PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is an update to current templates from Protocol Builder make sure the information throughout the protocol includes the most current information.

Since the majority of day-to-day care in diabetes is handled by patients and/or their families [1], appropriate self-management in type one diabetes (T1D) is fundamental to successful treatment [2]. Therapy profiles, including insulin basal rate, insulin-to-carbohydrate ratio (grams of carbohydrates per unit of insulin), and insulin sensitivity factor (number of mg/dL of glucose per unit of insulin), should be periodically adjusted based on review of measurements from self-monitoring blood glucose (SMBG) meters or continuous glucose monitoring (CGM) sensors. As part of the patient's routine care, when a new pattern of glycemic risk is identified by the clinical team or the patient, new insulin dosing parameters must be calculated and implemented. Data reports, like the Ambulatory Glucose Profile (AGP) report where the patient's diabetes data are processed and presented as graphs and tables, facilitate the decision-making process related to insulin therapy optimization. For instance, if a pattern of hypoglycemia was detected during the early morning hours, one decision could be to reduce the insulin basal rate before that time period.

Self-management of T1D can be a time-consuming and challenging task, requiring data to be downloaded from multiple devices for evaluation. Fortunately, information technology is increasingly playing a role in improving the management of chronic illnesses [3], [4], including diabetes [5]. However, most people with T1D still struggle to achieve the glycosylated hemoglobin (HbA1c) target set by the American Diabetes Association (ADA) [6]. This can be

explained, in part, by considering that although chances of developing diabetes complications can be substantially reduced by improving self-care therapies [7], only few patients perform a fine-tuning of their therapy strategies to reach optimal glycemic control [8].
Encouraging results from an uncontrolled trial give credence to the feasibility of combining modeling, simulation, self-management education, and decision support [9]. Empowering effective self-management of T1D is in itself associated with better glycemic control and quality of life [10], and decision-support software is now considered an effective tool in diabetes care [11]. But only their combination is expected to help patients with T1D to implement and sustain the ongoing skills and behavioral changes necessary to manage their disease [12].

Thus, this project focuses on embedding the participants' own diabetes data into state-of-the-art technology platforms to constitute a novel educational simulation interface for decision-support in T1D — the Web-based Simulation Tool (WST). It is an educational tool, and as such, it does not have prescriptive power. WST was developed by the Principal Investigator (PI) and allows patients with T1D to not only visualize their data, but also to explore changes to their meals and insulin parameters, and easily estimate their potential clinical impact. To this end, WST collects glucose, insulin and meal data from the participants' insulin pump, and generates personalized models of their glucose metabolism. Both data collection and model personalization are backend processes, that is, without user intervention. Participants can interact with WST through a user interface (UI) that is equipped with a dashboard page (main screen of the UI), where they can:

- select a particular date range using a calendar to visualize their historical glucose control, such as glucose traces, and time in range;
- control the amount of information on the screen — users can show/hide more details, such as glucose variability;
- select different insulin therapy parameters:
    - basal rate,
    - insulin sensitivity factor, and
    - carbohydrate ratio,
- change their values by moving a slider;
- select informed meals within the selected date range, and modify their time and size by moving a slider;
- run a simulation with the modified insulin therapy parameters and meals by tapping a button;
- save the insulin and meal settings of the simulations to compare multiple configurations; and
- generate a report from the selected simulation, comparing both original and simulated or replay data.

Figure 1 illustrates the process of how a simulation is performed. Once the participant sets the desired simulation (for example, a change to the basal rate profile and/or a meal), he/she can tap the Run button on the UI to send a request to the system to run a simulation. The system receives the request, queries model, insulin, and meal data from the database, runs the simulation, and sends the results back to the UI, where they are displayed to the participant.

Figure 1: Block diagram of how a simulation is performed

It is important to note that WST does not identify patterns of glycemic risks or recommend changes to therapy parameters. Its dashboard page allows the participants to inspect their data,

similarly to how they would do with an AGP report, but also having the possibility of running simulations under alterations of their historical records. Thus, the spirit of this project is to pioneer the use of metabolic simulators in empowering patients to fully leverage the data they generate.

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

The primary outcome of this study is to assess WST's usability. The secondary outcome is to track changes in treatment satisfaction. The exploratory endpoint is to investigate potential correlation between system use, treatment satisfaction, and glycemic control.

