# Texting in Community Health Center Dental Clinics to Reduce HIV Risk: RCT

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**Version 1.0**

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## STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects' protection training.

## SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

**Multiple Principal Investigators (MPI):**

Signature: _____ Date: _____
Dr. Michelle Henshaw
*DD – MMM – YYYY*

Signature: _____ Date: _____
Dr. Curt Beckwith
*DD – MMM – YYYY*

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## LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AE | Adverse Event/Adverse Experience |
| BEDAC | Biostatistics and Epidemiology Data Analytics Center |
| BMFVP | Behavioral Model for Vulnerable Populations |
| C-CERC | CFAR Community Engaged Research Council |
| CFAR | Center for AIDS Research |
| CFR | Code of Federal Regulations |
| CHC | Community Health Center |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSOC | Clinical Study Oversight Committee |
| DCC | Data Coordinating Center |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| EtHE | Ending the HIV Epidemic |
| GCP | Good Clinical Practice |
| GSDM | Goldman School of Dental Medicine (Boston University) |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ICMJE | International Committee of Medical Journal Editors |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |

| | |
|---|---|
| MOP | Manual of Procedures |
| MPI | Multiple Principal Investigator |
| N | Number (typically refers to subjects) |
| NIDCR | National Institute of Dental and Craniofacial Research, NIH, DHHS |
| NIH | National Institutes of Health |
| OCTOM | Office of Clinical Trials Operations and Management, NIDCR, NIH |
| OHRP | Office for Human Research Protections |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| RA | Research Assistant |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SOP | Standard Operating Procedure |
| TM | Text Message |
| TM HIV | Text Messages regarding HIV |
| TM HL | Text Messages regarding Heathy Living |
| UP | Unanticipated Problem |
| US | United States |

## PROTOCOL SUMMARY

**Title:** Texting in Community Health Center Dental Clinics to Reduce HIV Risk

**Précis:** This is a text message-based intervention among individuals with at least one risk factor for HIV from targeted community health center dental clinics. The purpose of the intervention is to reduce HIV risk factors and promote HIV testing. This will be accomplished through delivering the text message program to English and Spanish-speaking dental patients (n=266) who are 18 years or older. Patients across all sites will be randomized to receive either text messages regarding HIV Risk Reduction (TM HIV) or healthy living (TM HL) over the course of 6 -months (24 -weeks). The outcome will be measured using questionnaires at 90, 180 and 365 days.

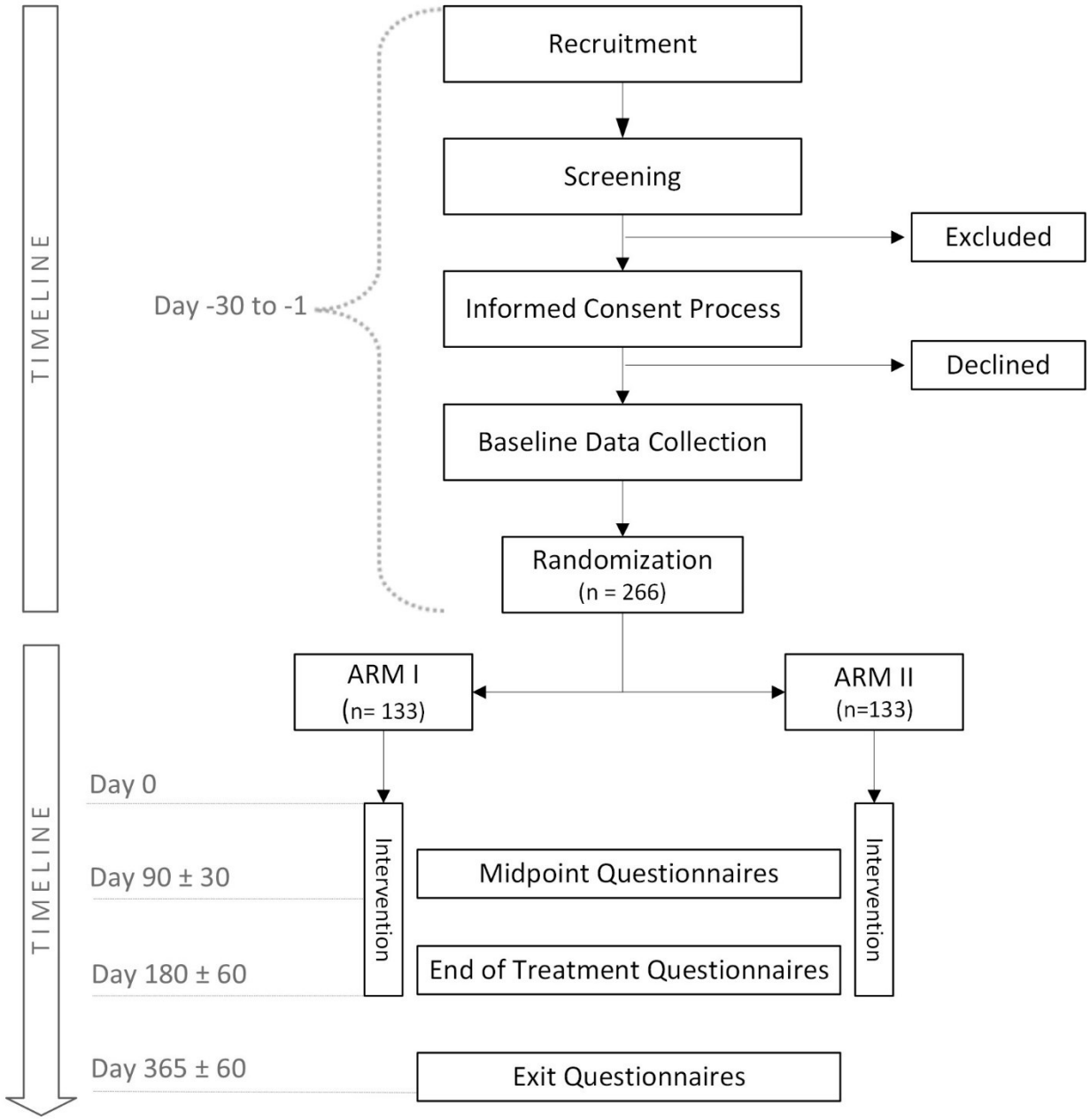
**Objectives:** To determine if HIV related text messages could decrease the risk of acquiring HIV by increasing the utilization of HIV prevention services (e.g., repeat HIV testing, PrEP uptake, etcetera) and behavioral change when compared to the control text messages. To assess the mechanisms through which the intervention effects occur (mediation).

**Population:** The target population is adult dental patients at Community Health Centers (CHC) in Suffolk County, Massachusetts.

