

ORIGINAL STUDY

A core outcome set for vasomotor symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative

Sarah Lensen, PhD,¹ David Archer, MD,² Robin J. Bell, MB, BS, PhD,³ Janet S. Carpenter, PhD, RN, FAAN,⁴ Monica Christmas, MD,⁵ Susan R. Davis, MBBS, PhD,³ Karen Giblin, BA,⁶ Steven R. Goldstein, MD,⁷ Tim Hillard, DM, FRCOG,⁸ Myra S. Hunter, PhD,⁹ Stamatina Iliodromiti, MD, MRCOG, PhD,¹⁰ Unnop Jaisamrarn, MD, MHS,¹¹ Hadine Joffe, MSc,¹² Sunila Khandelwal, MS, FICOG, FICMCH, FICS,¹³ Ludwig Kiesel, MD, PhD,¹⁴ Bobae V. Kim, MAudA,¹⁵ Cornelis B. Lambalk, MD, PhD,¹⁶ Mary Ann Lumsden, OBE, FRCOG, FACOG, MB, BS, BSc,¹⁷ Pauline M. Maki, PhD,¹⁸ Rossella E. Nappi, MD, PhD,¹⁹ Nick Panay, BSc, MB, BS, FRCOG, MFSRH,²⁰ Helen Roberts, MB, MPH, FNZCSRH,²¹ Jan Shifren, MD,²² James A. Simon, MD, CCD, NCMP, IF, FACOG,²³ Amanda Vincent, MD, PhD,²⁴ Wendy Wolfman, MD,²⁵ and Martha Hickey, BA (Hons), MSc, MBChB, FRCOG, FRANZCOG, MD¹

Abstract

Objective: Vasomotor symptoms (VMS) (hot flashes and night sweats) affect most women over the menopause transition. Comparing the safety and effectiveness of treatments for vasomotor symptoms is limited by the use of inconsistent outcome measures, and uncertainty as to which outcomes are most important to symptomatic women. To address this, we have developed a Core Outcome Set (COS) for use in clinical trials of treatments for VMS.

Methods: We systematically reviewed the primary outcomes measured in randomized controlled trials of treatments for VMS. These were refined and entered into a two-round modified Delphi survey completed by clinicians, researchers, and postmenopausal women between November 2019 and March 2020. Outcomes were scored on a nine-point scale from “not important” to “critically important.” Two international consensus meetings were held to finalize the COS.

Received November 10, 2020; revised and accepted January 20, 2021. From the ¹Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia; ²Obstetrics and Gynaecology, Eastern Virginia Medical School, Norfolk, VA; ³Women’s Health Research Program, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; ⁴School of Nursing, Indiana University, Indianapolis, IN; ⁵Department of Obstetrics and Gynaecology, University of Chicago, Chicago, IL; ⁶Red Hot Mamas North America, Inc, Town of Ridgefield, CT; ⁷Obstetrics and Gynecology, New York University School of Medicine, New York, NY; ⁸Department of Obstetrics and Gynaecology, University Hospitals Dorset NHS Trust, Poole, Dorset, UK; ⁹Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; ¹⁰Centre for Women’s Health, Institute of Population Health Sciences, Queen Mary University London, London, UK; ¹¹Department of Obstetrics and Gynaecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; ¹²Connors Center for Women’s Health and Gender Biology and the Department of Psychiatry, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; ¹³Department of Obstetrics and Gynaecology, Fortis Escort Hospital, Jaipur, India; ¹⁴Department of Gynaecology and Obstetrics, University of Muenster, Muenster, Germany; ¹⁵Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia; ¹⁶Amsterdam Reproduction and Development, Center for Reproductive Medicine, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands; ¹⁷Department of Reproductive and Maternal medicine, School of Medicine, University of Glasgow, Glasgow, UK; ¹⁸University of Illinois at Chicago, Departments of Psychiatry,

Psychology and Obstetrics and Gynecology, Chicago, IL; ¹⁹Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, IRCCS San Matteo Foundation, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; ²⁰Queen Charlotte’s and Chelsea and Chelsea and Westminster Hospitals, Imperial College London, London, UK; ²¹Auckland District Health Board, Auckland, New Zealand; ²²Midlife Women’s Health Center, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ²³Department of Obstetrics and Gynecology, George Washington University, Washington, DC; ²⁴Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Victoria, Australia; and ²⁵Department of Obstetrics and Gynaecology, University of Toronto, Toronto, Canada.