Study Design: Biomedical

1. Will controls be used?

No

►**IF YES, explain the kind of controls to be used.**

2. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question.
https://hrpp.irb.virginia.edu/learningshots/Writing_protocol_June09/player.html

Single-arm, single center, non-randomized, uncontrolled pilot clinical trial

3. Does the study involve a placebo?

No

►**IF YES, provide a justification for the use of a placebo**

Human Participants

Ages: Age ≥21.0 and ≤65 years old at time of consent

Sex: Male and Female

Race: Any

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. Provide target # of subjects (at all sites) needed to complete protocol.

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Fifteen (15) participants are needed to complete the study.

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

25%

3. How many subjects will be enrolled at all sites?

INSTRUCTIONS: This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

Twenty (20) participants to account for potential screen failures, dropouts and withdrawals.

4. How many subjects will sign a consent form under this UVA protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Twenty (20) participants may sign consent.

Inclusion/Exclusion Criteria

INSTRUCTIONS:

- The inclusion and exclusion criteria should be written in bullet format.
- *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population (e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below:

pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non-English speaking subjects .

- If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
- If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
- The stop date must be prior to the version date of this protocol.
- *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

- Age ≥21.0 and ≤65 years old at time of consent.
- Clinical diagnosis, based on investigator assessment, of T1D for at least one year.
- Using insulin for at least 1 year prior to study enrollment.
- Using an insulin pump for at least 6 months prior to study enrollment.
- Currently using a CGM for at least 6 months.
- Willingness to use a Dexcom G6 CGM during the study; a study Dexcom CGM will be provided if needed.
- Current user of the Tandem t:slim X2 insulin pump.
- Total daily insulin (TDI) dose at least 10 U/day.
- HbA1c ≤9.0% at screening; if HbA1c <6.0%, then TDI must be ≥ 0.5 U/kg.
- Having access to internet (Wi-Fi or 3G, 4G, 5G, or similar).
- Willingness to interact with a computer program.
- An understanding of and willingness to follow the protocol and sign the informed consent form (ICF).

The reason for requiring Tandem and Dexcom is that Tandem's t:connect technology was integrated into WST to automatically consolidate, aggregate and transmit data from the glucose sensor and insulin pump to the system’s database. In this way, participants do not have to manually upload their data to WST on a daily basis, which could impact negatively on participants' attitude towards using the system.

2. List the criteria for exclusion

- Participants who are not able to read and complete questionnaires on the computer or interact with a program for which they will be trained because of language, reading, or cognitive issues.
- Severe hypoglycemia resulting in seizure or loss of consciousness in the 6 months prior to enrollment.
- History of a seizure disorder (except hypoglycemic seizure), unless written clearance is received from a neurologist and not currently on a seizure medication.
- Pregnancy, breast-feeding, or intention of becoming pregnant over time of study procedures.
- If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study.
- A known medical condition that in the judgment of the investigator might interfere with the completion of the study.*
- Abuse of alcohol or recreational drugs.
- Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis, etc).
- Uncontrolled arterial hypertension (resting diastolic blood pressure >90 mmHg and/or systolic blood pressure >160 mmHg).
- A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol.
- Current use of the following drugs and supplements:
    - Any drug other than insulin to treat diabetes.
      Treatment with any non-insulin glucose-lowering agent (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals)

**<u>Note</u>: The software implementation, in the current development status, is designed to interact with subjects with T1D that only use insulin for diabetes treatment and do not present any comorbidity related to diabetes.*

3. List any restrictions on use of other drugs or treatments.

INSTRUCTIONS: List only those drugs or treatments that are prohibited while on study, not those listed as an exclusion criteria.

None.

Statistical Considerations

1. Is stratification/randomization involved?

No

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVA Statistician. Insert name
_____ UVA Investigational Drug Service (IDS)
_____ Other*:* Specify

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.
The answer to this question should include:
--Study Design/Endpoints

--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

This pilot clinical trial is not powered to run statistics. However, as a qualitative analysis, we will use regression analysis to infer the impact of the duration and frequency of participants' interaction with WST and/or participants' characteristics (predictor variables) on variations in metabolic control and treatment satisfaction (response variables).

3. Provide a justification for the sample size used in this protocol.

Include sample size calculations or statistical power estimation. If not applicable, please provide explanation.
Also include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Given the nature of this study as a pilot clinical trial to evaluate the functioning of the WST for the first time, it is not powered to run statistics.

4. What is your plan for primary variable analysis?

Include primary outcome(s)/predictor variable(s), statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.