**Number of Sites:** The study sites will include Codman Square CHC, South End CHC (part of East Boston CHC), East Boston CHC, Geiger Gibson CHC, and Uphams Corner CHC. All clinics are in the Greater Boston Area. The clinics serve an urban, ethnically diverse, and low-income population and have a primary affiliation with Boston Medical Center (BMC), the primary teaching affiliate of Boston University (BU).

| | |
|---|---|
| **Description of Intervention:** | Patients will be recruited and enrolled into the trial. Baseline and follow-up questionnaires will be completed at the beginning, midway, end of treatment and end of the study. Patients will be randomized into either the intervention group receiving the HIV prevention TM intervention (TM HIV) or the comparison group receiving the TM intervention focused on achieving a healthy lifestyle (TM HL). All participants will receive the respective text message intervention over 24-weeks. |
| **Study Duration:** | 36-months |
| **Subject Participation Duration:** | 12-months |
| **Estimated Time to Complete Enrollment:** | 24-months |

## SCHEMATIC OF STUDY DESIGN



# 1 KEY ROLES AND CONTACT INFORMATION

| | |
|---|---|
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| | |
|---|---|
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# 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background Information

Fourteen percent of people living with HIV (PLWH) do not know they are infected, so they do not benefit from antiretroviral therapy (ART) and may spread the virus.[1,2] To reach these individuals, the CDC recommends incorporating HIV testing into all aspects of primary health care, including dental care.[3] Dentists are already trained to detect and monitor medical conditions and, therefore, are "well-positioned to be the first line of screening" for multiple health conditions[4] including HIV infection.[5] HIV interventions in dental clinics have the potential to play a key role in the Ending the HIV Epidemic (EtHE) initiative because 25% of adults do not seek medical care annually, but 23% of these individuals do receive dental care.[6] Since rapid HIV tests (RHT) use oral fluid specimens, both dental providers and patients feel that dental clinics are logical sites for HIV prevention and testing efforts.[5] Given this, delivering HIV interventions as part of routine dental care has the potential to make important contributions to EtHE.

CHCs in the U.S. provide coordinated medical and dental health care to an estimated 30 million people, two-thirds of whom are from racial and ethnic minority groups who experience a disproportionate burden of HIV infection.[7,8] However, the use of text messaging (TM) to support HIV prevention in CHC dental clinics has not been studied. In response, this study will evaluate TM ability to support HIV prevention for dental clinic patients to address the prevention pillar of EtHE. Specifically, the hypothesis we are testing is: H1: Participants randomized to receive the HIV prevention TM intervention (TM HIV) will have higher proportion of repeat HIV testing within 12-months compared to the participants who receive the TM control condition, which is a TM intervention focused on achieving a healthy lifestyle (TM HL). $H_2$: Participants randomized to receive TM HIV will have higher proportion of HIV pre-exposure prophylaxis (PrEP) uptake and condom use within the past 6-months compared to the participants who receive the TM HL.

This study will rely on a conceptual framework informed by the Behavioral Model for Vulnerable Populations (BMVP), an adaption of Anderson's Behavioral Model of Health Care Utilization, which has been used extensively to examine the multi-faceted and multi-level factors that affect health behaviors, use of health services, and health outcomes among vulnerable populations.[12-14] The model posits that a series of individual, social, and structural predisposing factors, in addition to enabling or impeding factors and need factors, collectively influence health behaviors and the use of health services, which in turn produce health outcomes.[15] Individual and structural vulnerabilities may affect individuals' utilization of HIV testing services, uptake of PrEP, and health-promoting behaviors. Predisposing (sociodemographic variables, community norms), enabling (personal, clinic, and community resources), and perceived need (perceived risks and community burden) factors are hypothesized to influence health-promoting behaviors and linkage and access to HIV testing and PrEP. We will augment this model by utilizing Social Cognitive Theory (SCT) to support individual behavior

change and uptake of HIV prevention services through our TM intervention. SCT has been used successfully to achieve sustained behavior change and improve outcomes for many conditions, including HIV risk reduction).[16] SCT posits that goal setting, feedback on progress, and rewards increase self-efficacy (perceived capability of performing the behavior) and outcome expectations (belief that performing the behavior will result in a positive outcome), which leads to increased motivation, attempts to change, and positive health behavior outcomes.[17-19] In this project, we propose that enhancing self-efficacy and outcomes expectations through TM in those individuals with perceived need will foster behavior changes such as HIV testing, PrEP uptake, and risk reduction, including condom use.

## 2.2 Rationale

Dentists and dental clinics can play an important role in expanding HIV testing and facilitating access to HIV prevention services for at-risk populations in highly impacted areas. This study will test an interactive text messaging intervention to reduce HIV risk and promote testing: supporting both the diagnosis and prevention pillars of the Ending the HIV Epidemic initiative. If successful, this model which targets dental patients in community health centers in Suffolk County, MA, a designated hotspot, can be replicated at low cost within other high-risk communities.

## 2.3 Potential Risks and Benefits

## 2.4 Potential Risks

This study poses minimal risk to the participant. Listed below are the risks:

- It is possible that some aspects of the assessments (e.g., answering questions about HIV risk) or text messages may be uncomfortable or embarrassing. To address this risk, participants will be clearly informed of the topics to be addressed when completing questionnaires or during text message delivery. Also, participants will be told that they are free to skip any question they prefer not to answer.
- There are two potential consequences of text messaging: accidents and thumb and joint pain. Texting while driving or walking could increase the risk of accidents. Research subjects will be cautioned about reading and responding to texts while engaging in such activities. Additionally, research subjects will be instructed on Massachusetts' *"Hands-Free*" and "*Comparative Negligence*" Laws. Frequent texting may increase the risk of thumb and joint pain. The number of texts involved in this study is unlikely to result in thumb and joint pain.
- Loss of privacy
    - "Agile Health" is the health communications company that will be programming our text messages. Their database will contain the text messaging system, including information on what text messages each participant has received, which text messages participants have

responded to, their actual responses, and feedback about individual messages. This database is HIPAA compliant.

- For all data collected, confidentiality will be maintained by numerically coding all data with a unique identifier. All electronic data will be stored in password-protected, secured computer systems. Data will be collected through 1) secure web-based REDCap, 2) paper and pencil questionnaires (in the event of REDCap failure), and 3) the Agile Health database, which is HIPAA compliant. Paper forms may be used for any eCRF if electronic versions are unavailable (e.g., REDCap is down). Only the participant's study identification number will appear on any paper data or transcripts. Any paper data will be stored in a secured-locked filing cabinet at the Research Project Director's office at GSDM's Department of Health Policy and Health Services Research at 560 Harrison Ave. in Boston, Massachusetts. Only the Principal Investigators and the Research Project Director will have access to the locked cabinets. An electronic file will be maintained that associates the participant's name with that participant's study identification number. This file will be kept in a secure, locked, and password-protected location, separate from the actual study data (e.g., screener and questionnaire data).
- Participant information will be accessible only to research staff. Study data will be kept secured for 7 years after the study ends and then will be destroyed.