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Address correspondence to: Martha Hickey, MBChB, MSc, FRCOG, FRANZCOG, Department of Obstetrics and Gynaecology, University of Melbourne, Victoria 3052, Australia. E-mail: hickeym@unimelb.edu.au

Results: Based on the systematic review, 13 separate outcomes were included in the Delphi process. This was completed by 227 participants of whom 58% were postmenopausal women, 34% clinicians, and 8% researchers. Predefined thresholds were applied to categorize importance scores obtained during Round 2 of the Delphi survey. These informed discussions at the consensus meetings which were attended by 56 participants from 28 countries. The final COS includes six outcomes: 1) frequency of VMS, 2) severity of VMS, 3) distress, bother or interference caused by VMS, 4) impact on sleep, 5) satisfaction with treatment, and 6) side-effects of treatment.

Conclusion: Implementation of this COS will: better enable research studies to accurately reflect the joint priorities of postmenopausal women, clinicians and researchers, standardize outcome reporting, and facilitate combining and comparing results from different studies, and ultimately improve outcomes for women with bothersome VMS.

Key Words: Clinical trials – COMMA – Core Outcome Set – COS – Menopausal symptoms – Menopause – Vasomotor symptoms.

Video Summary: <http://links.lww.com/MENO/A763>.

Vasomotor symptoms (VMS) are common, affecting around 75% to 85% of women over the natural menopause transition and persisting for around 4 to 7 years on average.¹⁻³ An estimated 25% of women experience severe VMS which may persist for decades. However, there is substantial variation between women and by geographical and racial background in the prevalence and experience of VMS.^{4,5} It remains uncertain whether VMS are more severe or prolonged after premature/early menopause or whether the type of menopause (spontaneous or iatrogenic) affects the severity or persistence of VMS. Several studies suggest that VMS may be more severe after breast cancer treatment compared with the natural menopause transition.^{6,7} Vasomotor symptoms are the leading patient priority for treatment at menopause, and have been the major focus of clinical trials evaluating interventions for menopausal symptoms.⁸

Randomized trials of interventions for VMS have reported different outcomes and measured these outcomes in different ways.⁸ Commonly used outcome measures include the frequency and/or severity of VMS, or composites of these measures, which are sometimes reported separately for day-time and night-time. The degree of interference and bother has also been measured to evaluate the impact of VMS on daily life and activities and is the main driver of treatment-seeking for VMS.⁹ However, many clinical trials have not included these outcome measures. This may be partly due to a focus on obtaining regulatory approvals, particularly in the USA where draft guidance on evaluating hormone therapies from the Food and Drug Administration has driven research design and measures of treatment efficacy of hormonal and nonhormonal therapies.¹⁰ This variation in outcomes measures in trials of interventions for VMS restricts the ability to combine data from different trials and to compare results across trials. Hence, there is uncertainty as to which treatments are most effective, and also whether treatment effects differ according to patient characteristics such as age or cause of menopause. Despite the large number of published clinical trials of treatments for VMS,⁸ these

methodological differences impede the translation of their findings into evidence-based care in menopause, since neither clinicians nor symptomatic women can directly compare treatment benefits to make informed decisions about treatment.

Across many health domains, a standardized approach to address the variations in outcome reporting is the development and implementation of a Core Outcome Set (COS).¹¹ A COS is an agreed minimum data set to be routinely collected in all treatment studies for a specific condition. COS are developed in collaboration with clinicians, researchers, and people with lived experience of the condition.¹¹ The implementation of a standardized COS addresses the inconsistency in outcome reporting for a given clinical condition which consequently improves the quality and relevance of future research. The COMET (Core Outcomes Measures in Effectiveness Trials) initiative provides guidelines and support for the development of COS for health conditions.¹¹ The translational importance of these efforts is recognized by the Core Outcomes in Women's and Newborn Health (CROWN) initiative, and menopause has been recognized as a clinical area in need of standardized, patient-focused outcomes.^{12,13} The COMMA: Core Outcomes in Menopause initiative was established to develop, disseminate, and implement a COS to be used in future clinical trials evaluating interventions for VMS associated with menopause.

