subgroups. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate to examine clinical heterogeneity.

For any quantitative analyses, we will conduct sensitivity analyses including high risk-of-bias studies. Planned stratifications or categories for subgroup analyses include the subgroups listed in the analytic framework and geographic location of studies. When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

Grading the Certainty of Evidence

We will grade the certainty of evidence based on the guidance established by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.[14] We will ask for input from the Technical Expert Panel (TEP) to determine minimally important differences, which we will use to grade precision. Grades reflect the certainty of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two trained reviewers will assess each domain for each key outcome, and differences will be resolved by consensus. One of the two reviewers will always be a senior researcher with experience in grading the certainty of evidence. We will grade the certainty of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those commonly reported in the literature by carefully considering the ratings of each domain.

Appendix: Cochrane classification of psychological therapies

CCDAN Topic List: Intervention – Psychological therapies

BEHAVIOR THERAPY / BEHAVIOR MODIFICATION

- ACTIVITY SCHEDULING
- ASSERTIVENESS TRAINING
- AVERSION THERAPY
  - COVERT SENSITIZATION [APA]
- BEHAVIOR CONTRACTING
- BEHAVIOR MODIFICATION
- BIOFEEDBACK, PSYCHOLOGY
  - FEEDBACK, SENSORY
- CONTINGENCY MANAGEMENT
- CONVERSION THERAPY
- DISTRACTION THERAPY
- EXPOSURE THERAPY
  - Abreaction Therapy
  - Sensitivity Training
  - Systematic Desensitization Therapy (APA)
  - Eye Movement Desensitization Reprocessing [MeSH]
  - Implosive Therapy [APA, MeSH]
- PLEASANT EVENTS
- PSYCHOEDUCATION
- PROBLEM-FOCUSED
- RECIPROCAL INHIBITION THERAPY
- RELAXATION TECHNIQUES
  - Autogenic Training
  - Distraction [CINAHL]
  - Guided Imagery [CINAHL]
- RESPONSE COST (APA)
- SLEEP PHASE CHRONOTHERAPY
- SOCIAL SKILLS TRAINING
  - Social Effectiveness

COGNITIVE BEHAVIORAL THERAPY

- PROBLEM SOLVING
- RATIONAL EMOTIVE THERAPY
- REALITY THERAPY
- RESTRUCTURING
- ROLE PLAY
- SCHEMAS
- SELF-CONTROL
- STRESS MANAGEMENT

THIRD WAVE COGNITIVE BEHAVIORAL THERAPIES

- ACCEPTANCE AND COMMITMENT THERAPY
- BEHAVIORAL ACTIVATION
- COGNITIVE BEHAVIORAL ANALYSIS SYSTEM OF PSYCHOTHERAPY
- COMPASSION-FOCUSED
- DIALECTICAL BEHAVIOR THERAPY

- DIFFUSION
- FUNCTIONAL ANALYTIC PSYCHOTHERAPY
- METACOGNITIVE THERAPY
- MIND TRAINING
- MINDFULNESS

PSYCHODYNAMIC THERAPIES

- BRIEF PSYCHOTHERAPY
- COUNTERTRANSFERENCE
- FREUDIAN
- GROUP THERAPY
  - Balint Group Therapy
- INSIGHT ORIENTED THERAPY
- JUNGIAN
- KLEINIAN
- OBJECT RELATIONS
- PERSON CENTRED THERAPY, CLIENT-CENTRED THERAPY
- PSYCHOANALYTIC THERAPY
  - Alderian Therapy
  - Dream Analysis
  - Free Association
  - Self Analysis
- SHORT-TERM PSYCHOTHERAPY
- TRANSFERENCE

HUMANISTIC THERAPIES

- EXISTENTIAL THERAPY
- EXPERIENTIAL THERAPY
  - PROCESS-EXPERIENTIAL
  - GESTALT THERAPY
- EXPRESSIVE THERAPY
- GRIEFWORK
- ROGERIAN
- NON-DIRECTIVE THERAPY
- SUPPORTIVE THERAPY
- TRANSACTIONAL ANALYSIS

INTEGRATIVE THERAPIES

- COGNITIVE ANALYTICAL THERAPY
- COUNSELLING
- ECLECTIC THERAPY
- INTERPERSONAL THERAPY
  - Psychodynamic Interpersonal Therapy
- MULTIMODAL
- TRANSTHEORETICAL

SYSTEMIC THERAPIES

- CONJOINT THERAPY
  - COUPLES, MARITAL OR RELATIONSHIP THERAPY

- EMOTION FOCUSSED THERAPY
  - FAMILY THERAPY
- INTEGRATIVE BEHAVIORAL COUPLE THERAPY (IBCT)
- NARRATIVE THERAPY
- PERSONAL CONSTRUCT
- SOCIOENVIRONMENTAL THERAPY
  - Milieu Therapy
  - Therapeutic Community
- SOLUTION FOCUSED BRIEF THERAPY