### *2.4.1 Potential Benefits*

Participants may not receive any direct benefit from participating in this study; however, participants may learn more about HIV prevention, health, and wellness. Participants could also have the satisfaction of helping the scientific community to learn more about how to use text messaging programs: (1) to prevent new HIV infection or (2) to foster the adoption of health-conscious lifestyle decisions and/or behaviors.

# 3 OBJECTIVES

## 3.1 General Study Objective

- To determine if HIV related text messages could decrease the risk of acquiring HIV by increasing the utilization of HIV prevention services and behavioral change when compared to the control text messages.
- To assess the mechanisms through which the intervention effects occur (mediation).

## 3.2 Study Objectives and Outcome Measures

### *3.2.1 Primary*

HIV Testing: To compare the proportion of participants in the active (TM HIV) arm and control (TM HL) arm reporting HIV testing at month 3, 6, & 12.

- Assessment tool -> *HIV/HCV Testing Domains Measure* [33, 34]
  - "*Have you ever been tested for HIV?*
    - *Yes*
    - *No*"

### *3.2.2 Secondary*

PrEP Adherence: To compare the proportion of participants in the active (TM HIV) arm and control (TM HL) arm who reported PrEP adherence at month 3, 6, & 12.

- Assessment tool -> *PrEP Adherence Self-Efficacy Scale* [24]
  - "*What is your experience in using PrEP?*
    - *I've never used PrEP.*
    - *I used PrEP over a year ago but I'm not currently taking it.*
    - *I have a prescription for PrEP but don't take it every day.*
    - *I take my PrEP medicine every day.*
    - *Prefer not to answer.*"

PrEP Uptake: To compare the proportion of participants in the active (TM HIV) arm and control (TM HL) arm who started PrEP at month 3, 6, & 12.

- Assessment tool -> *PrEP Adherence Self-Efficacy Scale* [24]
  - "*What is your experience in using PrEP?*
    - *I've never used PrEP.*
    - *I used PrEP over a year ago but I'm not currently taking it.*
    - *I have a prescription for PrEP but don't take it every day.*
    - *I take my PrEP medicine every day.*
    - *Prefer not to answer.*"

Condom Use: To compare the proportion of participants in the active (TM HIV) arm and control (TM HL) arm who used condoms at their last sexual encounter at month 3, 6, & 12.

- Assessment tool -> AIDS Risk Behavior Assessment [21]

- "*The last time you had … sex …, did you or your partner use condoms/latex protection?*
  - *Yes*
  - *No*
  - *Don't know*
  - *Prefer not to answer"*

Injection Drug use: To compare the proportion of participants in the active (TM HIV) arm and control (TM HL) that reported intravenous drug injection at month 3, 6, & 12. And among these individuals the proportion that reported using clean needles, and clean "*works*".

- Assessment tool -> *TCU HIV/AIDS Risk Assessment* [20]
  - "In the past … did you injected drugs with a needle?
    - *Yes*
    - *No*
    - *Prefer not to answer"*

Self-Efficacy: To compare the participants' self-efficacy to obtain HIV tests, to use condoms, and to start/ adhere to PrEP in the active (TM HIV) intervention arm and control (TM HL) arm at month 3, 6, & 12.

- Assessment tool -> *Confidence Assessment* [35]
  - "*How confident are you that you … next time you have sex?*
    - *1- Not at all*
    - *2*
    - *3*
    - *4*
    - *5 - Very much*
    - *Prefer not to answer*"

Motivation: To compare the participants' motivation to obtain HIV tests, to use condoms, and to start/ adhere to PrEP in the active (TM HIV) intervention arm and control (TM HL) arm at month 3, 6, & 12.

- Assessment tool -> *Confidence Assessment* [35]
  - "*How motivated are you … next time you have sex?*
    - *1- Not at all*
    - *2*
    - *3*
    - *4*
    - *5 - Very much*
    - *Prefer not to answer*"

Outcome Expectations: To compare the participants' perception in the preventing effects of obtaining HIV tests, using condoms, and starting/ adhering to PrEP will be successful at preventing HIV at month 3, 6, & 12.

- Assessment tool -> *Confidence Assessment* [35]
  - *How much do you believe that … will prevent you from getting HIV?*
    - *1- Not at all*
    - *2*
    - *3*
    - *4*
    - *5 - Very much*
    - *Prefer not to answer"*

For more information on the assessments tools please see document tittle "*Assessment Compendium*".

# 4 STUDY DESIGN

This is a single-masked, randomized control trial (RCT) designed (1) to reduce the risk of acquiring HIV and (2) to promote HIV testing. The target population consists of dental clinic patients who are 18 years of age or older with at least one HIV risk factor. The participating dental clinics are in urban, ethnically diverse, and low-income areas. The RCT has been informed by the initial phases of the UG2-funded study (patient and provider interviews, advisory board meetings).

The study will be conducted with participants recruited at 5 CHC dental clinics. We will recruit 266 participants (n= 266) over a 24-month period with an expected drop-out rate of 30% for a final sample of 186 participants. Participants will be recruited in the dental clinic waiting area and if there is time, they will be screened for eligibility at the clinic, and if they are eligible and interested, they will be guided through the informed consent process. Participants will then complete a baseline questionnaire, after which they will be randomized to receive either TM HIV or TM HL messages.

The intervention will last 6 -months. Participants will receive 5 messages per week for the first 3 months and 3 -messages per week for the last 3 -months of the intervention. Participants will be able to choose different blocks of time in which they could receive texts (e.g., morning, afternoon, evening). The text messages will be delivered using an automated system; at least one message per week will be interactive (require answers or clicking on a link for more information) and will be customized to participants based on their answers on the baseline questionnaire (language, gender identity, IDU use and PREP use).

Participant assessments will be completed through follow-up questionnaire accessed through text message links that will be sent at 3-, 6-, and 12-month. In addition, participants will receive a monthly set of TMs with Yes or No, or 5-Likert scale questions to assess: 1) motivation, 2) self-efficacy as it relates to outcome expectations related to condom use PrEP use and HIV testing. Assessments will be completed using the same assessment tools utilized in the baseline questionnaire. If requested by participants, the assessment links could be sent by email.

# 5 STUDY ENROLLMENT AND WITHDRAWAL

## 5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all the following criteria:

- Be 18 years of age or older.
- Be able to read in English or Spanish.
- Be a registered dental patient at one of the participating community health centers.
- Be able to give written informed consent by signing and dating the study's informed consent form in REDCap.
- Be willing to comply with all study procedures and able to participate in the study for its entire duration.
- Have unlimited Text Message on their mobile phone plan or be willing to pay for data consumption for the text messages that are sent or received.
- Have used any type of text messaging at least once in the past.
- Has at least one self-reported risk factor for HIV including any of the following:
    - Be a sexually active Man who has sex with men within the past 12 months.
    - Multiple sex partners within the past 12 months independent of gender or sex.
    - Intravenous drug injection within the past 12 months.
    - At least one current sexual partner within the past 12 months and inconsistent or no condom use.
    - Within the past five years, history of being sexually active and no history of HIV testing, where sexual activity is defined as:
        - Insertion of a penis into a vagina or anus.
        - Cunnilingus
        - Fellatio.