METHODS

The protocol for COMMA has been previously described.¹⁴ The project was prospectively registered with the CROWN and COMET initiatives (registration no. 917). Briefly, an international, multidisciplinary Steering Group was established to provide oversight on the scope and progress of COMMA. The Steering Group included broad international representation from the three key participant groups: women who had experienced menopause (postmenopausal women), clinicians, and researchers in menopause. Individual Steering Group members were identified via existing networks of the study lead (MH), and through contacts of these. The scope of

the COS was to establish a standardized list of outcomes to be reported in all clinical trials evaluating interventions for VMS, regardless of the cause of menopause or the intervention being studied.

Systematic review and Delphi survey

A systematic review was undertaken to collect primary outcomes reported in randomized controlled trials of interventions for VMS.⁸ All the identified primary outcomes were compiled into a comprehensive list, reviewed by the Steering Group to identify duplicates, combine similar outcomes (eg, severity of hot flashes and intensity of hot flashes were merged into one outcome) and provide accessible lay terminology for each outcome. The resulting list was entered into a modified two-round Delphi survey, completed by postmenopausal women, clinicians, and researchers, with lay definitions and appropriate terminology provided to reduce ambiguity. The Delphi survey used a hover function providing explanations in lay terminology including specific plain language explanations for any technical terms to support effective participation from postmenopausal women. The survey was pilot-tested amongst the Steering Group prior to launch. The Delphi survey was distributed as widely as possible, including community and advocacy groups in menopause, relevant professional societies internationally (in endocrinology, obstetrics and gynecology, menopause and primary care), specialists in breast, gynecologic and hematological cancers, nurses, nurse practitioners, psychologists, physiotherapists, journal editors, funding bodies, the Cochrane Collaboration, researchers and clinicians working in menopause, and through personal contacts of the Steering Group. The COMMA initiative specifically sought representation from low- and middle-income countries to better yield a balanced representation internationally. Women self-identified as having experienced menopause. Reproductive stage was not formally evaluated,¹⁵ and we made no attempt to verify menopausal status or restrict participation based on age. However, the women likely represent predominantly postmenopausal woman and we therefore use the term “postmenopausal” to refer to these participants, although women in the menopausal transition also participated.¹⁵ Women likely considered their experience of both the menopause transition and postmenopause in contributing to this study. These women were recruited from the community and included those experiencing spontaneous menopause at the average age, primary ovarian insufficiency, premature menopause (before the age of 40 y) or early menopause (before the age of 45 y), iatrogenic menopause due to surgery, radiation or chemotherapy, and menopausal symptoms secondary to endocrine therapy for breast cancer.

Participants were asked to complete two rounds of the Delphi survey. In each round, participants rated the importance of each outcome on a Likert scale from 1-9 (1 “not important,” and 9 “of critical importance”), or indicated that they were unable to score the outcome. In Round 1, participants were invited to suggest additional outcomes for

consideration to be entered into Round 2. Only participants who had completed Round 1 were able to contribute to Round 2. In Round 2, each participant was presented with the aggregate outcome scores from Round 1, organized by participant group, and was able to view how they had scored each item in the previous round. This process reminds participants of their previous scores and permits them to consider the views of others when rescoring each item, thereby helping to achieve convergence over multiple rounds.¹¹

Following the completion of Round 2, predefined consensus criteria were applied to classify each outcome as:¹⁴

- Consensus in: outcomes which more than 70% of participants in each group scored as “of critical importance” and fewer than 15% of participants in each group scored as “not important”
- Consensus out: outcomes which more than 70% of participants in each group scored as “not important” and fewer than 15% of participants in each group scored as “of critical importance”
- No consensus: outcomes not meeting either of the above criteria

To explore consensus between participant groups we produced scatterplots of median scores for each of the outcomes, for the three different pairs of participant groups (clinicians vs postmenopausal women, researchers vs postmenopausal women, and researchers vs clinicians) to visualize the similarity of priority ratings between participant groups.