To analyze system's usability, technology expectation and acceptance questionnaires will be performed at baseline and at the end of the trial, respectively, to determine expectations and rate different aspects of the application. In addition, a follow-up interview will be conducted by the study team within 30 days of completing the study to allow the participants to describe their experience with the system.

5. What is your plan for secondary variable analysis?

Include the following:

--Secondary outcome(s)/predictor variables, statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.
--For phase III studies, the power/precision of the study to address the secondary objective(s).

The Diabetes Distress Scale questionnaire will be performed at baseline and at the end of the trial to assess changes in treatment satisfaction.

6. Have you been working with a statistician in designing this protocol?

Consultation with a professional statistician is highly recommended to ensure good science of the study and facilitate the review process.

No

IF YES, what is their name?

7. Will data from multiple sites be combined during analysis?

No

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

IF YES, will randomization be done at each site or among sites?

7(b). Has the sample size calculation considered the variation among sites?

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

7(d). Is there a common protocol used in all sites?

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:

This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and

experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

Special note for studies with waiver of consent/waiver of documentation of consent: Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

A study schematic is presented in Figure 2. Study participants will be instructed how to use the proposed WST. They will use their own personal Tandem t:slim X2 insulin pump and supplies. All participants will be provided Dexcom G6 CGM supplies (transmitter and sensors) to use over the course of the study. The first week (about 7 days) will be purely observational, and data collected during that time will be used to estimate baseline glucose metrics. For the remaining 4 weeks (about 28 days), participants will be asked to interact with WST at least once a week. Participants will see the results of their entries but will be informed to speak with their Endocrinologists prior to making changes to their treatment parameters. Participants can generate reports that can be provided to their physicians. It is important to clarify that there is no intention to ask physicians to provide support for WST. It is assumed that they will continue to support their patients with routine care.

Participants will receive and complete via email specifically curated technology expectation and psychobehavioral questionnaires at the training visit (to identify participants' expectations) and at the completion of the trial (to assess the impact of system use). In addition, weekly glucose metrics will be computed from CGM data as per current consensus CGM-based metrics guidelines [13], e.g., percentage of total time spent in desirable range (70-180 mg/dl) or in hypoglycemia (<70mg/dL). A follow-up interview with a study team member will be scheduled within 30 days of completing the study to allow the participant to describe his/her experience with WST.

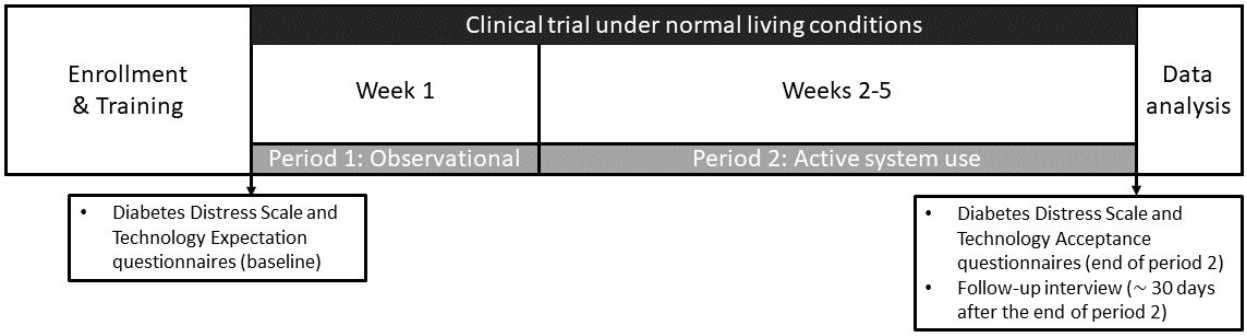


Figure 2: Study Schematic

Participants will have the option of giving the study team access to an existing t:connect account, or to create a personal or study account and associate it with their personal insulin pump for about 5 weeks.

Visit 1 Screening Appointment

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed study personnel, a blood draw and urine pregnancy testing (if applicable) may be ordered to screen for exclusionary medical conditions.