## 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Self-report HIV infection at the time screening. *
- Participating in another HIV study or another text message study.

- A woman who reports having sex exclusively with women.
- Does not have a mobile phone or other device which can receive text messages from Agile Health.

* **Note:** Data from individuals who develop HIV while on the study will be kept and analyzed using the intention to treat principle.

### 5.3 Recruitment and Retention Strategies

The target population is dental clinic patients (≥18 years old) at one of the four participating community health centers with 5 dental clinics (Codman, Geiger Gibson, Uphams, East Boston (East Boston and South End locations) with at least one risk factor for HIV.

The primary recruitment method will be RAs, or other trained study personnel, approaching all patients in the dental clinic waiting rooms (and other clinic spaces deemed appropriate by clinic partners) who appear to be over age 18. The eligibility screener would include age as the first question so if the person approached is not 18 years of age or older, the screening will immediately cease.

Other strategies to identify potentially eligible participants may include: (1) CHC staff informing patients about the study and directing them to a RA (if the RA isn't present, the clinician will give the potential participant a study flyer with information on how to contact the study team and will ask the potential participant to complete a consent to contact form so the study team can contact the potential participant at a later time). Completed consent to contact forms will be placed in a locked drop box at the site; (2) bilingual study advertising, with RA contact information, will be on display in study clinics (flyers); and (3) distributing recruitment materials (flyers) at other clinics within the CHCs so potential participants can contact the study team via the study phone number listed on the flyer.

Each participating site has designated its own secure location for locked boxes in which completed permission to contact forms will be stored on site until a member of the study staff is able to collect them. Only the study team has keys to the lock boxes. After collection, study staff will attempt to contact all potential participants to tell them more about the study. After successfully or unsuccessfully attempting to contact the potential participant, all completed permission to contact forms will be stored in a locked filing cabinet in the Research Project Director's office.

For all consent to contact forms received by the study staff, the study staff will contact the participant a maximum of 5 times over a 3-week period, using the participants preferred modes of contact. If no contact has been made after 5 attempts, no further contacts will be attempted and the consent to contact form will be destroyed.

An informational letter may be sent from the CHC dental clinic directors that will inform patients that the health center is partnering with Boston University to study the effectiveness of a text message program to reduce the risk of HIV infection. Study staff

contact information will also be included in the letter, should a patient be interested in assessing eligibility or asking questions about the study.

### *5.3.1 Retention Procedures*

To maximize completion of the follow-up study questionnaires, participants will receive a TM with the link to the 3-month and 6-month questionnaires 85 days and 175 days, respectively, after the first day of the TM intervention. If the participant does not complete the 3-month questionnaire after receiving the first link, subsequent reminder TMs will be sent 4 and 9 days later. If not completed by day 8, the RA will make additional attempts to contact the participant via email and phone between days 8 and 10. For the 6- and 12-month questionnaires, the link will be resent 5, 10 and 15 days after the initial email. The RA will make an additional contact via email or phone between day 15 and 25. A postcard (questionnaire reminder) will be placed in an envelope and mailed to participants on an as-needed basis to remind participants to complete their 3-, 6- or 12-month follow-up questionnaires if other forms of outreach have proven unsuccessful.

In addition, if we are unable to contact hard-to-reach participants, we will use the White Pages, a paid online directory or people search engine to verify or update participant contact information. Data that are accessible with a paid membership include: mobile phone numbers, previous and current street addresses, landline phone numbers, previous cities of residence, relatives, and associates. Hard-to-reach participants may include those who we discover have incorrect contact information and study staff attempts to use alternate means have been exhausted. For example, study staff may reach out to a participant's listed cell phone number and discover the phone number has been disconnected or now belongs to a different person, or participants may have a change of address during the conduct of the study. When these changes are identified, staff will attempt to contact the participant via newly obtained contact information (e.g., phone number, email, letter, or alternate contact). If these methods prove to be unsuccessful, study staff would then utilize an online directory or people search engine to find updated contact information.

If a potential match is found through an online directory or people search engine, study staff will reach out and confirm the participant's identity by having the participant confirm their birthdate or the home address on file. Once determined that the individual is a participant, their contact information will be updated directly into REDCap. To retain participants during the study, we will provide compensation for their time and effort spent completing the baseline and follow-up questionnaires. It is anticipated that most individuals will complete the questionnaire in 45 – 60 minutes.

Participant Compensation is as follows:

- A $60.00 gift card after 'opting' into the text message program by replying to an initial text and completing the first questionnaire.
- A $60.00 gift card after completing questionnaires at 90-, 180- and 365-day timepoints (potential compensation of $180 in total).

- If all questionnaires are completed participants will receive a bonus $60 gift card.
- The total possible compensation participants may receive is $300.00 in gift cards.

During the text message program, participants will be asked assessment questions that have a "$" sign. Each time they provide an answer to these questions, their name will be entered into a monthly raffle for a $100.00 gift card. The number of $ questions will range from 1-4 questions each month. After the name is randomly drawn by the study team for that month, a new month will begin, and all previous entries will be cleared. Because text messages are received over the course of 6-months, they will have the opportunity to earn entries in 6 monthly raffles.

If participants are not responding to the text message program, we will contact them to check in with them to problem-solve any technical issues and discuss their satisfaction with the program. A postcard will be sent if we are unable to reach a participant via email or text.

## 5.4 Treatment Assignment Procedures

### *5.4.1 Randomization Procedures*

To randomly assign participants to treatment groups at baseline, we will use a permuted randomized block design (random-sized blocks of 2 or 4 participants), stratified by study site [Codman Square, Geiger Gibson, Uphams Corner, South End (part of East Boston), and East Boston Community Health Centers] and preferred language (English or Spanish) of the patient to yield 10 strata. The randomization list will be created using REDCap. Participants will be randomized by the web-based REDCap randomization module. Once the baseline questionnaire is completed, REDCap will automatically randomize participants into TM HIV or TM HL, and this code, as well as the TM personalization options from the baseline questionnaire, will be transferred via secure API to the Agile Health system so the first TM (HIV or HL) will occur within 24 hours after randomization.

The randomization list will be maintained by the BEDAC group, and the study staff will not have access to that data until the conclusion of the data collection.