Consensus meetings

As a result of the COVID-19 pandemic, the planned face-to-face consensus meeting was replaced by virtual meetings. Two international videoconferencing meetings were held in May 2020, timed to accommodate attendees from different time-zones. The aim of these meetings was to consider the results of the Delphi survey, including the categorization of outcomes as consensus in, consensus out, and no consensus, and to ultimately reach agreement about which of the scored outcomes should be included in the final COS. Each meeting was 2 hours in duration and conducted using an informal approach, moderated by an assigned Chair (SL), using voting when clear consensus was not reached by discussion. The meetings were attended by postmenopausal women from the community, clinicians, and researchers with wide geographic representation. Individuals attending the two consensus meetings were identified as either clinicians or researchers working in menopause by members of the Steering Group and snowballing amongst those initially invited. This included journal editors from major reproductive and menopause journals. Postmenopausal women were identified through advocacy groups and clinical contacts of the Steering Group. This methodology was undertaken in parallel with the development of a COS for genitourinary symptoms in menopause, the results of which will be reported separately.

Sample size

Sample size for the Delphi technique is not based on statistical power. Previous research has demonstrated that between 10 and 15 participants per group is sufficient to

ensure validity.¹⁶ We therefore aimed to recruit at least 20 participants per representative participant group.

Ethics approval was not required as this was considered a service evaluation and development project.

RESULTS

The literature review identified 49 primary outcomes reported in randomized trials of interventions for menopausal VMS.⁵ The Steering Group reviewed these and merged similar outcomes into outcome types, resulting in 13 unique outcomes being entered into Round 1 of the Delphi survey (Supplemental Table S1, Supplemental Table S2, Figure 1, <http://links.lww.com/MENO/A762>). In total, 315 participants completed Round 1, which was open from November 26 to December 28, 2019 (Supplemental Table S3, <http://links.lww.com/MENO/A762>). In response to the question about additional outcome measures that should be considered in clinical trials for menopausal symptoms, a total of 193 additional outcomes were suggested by Round 1 participants. These most commonly related to psychological symptoms, changes in memory and concentration, sleep disturbance, and joint pains. These outcomes were merged into broad outcome types (eg, irritability and mood swings were merged into mood disturbance) and a total of nine additional outcome types were entered under a new domain into Round 2. As the purpose of this COS was to develop a COS for VMS, scoring data relating to these additional outcomes will be reported separately. Hence, the original 13 VMS outcomes were entered into Round 2 of the Delphi survey which was open from February 1 to March 15, 2020. A total of 227 participants completed the Round 2 survey which constituted 72% of those who had completed Round 1. Of these, 135 (58%) primarily self-identified as postmenopausal women, 80 (34%) as clinicians, and 19 (8%) as researchers (Supplemental Table S3, <http://links.lww.com/MENO/A762>). Many of the clinicians and researchers who completed the survey were also postmenopausal women. Across all participant groups, 85% of those who completed the survey were postmenopausal women. Visualization of scatter plots suggested that importance rankings were similar between the participant groups, which indicated appropriate agreement across the two rounds and therefore that a third round of the Delphi survey was not necessary (Supplemental Figure S1, <http://links.lww.com/MENO/A762>).¹¹ Application of the predefined consensus criteria resulted in the classification of four outcomes as “consensus in,” and the remaining nine as “no consensus” (Supplemental Table S2, <http://links.lww.com/MENO/A762>). None of the included outcomes met the criteria for “consensus out,” and all 13 outcomes were brought forward to discuss at the consensus meetings.