OTHER PSYCHOLOGICALLY-ORIENTED INTERVENTIONS

- ACTING OUT
- AGE REGRESSION THERAPY
- ART THERAPY
- BIBLIOTHERAPY
- CATHARSIS
- COLOUR THERAPY
- CRISIS INTERVENTION
- DANCE THERAPY
- DRAMA THERAPY
- EMOTIONAL FREEDOM TECHNIQUES
- HYPNOTHERAPY
  - Autosuggestion
  - Neuro-Linguistic Programming (NLP)
  - Persuasion
- MEDITATION [CINAHL]
- MORITA THERAPY
- MUSIC THERAPY
- PLAY THERAPY
- PRIMAL THERAPY
- PSYCHODRAMA
- REMINISCENCE THERAPY
- SEX THERAPY

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095-105.
3. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? *Journal of Clinical Psychiatry*. 2003;64(12):1465-75.
4. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: The National Academies Press; 2001. ISBN: 9780309072809
5. Mojtabai R, Olfson M. National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the national comorbidity survey replication. *Journal of Clinical Psychiatry*. 2008;69(7):1064-74.
6. Gaynes BN, Rush AJ, Trivedi MH, et al. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. *Journal of General Internal Medicine*. 2008;23(5):551-60.
7. Gaynes BN, Lux LJ, Lloyd SW, et al. *Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011. Available from: www.effectivehealthcare.ahrq.gov/reports/final.cfm.
8. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *American Journal of Psychiatry*. 2006;163(11):1905-17.
9. Tsertsvadze A, Maglione M, Chou R, et al. Updating Comparative Effectiveness Reviews: Current Efforts in AHRQ's Effective Health Care Program. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet] Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-*. 2011.
10. Research AfH, Quality. *Methods guide for effectiveness and comparative effectiveness reviews*: Agency for Healthcare Research and Quality; 2014.
11. . Available from: https://methods.cochrane.org/risk-bias-2 (accessed December 9, 2020).
12. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *bmj*. 2016;355.
13. West SL, Gartlehner G, Mansfield AJ, et al. *Comparative Effectiveness Review Methods: Clinical Heterogeneity*. Rockville MD: Methods Research Report. (Prepared by the RTI International-University of North Carolina Evidence-based Practice Center (EPC) under Contract No. 290-2007-10056-I.); 2010. Available from: www.effectivehealthcare.ahrq.gov.
14. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*. 2011;64(4):401-6.

Topic Suggestion Description

Date submitted: July 16, 2020

Update to Treatments for Fecal Incontinence II

1. What is the decision or change you are facing or struggling with where a summary of the evidence would be helpful?

We recommend that AHRQ update its March 21, 2016 systematic review entitled "Treatments for Fecal Incontinence" (FI) to reflect the latest evidence about treatment modalities, specifically including the latest evidence about perianal bulking with non-animal stabilized hyaluronic acid/dextranomer [NASHA/Dx FI]), a biocompatible injectable bulking agent, which is the only bulking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of FI.

2. Why are you struggling with this issue?

AHRQ's 2016 review was issued prior to availability of more recent studies demonstrating the long-term efficacy, safety, and durability of NASHA/Dx FI. This new evidence warrants an update, as the 2016 document ends with the words: "future studies with higher quality could change the conclusions of this review." Moreover, other bulking agents have not been studied to this degree or achieved approval by FDA for this indication, so we struggle with AHRQ's prior guidance generalized to all bulking agents, as they are not comparable

3. What do you want to see changed? How will you know that your issue is improving or has been addressed?

We would like to see all evidence of NASHA/Dx FI's safety and effectiveness considered, including:

- Mellgren et al., 2014 Publication: Reports long-term efficacy of Solesta® at 12 and 36 months, yet was not included among the sources cited for AHRQ’s 2016 guideline.
- Franklin et al., 2016 Publication: Analyzed & highlighted the benefit of NASHA/Dx FI vs Sham in specific key patient subgroups.
- NASHA/Dx FIPost Approval Study (PAS), 2020: 283-patient, 36-month, multi-center PAS with robust long-term outcomes data (recently accepted by FDA & publication pending) demonstrates:
  - Real-world safety, efficacy, and medical appropriateness of NASHA/Dx FI
  - Significant improvements in objective clinical measures, re-intervention rate (>80% of patients treated do not require re-intervention through 36-months post treatment), and durability
  - Sustained statistically & clinically significant improvement in the CCFIS and FIQL scales

Also, we believe this evidence warrants a recommendation for NASHA/Dx FI that is separate and distinct from that for other bulking agents, as none of the other approved by FDA for this indication and none have produced evidence of sustained safety and effectiveness in real-world use.

4. When do you need the evidence report?

Monday, March 15, 2021

5. What will you do with the evidence report?

We will use the updated guideline primarily to educate physicians, patients, and third-party payers with respect to the current state of evidence in the treatment of fecal incontinence, which affects up to 8.3% of non-institutionalized adults, drives over $11B in annual healthcare spending, and increases the likelihood of referral to a nursing home by 10–15%.

(Optional) About You

What is your role or perspective? Physician

If you are you making a suggestion on behalf of an organization, please state the name of the organization: Ohio

May we contact you if we have questions about your nomination? No

Title: Staff Surgeon

Agency for Healthcare Research and Quality
5600 Fishers Lane
Rockville, MD 20857
Telephone: (301) 427-1364