### *5.4.2 Masking Procedures*

The Project Directors are the only research staff members who will be interacting with the text messages; consequently, they will be the only study staff members that will be unmasked. All study staff collecting data, including the RAs, will be masked to treatment condition as will the MPIs and study statistician. The data collection procedures will be identical across treatment conditions, and the study staff collecting data will not be privy to participant condition group (TM HIV or TM HL) assignment. It is possible that a participant could reveal the content of their study text messages during follow-up questionnaires if the RA is assisting the participant in assessment. However, to encourage maintenance of the study masking, participants will be instructed during the informed consent process of the importance of masking and told not to discuss study

activities with the RAs at follow-ups. Additionally, RA will remind participants to refrain from disclosing the content of their TM prior to providing them assistance if requested. If the study arm assignment of a participant becomes known by an RA, that RA will not be involved with subsequent assessment activities for that participant.

Since the intervention is a text messaging intervention, we do not anticipate a need for unmasking. However, if it becomes necessary to unmask an enrollee, the Research Project Director will have the ability to unmask an enrollee by disclosing the status of the participant's randomization after approval by the MPIs.

## 5.5 Subject Withdrawal

Subjects are free to withdraw from the study at any time. During the TM program, the participant can text 'stop' at any time, and the messages will cease. If they request that the TM be stopped, then the research team will contact the participant to see if they want to continue in the study and complete follow-up questionnaires. To avoid silent withdrawal, the project director will measure participants engagement through their interactions with the TM (e.g., Responses to TM that ask questions). Participants that had been inactive for more than two weeks without interacting with the TM will be follow up with a phone call or email to rule-out silent withdrawal.

Subjects who want to withdraw from the study after ending the intervention, but before the final assessment, would be able to do it by contacting the study staff through e-mail, phone call, or text. After the TM program is finished, participants can e-mail, call, or text study staff to state that they want to withdraw from the program. If a study subject requests to be withdrawn from the study through either of these procedures, the research team will attempt to ascertain the reason for withdrawal. The Principal Investigators will also have the option to withdraw a participant if continued participation is not in the best interest of the participant.

### *5.5.1 Reasons for Withdrawal*

Subjects are free to withdraw from participation in the study at any time upon request.

We anticipate that reasons for a subject's withdrawal may include one or more of the following:

- Does not have time to participate.
- Does not want to receive TMs.
- Does not feel the need for health information.

A study subject may be withdrawn from study participation by the investigative team if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation as

determined by the MPIs. All collected data pertaining to randomized participants will be analyzed.

### *5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention*

Participants can stop the text message program at any time by typing in the keyword "stop." They can also withdraw from the program by calling or emailing program staff. If a participant wants to withdraw from the text message program, we will ask them if they would still like to complete the questionnaires at the time when their text message program would have ended if they did not withdraw (to be consistent with other participants). If they do not want to complete the questionnaire, we will withdraw them from the study. We will ascertain all reasons for withdrawal—whether from the text message program, from questionnaire completion, or both. All data collected while the participant was enrolled in the study will be retained and analyzed.

## 5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the PI, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

# 6 STUDY INTERVENTION

## 6.1 Study Behavioral or Social Intervention(s) Description

The intervention is a theory-based, dose-matched, interactive, and automatic text messages system aimed to reduce HIV risk factors in dental patients from community health centers located in areas with high HIV prevalence (e.g., Suffolk County, MA). The intervention will be delivered through a secure messaging engine (Agile Health). Agile Health platform uses data-driven algorithms and personalization rules to automate much of the member experience, while queuing up digital coaches for live member support, when needed [36]. Agile Health will not collect personal health or personal identifiable information, except for subjects' phone number, which will be used to deliver the intervention. For more information on *Agile Health Privacy policies.*

All qualifying subjects, that had accepted to participate in the study, will be randomized and enrolled through the Agile Health platform in either the active group treatment (AGT) or control group treatment (CGT) text message curriculum. Agile Health will start sending text messages within 24 hours of randomization. The intervention will last 6-months and will consist of text messages sent to participants cell phones addressing HIV prevention (active group) or having a healthy lifestyle (control group). Participants will choose the time at which they expect the text message delivery during baseline. AGT and CGT will be match in the number of the topics, engagement strategies, and program features.

Agile Health will deliver four types of messages:

- ***Introduction Messages:*** Present the program to participants and explain how the member can earn raffle entries and a gift card. This message will be sent in week 1 after randomization.
- ***Core Messages:*** These messages are designed to educate participants on HIV prevention (AGT) or wellness (CGT), and they will be delivered in questions or simple statement format. They will be sent from week 2-12 on Monday, Tuesday, Friday, and Saturday, and from week 13-24 on Mondays, Wednesday, and Friday. They will present information or ask questions related to five core topics of each study arm. The five core topics for each study arm are:
    - AGT: HIV testing, condom use, PrEP, partner communication strategies, and substance use.
    - CGT: physical activity, nutrition, stress management, sleep habits, and general wellness.
- ***Assessment Messages:*** Sent on Saturday of weeks 4, 8, 12, 16, 20, and 24, and will cover core topics and mediators for motivation, self-efficacy, and outcome expectations.

- ***Check-in Messages:*** Sent on Wednesday of each week and will ask participants open ended questions related to core topics (e.g., HIV testing, condom use, healthy eating, and physical activity).

## 6.2 Administration of Intervention

The TM intervention is automated and interactive. The program will begin sending TMs within 24 hours of randomization. Both arms will be 6-months in duration. The TMs will be delivered 5 times per week for the first 3-months and 3 messages per week for the last 3-months (exclusive of brief assessment questions, which occur once per month). The number of texts, dose, and duration will be equivalent between the two groups. Participants in both groups will be assessed monthly via TM on core topics (testing for TM HIV or physical activity for TM HL) and mediators (motivation, self-efficacy, and outcome expectations).

### *6.2.1 Intervention Fidelity*

The TM interventions will not use human providers. They will be delivered by a text message engine exactly as designed. The aforesaid allow us to anticipate a 100% reliable intervention and give us confidence that intervention will be delivered as expected. All subject responses that are not recognized by the system will be flagged for the project manager to evaluate and respond to if required. Because of this, a designated member of the study staff will review a portion of the project director's responses to ensure there is no treatment contamination.

### *6.2.2 Assessment of Subject Compliance with Study Intervention*

Agile Health platform keeps track of all text messages (sent and received), including both unprompted responses and expected responses from participants. This includes responses to assessment questions (e.g., motivation) and responses to the interactive intervention features of the text message programs.

Agile Health will send monthly reports to the study team. The monthly reports will contain the following numbers for the AGT and CGT: 1) participants enrolled in the TM program, 2) participants status, 3) number of text messages sent by system, 4) number of text messages received by system stratified by expected responses or unprompted engagement, 5) key words text by participants, 6) expected response rate and program engagement. The study team will review the reports to make sure subjects had not silently withdraw from the study.

# 7 STUDY SCHEDULE

The study schedule of event is outlined in appendix A, table 1. Participant will receive the assessment questionnaire through email or text message unless participant request to have an in-person or phone interview.