Fifty-six participants attended the consensus meetings, including postmenopausal women, clinicians, and researchers (Table 1). A number of participants declared financial relationships with pharmaceutical companies; however, these conflicts of interests were considered by the Steering Group as not being a threat to the integrity of the process. The

TABLE 1. Participants attending the COMMA consensus meetings

Consensus meeting participants (n = 56)	n (%)
Type of participant ^a	
Menopausal woman	26 (46)
Natural	17 (30)
Surgical	6 (11)
Treatment related	1 (2)
Unknown	2 (4)
Gynecologist	34 (61)
Endocrinologist	12 (21)
Menopause society member/representative	18 (32)
Researcher or methodologist	19 (34)
Journal editor/representative	3 (5)
General practitioner	1 (2)
Pharmaceutical industry	0 (0)
Gender	
Female	33 (59)
Male	23 (41)
Involved in menopause research	48 (86)
Age	
31-39	8 (14)
40-49	7 (13)
50-59	19 (34)
Over 60	22 (39)
Geographical place of birth	
Africa	5 (9)
Asia	10 (18)
Australia/New Zealand	9 (16)
Europe	18 (32)
North America	10 (18)
Middle East	0 (0)
South America	4 (7)

^aParticipants may contribute to more than one category type (eg, an individual participant may be a gynecologist, journal editor, and a menopausal woman).

conclusions reached by the two consensus meetings were very similar and were discussed at two final Steering Group meetings in June 2020. The final COS includes six outcomes to be included in all future clinical trials for VMS: 1) frequency of VMS, 2) severity of VMS, 3) distress, bother or interference caused by VMS, 4) impact on sleep, 5) satisfaction with treatment, and 6) side-effects of treatment (Fig. 1).

DISCUSSION

Through an international process, COMMA has achieved consensus on six core outcomes to be reported in clinical trials of treatments for menopause-associated VMS. The COS is applicable to all trials in women with VMS, including women in the menopause transition and postmenopause. This consensus was reached amongst a broad range of participants including clinicians, researchers, and postmenopausal women from the community.

This COMMA initiative is the first COS for menopause. The principal aim of COMMA is to harmonize research in menopause worldwide by standardizing the outcomes used in clinical trials, ensuring these reflect the priorities of those designing and delivering research, and importantly, those who are seeking effective treatments for their symptoms. Implementation of this COS will improve consistency of outcome reporting across clinical research in menopause, reduce the number of uninformative trials, and facilitate the findings from different trials to be compared and combined.