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed.
- Demographics (address, date of birth, gender, race, ethnicity).
- Contact information.
- Diabetic history.
- Medical history.
- Medications.
- Physical examination, tele-health equivalent, or a medical record with this information within the past 6 months
- Weight, height. This may be obtained in person, from the participant's most recent clinical visit, or a medical record with this information within the past 6 months
- Vital signs including measurement of blood pressure, temperature, and pulse. This may be obtained in person, from the participant's most recent clinical visit, or a medical record with this information within the past 6 months.
- Urine or serum pregnancy test for all females of child-bearing potential.
- HbA1c level will be measured using the DCA2000, a comparable point of care device or local laboratory (i.e. LabCorp). Chemistry panel, liver function tests (LFTs), and thyroid stimulating hormone (TSH) may be ordered to screen for exclusionary medical conditions. Measurement performed as part of usual care prior to obtaining informed consent for participation in the trial may be used if taken within 3 months for HbA1c, and within 6 months for chemistry, LFTs, and TSH.
- Diabetes Management Information: participant's typical insulin dosing routine including average total daily insulin use (calculated over 1 week), basal rates, carbohydrate ratio(s), and correction factor(s).

Screening procedures will last approximately 2 hours. Once all results of the screening evaluations are available, a decision will be made to determine the participant's eligibility for the

study or if one or more part of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the participant will be excluded from participation with follow up and referred to their primary care physician as needed. The study physician may elect to rescreen participants and collect additional laboratory values if their clinical situation changes.

Visit 2 Training Session (about 2 hours)

Study Participants will be sent the following questionnaires, and be trained on how to complete them:

List of Questionnaires:

- Diabetes Distress Scale.
- Technology Expectation questionnaire.

Study Continuous Glucose Monitor Training:

Dexcom G6 CGM supplies (transmitter and sensor) will be provided to all participants. Participants will be instructed to use the study CGM on a daily basis and in accordance with manufacturer recommendations. If the participant has prior use of the CGM, re-training will be specific to the individual. The study team may elect to have less frequent CGM users watch the Dexcom online training videos (https://www.dexcom.com/training-videos) to assist in the training session. New users will also watch the online training videos and will receive comprehensive instructions and training by a qualified study staff member. Study staff will specifically identify how alarms are set using the app and the frequency that these alarms will repeat when enabled.

The participants personal CGM may be discontinued. The participants will be observed placing the sensor and will learn/review how to access the CGM trace via the t:slim X2 insulin pump user interface. The participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labeling of the study CGM device.

An electronic copy of the CGM user's guide will be provided for the participants to take home. The study team will be sure that the participants will leave the clinic knowing how to properly use the CGM.

Participants will have the option of using their personal smartphone or receive a study smartphone to use in order to collect the data from the devices.

WST System Participation Period:

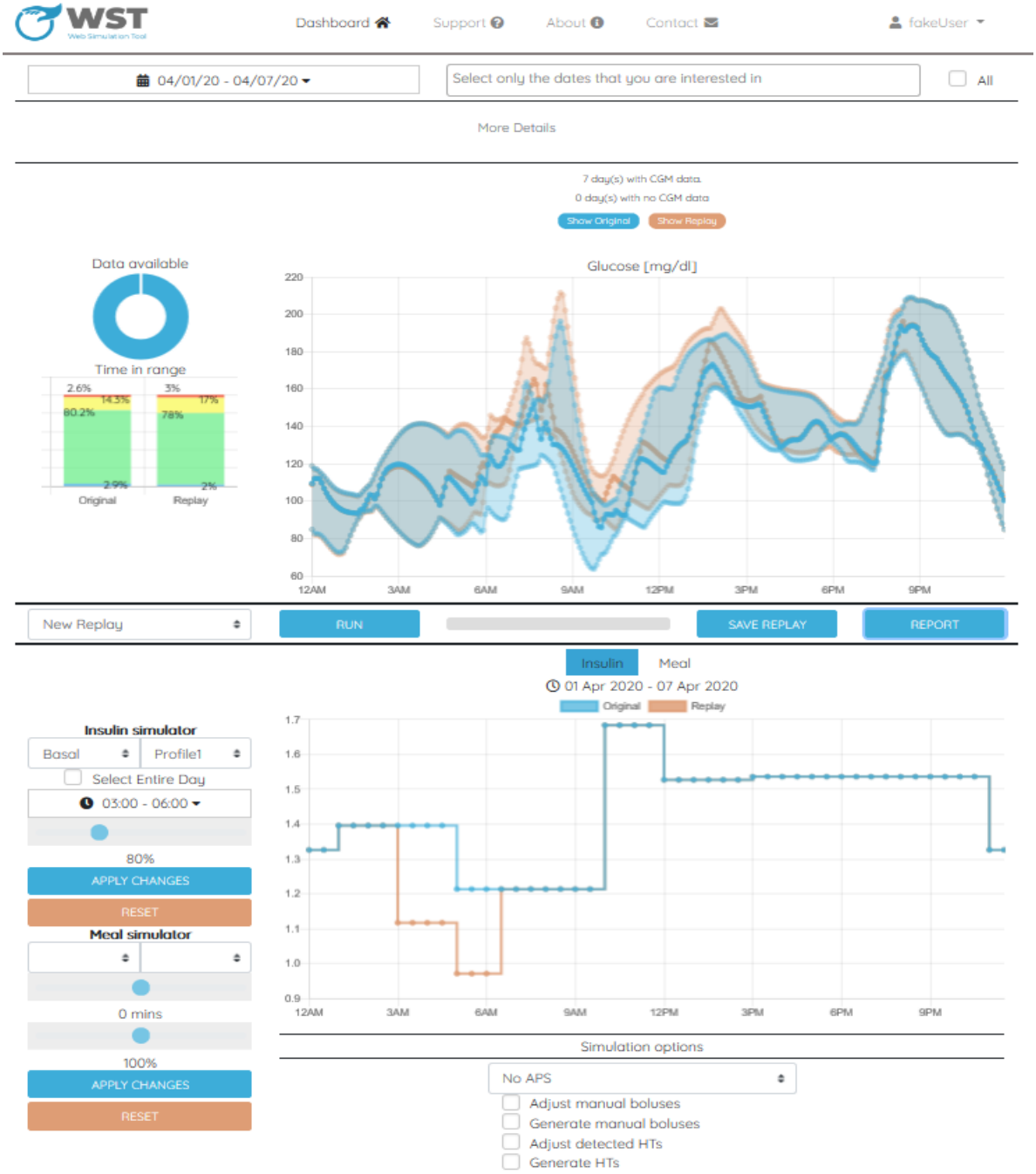
The study team will collect diabetes data from the study participant for about 7 days which will be used to provide the software preliminary priming data. Study participants will be trained on how to use and interact with the WST system. They will be instructed to interact with the system at least once a week for the next 4 weeks. They will be instructed to access WST, and use its dashboard page (see Figure 3) for visualization (Display Panel) and simulation (Replay Panel). To visualize their data, they will be instructed to select a date range using the calendar on the Display Panel, and read the information displayed on the screen (charts and metrics). To simulate a new scenario, they will be instructed on the use of the Replay Panel to simulate changes to their insulin therapy parameters and meals. They will also.be instructed to save their simulations and

generate reports that summarize their results.

Figure 3: Illustrative example of the dashboard page of WST

Visit 3: Questionnaires

Study participants will be sent the following questionnaires, and be trained on how to complete



them:

List of Questionnaires:

- Diabetes Distress Scale.
- Technology Acceptance questionnaire.

Visit 4: Follow-Up Interview

A study team member will perform a follow-up interview within 30 days of completing the study. Participants will be asked to describe their experience with the web-based simulation tool and what things they enjoyed most/least while using the app.

This interview will take about 30 minutes to complete.

All study visits may be completed at the clinical research Unit (CRU) or may be completed via a secure web-based video conferencing tool. This decision is at the discretion of the study team.

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Participants will return any remaining CGM supplies (e.g. transmitter, sensors) at the completion of the study and will resume their pre-study diabetic treatment plan.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
   Participants' interactions with WST will be monitored remotely. In the event that the participant does not interact with the system, the CRC will contact the participant to encourage a more frequent use of WST. If the situation persists, the CRC will contact the participant via telecommunication to encourage more active participation. The study team will determine if non-compliance should result in additional study weeks or discontinuation from the study.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
   Participants will be considered non-compliant if there is no use of the WST system.

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

[1] S. R. Shrivastava, P. S. Shrivastava, and J. Ramasamy, "Role of self-care in management of diabetes mellitus," *Journal of Diabetes and Metabolic Disorders*, vol. 12, no. 1. p. 14, 05-Mar-2013.

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[6] K. M. Miller *et al.*, "Current state of type 1 diabetes treatment in the U.S.: Updated data from the t1d exchange clinic registry," *Diabetes Care*, vol. 38, no. 6, pp. 971–978, Jun. 2015.

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[12] M. A. Powers *et al.*, "Diabetes self-management education and support in type 2 diabetes: A joint position statement of the American Diabetes Association, the American Association of diabetes educators, and the Academy of nutrition and dietetics," *Clin. Diabetes*, vol. 34, no. 2, pp. 70–80, 2016.

[13] T. Battelino *et al.*, "Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range," *Diabetes Care*, vol. 42, no. 8, pp. 1593–1603, Aug. 2019.