## 7.1 Screening (Day -1 to -30)

Subjects will be recruited at the participating community health centers (more information in manual of procedure). A designated study staff member will obtain verbal consent to start eligibility screening. If the participant screens eligible, the RA will enter the participants phone number into the Agile Health (AH) portal to generate a test text to ensure the participant will be able to receive the intervention. Phone numbers are not saved by Agile Health system during this process. Participants who cannot receive the intervention will be set as ineligible until they are able to receive text messages.

The screening process will end with one of three options:

- Exclusion: Participant did not meet the eligibility criteria.
- Declination: Participant met the eligibility criteria but declined to participate.
- Informed Consent Form (ICF) Signature: Participant met the eligibility criteria and accepted to voluntarily participate in the study after:
    - Having read and discussed ICF with a qualified study staff.
    - Asked question (if any) and have those being answered to their satisfaction.
    - Voluntarily signed the ICF.
    - Have received a copy of the signed ICF.

For more information on the tools used to collect the screening information, please see section *8.1.1 Screening.*

## 7.2 Baseline & Enrollment (Day -1 to -30)

Participants who consent to be in the study will complete the contact form and the baseline questionnaire. Only subjects completing the baseline questionnaire will be randomized. A copy of the participant's informed consent form (signed and dated) will be provided to the participant via email or text, depending upon the participant's preference. Participants who complete the baseline questionnaire will be randomized to one of two arms (HIV prevention or Healthy Lifestyle).

For more information on the tools used to collect baseline information, please see section *8.1.2 Baseline.*

## 7.3 Intervention initiation (Day 0)

The intervention will start within 24 hours of randomization. The first day of the intervention is day 0.

## 7.4 3-month assessments (90 days ± 30 days):

The 3-month assessment target date is 90 days after the start of the TM program with a window of plus or minus 30 days from that target date. For more information on tools used to collect information, please see section 8.1.5 *3- and 6-Months Questionnaires.*

## 7.5 End of intervention (Last day of week 24).

The intervention will last 6-months, each "month" consists of 28 days, which is a cumulative total of 168 days (24 weeks).

## 7.6 6-month assessments (180 days ± 60 days):

The 6-month assessment target date is 180 days after the start of the TM program with a window of plus or minus 60 days from that target date. For more information on tools used to collect information, please see section 8.1.5 *3- and 6-Months Questionnaires.*

## 7.7 Final Study assessment & End of Study Instructions (365 days ± 60 days)

The final study assessment target date is 365 days after the start of the TM program with a window of plus or minus 60 days from that target date. End of Study Instructions will be delivered to the subject using text message, phone call or email. For more information on tools used to collect information, please see section 8.1.6 *12-Months/ Final Questionnaire.*

## 7.8 Special situations during Screening, Baseline, and other assessments

### *7.8.1 Participant request in-person or phone interview.*

Participants that request assessment via phone interview or in person will have the assessment done as requested. RAs or designated research staff will contact the participant to arrange an in person or phone appointment to administer the corresponding assessment questionnaire. The data gathered during the in-person or phone assessment will be entered into REDCap.

### *7.8.2 Procedure or assessment interruption*

Participants that are unable to complete the screening process or informed consent process, due to any logistical reason (e.g., participant was called to his dental appointment) will be asked to complete a consent to contact form. Study team will contact the individual to complete the screening and informed consent at a future date using the contact form information.

## 7.9 Lost to Follow-up

RAs will make a maximum of 5 attempts to contact the study participant before they are considered lost to follow-up. For more information see Manual of Procedures.

## 7.10 Early Termination Visit

Not applicable.

## 7.11 Unscheduled Contact

An unscheduled visit would be considered to occur if a study subject was in contact with a member of the study team regarding HIV risk, attitudes, or practices if the contact was not: 1) part of standard texting procedures; 2) part of normal follow up for questionnaire completion or retention activities; or 3) related to the occurrence of adverse events or unanticipated problems. All unscheduled visits will be documented via a note to file and included in the participants' research record.

# 8 STUDY PROCEDURES /EVALUATIONS

All study assessment points include the completion of questionnaires by participants to assess each of the outcome measures described in section four of this protocol. All questionnaires and assessments will be recorded using Electronic Data Capture (EDC) system, REDCap (for more information on REDCap, please see the *Manual of Procedures*). All assessment tools used for this study will be listed and explained in the *Assessment Compendium*.

### *8.1.1 Screening*

Screening will occur between day -30 to day -1. A study staff will screen all potential participants in person at the screening site. Screening will start after verbal consent has been granted by participants. The Screening process will be divided into 5-stages, which are:

- Brief Screening Agreement
  - RA introduce themselves in the waiting room and requests permission to present the study.
  - Collection of the following information: 1) Participants language, 2) Site identification, 3) Screening date, 4) Consent to contact, and 5) Participants age.
  - Study presentation to participant.
- Screener
  - Collection of demographic and risk factors necessary to determine participants' eligibility (e.g., sex, HIV status, condom use, etcetera).
- Agile Health Phone Verification
  - Process done to ensure that participants can receive text message from the Agile Health system.
  - No data are saved in the Agile Health system during the test text.
- Eligibility determination
  - Will be determined by REDCap.
  - RA will confirm the eligibility.
- Informed Consent
  - A qualified study staff will go over the informed consent process with the participant.
  - The informed consent form will be collected electronically using REDCap.
  - A copy of the signed informed consent form will be delivered electronically through email to the participant.

### *8.1.2 Baseline*

The baseline will occur at day 0. It will be divided in two stages. In the first stage, a trained research staff member will obtain the participant's contact information by filling the Contact Form.

The second stage of the baseline may be conducted in person using EDC at the dental clinic in a private space or by phone. When not possible, participants will be able to complete the questionnaire via a secure website on their personal electronic device (e.g., laptop, tablet, or smartphone), or over the phone with the study team's assistance.

The following questionnaires and activities will occur at baseline assessment:

- First stage
  - Contact Form
    - It will be completed by a designated and qualified study staff.
    - It should be completed on the same day that the participant signs the Informed Consent Form.
- Second stage
  - Demographics
  - Behavioral Health History
    - Generalized Anxiety Disorder 7-item scale (GAD-7)
    - Center for Epidemiologic Studies - Depression 20 Item Scale (CES-D 20)
  - HIV Testing History assessment
    - HIV/HCV Testing Domains Measures
    - KAP Survey Questionnaire
    - Perceived Risk of HIV Scale (PRHS)
    - HIV Testing Self-Efficacy
  - PrEP related assessment
    - PrEP Knowledge
    - PrEP Stigma
    - PrEP Subjective Norms
    - PrEP Descriptive Norms
    - PrEP Experience
    - PrEP Adherence Self-Efficacy Scale (PrEP-ASES)
    - PrEP Uptake Self-Efficacy (IBM Model for PrEP Use)
    - PrEP Intentions
  - Condoms related assessments
    - Condom Use Self-Efficacy Scale (CUSES)
    - AIDS Risk Behavior Assessment (ARBA)
  - General substance uses assessment
    - Addiction Severity Index Lite (ASI-Lite)
  - Injectable drug use assessment
    - TCU HIV/AIDS Risk Assessment (TCU)
  - Confidence assessment
    - Confident, Motivation and Outcome Scales (SCT Mediators)
  - Social Support and Stigma assessment
    - Intersectional Discrimination Index - Anticipated (InDI-A)
    - Intersectional Discrimination Index - Day-to-Day (InDI-D)
    - Medical Outcomes Study Social Support Survey (mMOS-SS)

### *8.1.1 Randomization*

Randomization will be completed automatically by REDCap when the participant finishes the baseline questionnaires. For more information, please see section *5.4.1 Randomization Procedure.*

### *8.1.2 Intervention Initiation*

The intervention will start after the participant had been randomized and had opt-in to received message from Agile Health. The day the intervention initiates will be considered day 0. For information, please see section *6. Study Intervention*.