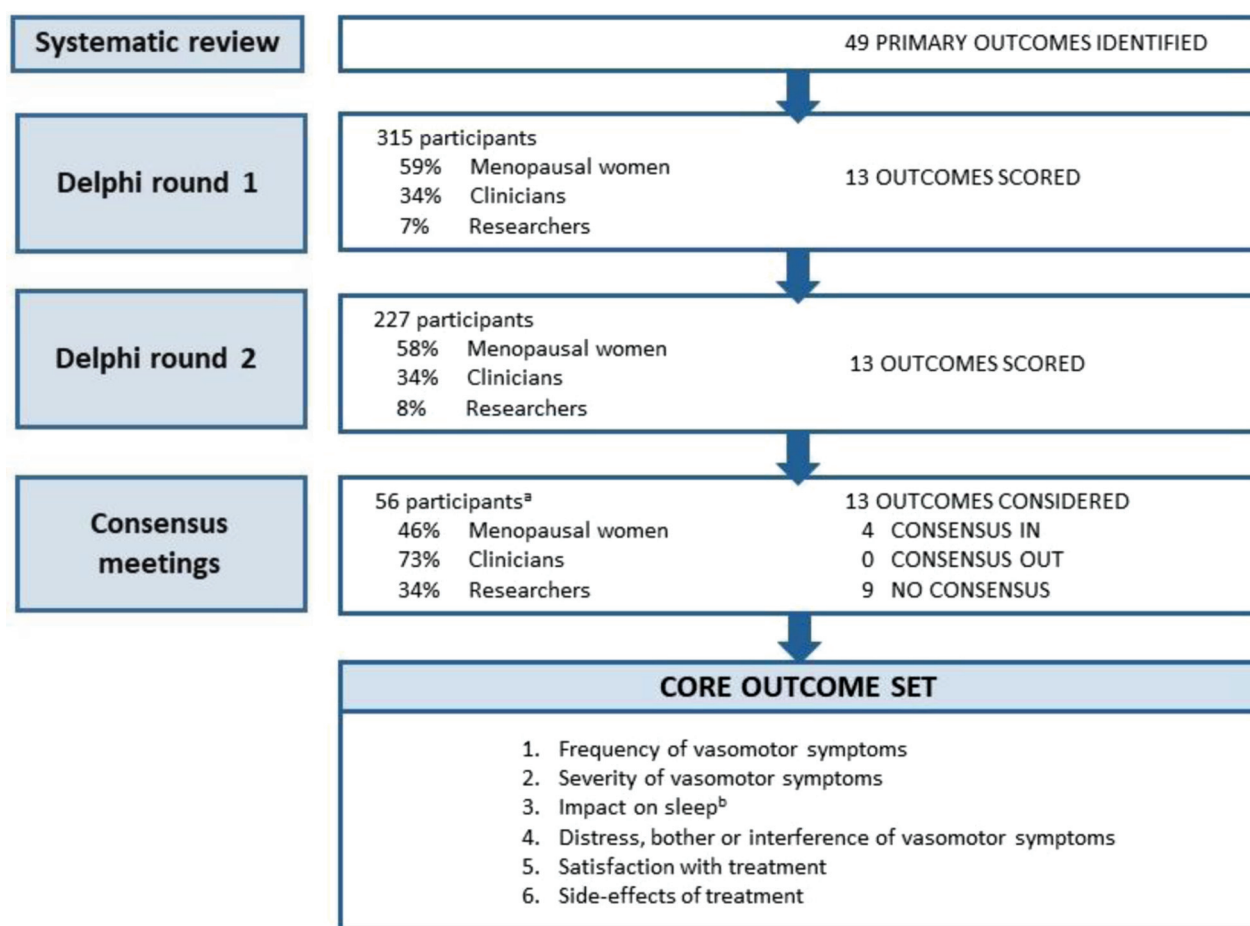


FIG. 1. Participants and outcomes contributing at each stage of the Core Outcome Set development. ^aFor the consensus meeting, participants were able to belong to multiple participant groups. ^bThis measure will either be included as a component of the outcome “Distress, bother or interference of VMS,” or will be included as a separate outcome measure, depending on available tools. VMS, vasomotor symptoms.

These six outcomes represent a minimum dataset. The COMMA process did not aim to weigh the importance of particular outcomes relative to each other, or to advise which should be considered the primary outcome/s in individual trials. We anticipate that researchers may wish to include additional measures relevant to specific studies, or specific regulatory requirements. The findings suggest a need to re-evaluate, update, and finalize the FDA draft guidance to reflect outcomes of importance to patients, clinicians, and researchers. Whilst this COS was primarily developed for randomized trials of treatments for VMS, it may also be relevant for reporting of other study designs, including observational studies. The COS includes measures of VMS frequency and perceived severity as well as degree to which these symptoms are problematic, as measured by distress/bother/interference due to VMS. The COS also recommends that sleep disturbance is measured, since this is a critical aspect of the patient experience of menopause with direct implications for daytime function and mood.^{17,18} Measurement of side-effects and patient satisfaction with treatment were also considered essential for the evaluation of interventions.

Next steps and implementation

The final COS was designed to be brief to optimize uptake. Previous evaluations of the uptake of COS in other health areas have indicated that outcome sets with more than six different measures are unlikely to be widely implemented.¹⁹ Additionally, we do not anticipate that this COS will increase the burden for researchers or participants since many of the measures included are already commonly reported in clinical trials.⁸ Whilst measures of frequency and severity of VMS are commonly reported, measures of bother and satisfaction are less common.⁸ Similarly, including these measures should not incur additional costs, equipment, or resources. For example, most clinical trials of treatments for VMS already measure frequency and severity and a growing number include validated measures of daily interference or a problem rating as a measure of symptom impact.^{9,20} Treatment side-effects and satisfaction with treatment have been measured less consistently and measures of sleep have varied considerably.^{17,18} We recognize that “side-effects” may differ substantially between treatment approaches, and our definition for this outcome will reflect this. For example, pharmacological interventions and

those aimed at modifying behavior are likely to have very different side-effect profiles.