### *8.1.3 3- and 6-month questionnaires*

The 3-month assessment target date is 90 days after the start of the TM program with a window of plus or minus 30 days from that target date. While the 6-month assessment target date is 180 days after the start of the TM program with a window of plus or minus 60 days from that target date.

The participants will receive a link on their assessment target day. This link will take them to a secure website where they will fill the assessment that correspond to the endpoint in which they are being evaluated. Participants will be able to access the link using a personal computer, a laptop, a tablet, or a smartphone. A designated study staff can assist the participant with the evaluation if they request it.

The following questionnaires and activities will occur at 3- and 6- months assessment:

- HIV Testing History assessment
  - HIV/HCV Testing Domains Measures
  - KAP Survey Questionnaire
  - Perceived Risk of HIV Scale (PRHS)
  - HIV Testing Self-Efficacy
- PrEP related assessment
  - PrEP Knowledge
  - PrEP Stigma
  - PrEP Subjective Norms
  - PrEP Descriptive Norms
  - PrEP Experience
  - PrEP Adherence Self-Efficacy Scale (PrEP-ASES)
  - PrEP Uptake Self-Efficacy (IBM Model for PrEP Use)
  - PrEP Intentions
- Condoms related assessments
  - Condom Use Self-Efficacy Scale (CUSES)
  - AIDS Risk Behavior Assessment (ARBA)
- Injectable drug uses assessment
  - TCU HIV/AIDS Risk Assessment (TCU)
- Confidence assessment
  - Confident, Motivation and Outcome Scales (SCT Mediators)
- Social Support and Stigma assessment
  - Intersectional Discrimination Index - Anticipated (InDI-A)

- Intersectional Discrimination Index - Day-to-Day (InDI-D)
- Medical Outcomes Study Social Support Survey (mMOS-SS)

- Text Messaging Program Satisfaction questionnaire

### *8.1.4 12-month/final questionnaire*

The final study assessment target date is 365 days after the start of the TM program with a window of plus or minus 60 days from that target date. The participant will do the following assessments: HIV Testing History, PrEP, Condoms, Injection Drug Use, Confidence, Social Support and Stigma, and Text Messaging Program Satisfaction questionnaire (assessment listed below). Participants will complete the questionnaire via a secure website using a personal computer, a laptop, tablet, smartphone, or over the phone with the study team's assistance.

The following questionnaires and activities will occur at the final study assessment:

- First Stage
  - HIV Testing History assessment
    - HIV/HCV Testing Domains Measures
    - KAP Survey Questionnaire
    - Perceived Risk of HIV Scale (PRHS)
    - HIV Testing Self-Efficacy
  - PrEP related assessment
    - PrEP Knowledge
    - PrEP Stigma
    - PrEP Subjective Norms
    - PrEP Descriptive Norms
    - PrEP Experience
    - PrEP Adherence Self-Efficacy Scale (PrEP-ASES)
    - PrEP Uptake Self-Efficacy (IBM Model for PrEP Use)
    - PrEP Intentions
  - Condoms related assessments
    - Condom Use Self-Efficacy Scale (CUSES)
    - AIDS Risk Behavior Assessment (ARBA)
  - Injectable Drug Use assessment
    - TCU HIV/AIDS Risk Assessment (TCU)
  - Confidence assessment
    - Confident, Motivation and Outcome Scales (SCT Mediators)
  - Social Support and Stigma assessment
    - Intersectional Discrimination Index - Anticipated (InDI-A)
    - Intersectional Discrimination Index - Day-to-Day (InDI-D)
    - Medical Outcomes Study Social Support Survey (mMOS-SS)
  - Text Messaging Program Satisfaction questionnaire

## 8.2 Text Message Delivery

The intervention will be delivered to participants via the Agile Health TM platform for 6-months. Participants will receive 5-intervention messages per week for the first 3-months and 3-messages per week for the last 3-months of the intervention. Participants will be able to choose different blocks of time in which they could receive texts (e.g., morning, afternoon, evening). The text messages (TM) will be generated from an automated system. The text messages are customized to the participant based on their characteristics and answers to the baseline questionnaire and text messages. If the participant texts back a response that is not recognized by our automated system, the system will alert the project director, who will be able to respond to the participant from either her desktop computer or phone. The project director is not masked to treatment condition because of this. However, they will not be administering participant assessments, so the lack of masking will have no impact on study outcomes. In addition to the interventional text messages, participants will receive monthly text messages assessing outcome expectation, motivation, and HIV risk behaviors.

## 8.3 Intervention Dose and Engagement:

Intervention dose: The participants will automatically receive messages for 6 months. For the first three months they will receive 5 TM per week regarding either HIV risk reduction or healthy lifestyle and 3 TM per week for the last 3-months.

Engagement: Agile Health will send regularly scheduled reports which will include data regarding 1) number of texts sent, 2) percent of texts responded to, 3) number prompted responses.

# 9 ASSESSMENT OF SAFETY

## 9.1 Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

### *9.1.1 Unanticipated Problems*

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### *9.1.2 Adverse Events*

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

### *9.1.3 Serious Adverse Events*

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

## 9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

## 9.3 Characteristics of an Adverse Event

### *9.3.1 Relationship to Study Intervention*

To assess the relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

### *9.3.2 Expectedness of SAEs*

The NIDCR Medical Monitor and the Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

### *9.3.3 Severity of Event*

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)

2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

## 9.4 Reporting Procedures

### *9.4.1 Unanticipated Problem Reporting to IRB and NIDCR*

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number.
- A detailed description of the adverse event, incident, experience, or outcome.
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR as soon as possible or within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR's centralized reporting system via the Clinical Research Operations and Management Support (CROMS) contractor, Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998

- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

### *9.4.2 Serious Adverse Event Reporting to NIDCR*

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

The study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

## 9.5 Halting Rules

There are no halting rules for the RCT.

# 10 STUDY OVERSIGHT

The PIs, Dr. Henshaw and Dr. Beckwith, will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity.