This process has defined the outcomes to be included in clinical trials of treatments for VMS. The next step includes determining how these outcomes should best be measured. This will involve the systematic identification and appraisal of existing definitions and tools for measuring each core outcome, in order to recommend the most appropriate measures. This process will include appraisal of measurement properties such as content validity, structural validity, and reliability of these measures in women with menopausal symptoms and will follow established CONsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and COMET methodologies.²¹

The COMMA project aims to establish COS for menopause, and the results of a parallel process to deliver a COS for genitourinary symptoms will be reported separately. We also recognize the importance of other symptoms associated with menopause such as psychological symptoms, changes in memory and concentration and joint pains, as proposed during the Delphi process which are not captured in this COS which only addresses VMS.

Strengths and limitations

Menopause has been identified as an area of unmet need for a COS because of inconsistent reporting of research outcomes.¹³ The COMMA project was guided by robust methodology as recommended by the COMET guidelines, and followed predefined methods as published in our study protocol.^{11,14} The methodology included input from a wide range of participants at all stages of the process, including the consensus meetings. However, participation was not sought from regulatory bodies, such as the Food and Drug Administration or European Medicines Agency. Participants included postmenopausal women from the community, relevant health-care professionals, and those likely to conduct and publish research in this field. Input from all three participant groups helps to ensure the core outcomes are important to women with VMS, which may not necessarily be the case in guidance on outcome reporting issued by other groups, such as regulatory bodies.¹⁰ Clinical trials aiming for regulatory approval should therefore ensure compliance with all relevant guidance, including this COMMA COS.

We maintained anonymity during the Delphi phase, to avoid the overt influence of powerful individuals or participant groups.²² There was a high level of congruence in scoring of outcome importance between participant groups, and across the two consensus meetings held. All outcomes rated as “consensus in” using the predefined consensus criteria were included in the final COS. Our findings may be limited by the 28% attrition rate between the two Delphi rounds, which may have influenced the final COS. However, retention rates were comparable to or higher than other similar COS Delphi processes.^{23,24} We did not hold focus groups or structured interviews with postmenopausal women, which may have limited our understanding of their priorities for

outcome measures. However, we included a large number of postmenopausal women across all stages of the COS development. We also acknowledge that methodologies vary between COS projects, and the choice of methods used may influence the final results. For example, the literature review conducted to inform the original list of outcomes only included randomized trials where VMS were the primary outcome, and it is acknowledged that primary outcome selection for clinical trials may be based on that mandated by relevant regulatory guidelines. However, the list was deemed comprehensive during review and pilot-testing by the Steering Group (which included postmenopausal women) and no relevant outcomes related to VMS were suggested during Round 1. We attempted to circulate the Delphi survey as broadly and inclusively as possible; however, the survey may not have reached all relevant clinicians and researchers working in this area. Due to the nature of the dissemination methods used, we are unable to assess the response rate or compare those taking part in the Delphi survey to those who declined. We acknowledge that selection of participants for the consensus meetings relied on recruitment of individuals known to the Steering Group and other participants. It is possible that attendance by a similar but different cohort of people may have yielded a different final consensus; however, we may be reassured by the similar consensus recommendations made at the two individual meetings.

We had strong input from postmenopausal women with 58% of those completing the Delphi survey and 46% of those attending the consensus meeting these criteria, and as such we are confident that these outcomes reflect the priorities of symptomatic women. Both the Delphi survey and consensus meetings had participation from a geographically diverse range of people. Although we actively sought participation from low- and middle-income countries, most participants were from high-income countries. The consensus meetings were conducted in an interactive forum to reach agreement on outcomes and to discuss the practical implementation of the COS. Replacing the planned face-to-face meetings with virtual meetings substantially increased participation from postmenopausal women and those from low- and middle-income countries, probably because the costs associated with traveling to and attending an international conference were not a barrier to participation.

CONCLUSION

The COMMA process has resulted in a final COS of six outcomes to be reported in all future randomized trials evaluating interventions for women with VMS. These include frequency of VMS, severity of VMS, distress, bother or interference of VMS, impact on sleep, satisfaction with treatment, and side-effects of treatment. This COS, together with the selection of specific outcome measurement instruments for their collection and reporting, will enable improved standardization of outcome reporting in future research, leading to improved capacity to compare and combine results from different studies, and ultimately better care for symptomatic women.

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