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the NIDCR Program Official. The PIs typically meet bi-monthly with the NIDCR program official. At these meetings, the study team will report data regarding enrollment and retention, unanticipated problems and protocol deviations, outcome measures, quality management findings, and other relevant parameters. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

# 11 CLINICAL SITE MONITORING

No outside clinical site monitoring will be employed for this study. The PIs and staff will closely monitor the subjects as they progress through the study. They will monitor and evaluate study processes and documentation based on the International Council for Harmonization (ICH), E6: Good Clinical Practice guidelines (GCP), and internal quality management plans. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

# 12 STATISTICAL CONSIDERATIONS

## 12.1 Study Hypotheses

- **H1:** Participants randomized to receive the HIV prevention TM intervention (TM HIV) will have higher proportion of HIV testing within 12-months compared to the participants who receive the TM control condition, which is a TM intervention focused on achieving a healthy lifestyle (TM HL).

- **H2:** Participants randomized to receive TM HIV will have higher proportion of PrEP uptake and condom use within the past 6-months compared to the participants who receive the TM HL.

## 12.2 Sample Size Considerations

With 266 enrolled participants (133 participants per arm), assuming 30% loss to follow-up during the follow-up period, we anticipate that 186 participants will complete the baseline and 12-month study assessments. For a 2-sided chi-square test with continuity correction and a significance level of 0.05, this sample size gives our study an 80% power to detect a 20% absolute difference in proportions who completed HIV testing between participants randomized to the TM HIV versus TM HL, assuming proportions of HIV testing of 50% and 30% for the TM HIV and TM HL groups, respectively.[26-29]

## 12.3 Final Analysis Plan

We will compute descriptive statistics on baseline variables overall and by randomization group to characterize the study population and to detect any baseline imbalance. For continuous measures, we will report the mean, standard deviation, median, interquartile range, and the minimum and maximum. For categorical data, we will report counts and percentages. For the primary outcome (at least one HIV test within 12-months), we will estimate the intention-to-treat effect by including all participants according to their randomized intervention. We will use multiple logistic regression models to determine the proportion of participants who tested for HIV where the main independent variable is a binary indicator representing assignment to the TM intervention (yes versus no). The models will be adjusted for the randomization stratification factors (clinic and self-reported primary risk factor) to improve efficiency. We will also adjust for baseline characteristics that differ by study arm despite randomization. We will use similar methods for other binary secondary outcomes (initiation of PrEP, condom use).

Missing data: To determine whether there is a potential for selection bias due to loss of follow-up, we will compare participants lost to follow-up and those who complete the study, using their baseline assessment, using the 2 independent samples t-test and Fisher's exact test, comparing characteristics such as age, sex, study site, and recent HIV. If either of these groups differs from those, we were able to follow, we will use inverse probability weighing to calibrate our estimates to the original group and compare these results to the main analyses. In addition, we will compare the data collected to the point of lost to follow-up to the data of those who complete the study, to examine missing data mechanisms. In situations where missing data occur, we will examine the reasons for the

missing data whenever possible. If it is reasonable to assume that data are missing at random, we will use multiple model-based imputation methods.

We will examine the mechanism of intervention effects of the TM intervention on HIV testing through mediation analysis. We hypothesize that HIV TM will lead to improved self-efficacy at 2 months (mid-treatment), which in turn will be associated with better proximal outcomes (increased motivation and positive behavior) at the end of treatment, 4 months. We will also assess changes in mediators over the course of treatment and their mediational effect on the primary outcome (HIV testing at 12-months). To this end, we will use methods for mediation analysis based on the counterfactual framework, which advanced mediation analysis beyond previous methods, to derive the direct and indirect effects for each of these mediators on the rate of HIV testing while accounting for potential interactions between the intervention and the mediator and adjusting for potential confounding between the mediator and the outcome. We will use the method proposed by Imai et al[30] and implemented in the R mediation package.[31] We will use generalized estimating equations to accommodate for the time-dependent exposure and mediator variables.[32] For each mediator, we will express the results of these analyses in terms of the proportion of the total effect of the intervention group on HIV testing that is explained by the mediator.

# 13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate research records for this study in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of the confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents for this study include:

- Screening forms (eCRF): Subject's eligibility will be determined via a questionnaire in REDCap. This data will be collected in the BU REDCap system and managed by BEDAC.
- Informed Consent documents (eCRF): The informed consent process will be documented and stored within the REDCap system and managed by BEDAC.
- Contact Information (eCRF): Contact information will be documented and stored within the REDCap system and managed by BEDAC. Research staff will have access to this information to contact participants.
- TMs sent: TM sent will be documented and maintained in the Agile Health platform.
- TMs responses: All TM responses will be recorded and maintained in the Agile Health platform. Unrecognized texts will also be included in the project dashboard so that the project director can respond.

Questionnaire responses (baseline, 3-, 6-, and 12-months) (eCRF) will be collected via REDCap. The data will be stored and managed by BEDAC.

Qualitative logs of procedural issues identified by the research staff will be collected and documented by the project director and stored on a password-protected computer.

It is expected that for all of the eCRFs listed above, data will be directly entered into the REDCap system, so this will be the primary data source. In the rare instances when a paper form is used instead of the eCRF, the paper form will be the primary data source.

# 14 QUALITY CONTROL AND QUALITY ASSURANCE

Ultimate responsibility for implementing and maintaining quality assurance (QA) and quality control (QC) systems with written operating procedures to ensure that the trial is conducted, and data are generated, documented, and reported in compliance with the protocol resides with the principal investigators of the study. The project director, BEDAC, and Agile Health will provide regular reports on the fidelity and administration of the intervention to the MPIs. These processes are outlined in the study's Quality Management Plan.

In addition to the reports, all eCRFs will use standard procedures to ensure data quality, such as required responses and maximum and minimum data ranges.

All staff will undergo required trainings for each task for which they assume responsibility. Trainings for responsibilities such as administration of questionnaires, recruitment, or obtaining informed consent will require the staff member to review the administration procedures with one of the MPIs or the project director and then successfully administer a minimum of three mock questionnaires with study staff or other department members. These mock administrations will be audio recorded and reviewed with the PIs or Project Director to ascertain if competency was met on that administration. All trainings will be documented on a training log. All assigned tasks will be tracked on a delegation of responsibility log.

For more information on the study's QA and QC, please see *the Quality Management Plan*.

# 15 ETHICS/PROTECTION OF HUMAN SUBJECTS

## 15.1 Ethical Standard

The PIs will ensure that this study is conducted in full conformity with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, as drafted by the *US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* (April 18, 1979) and codified in *45 CFR Part 46* and/or the *ICH E6*.

## 15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

## 15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects. A consent form describing in detail the study procedures and risks will be given to the subject either in hard or electronic copy. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to them.

The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records either via text or email. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

## 15.4 The consent process will be documented via REDCap.

For subjects who speak Spanish, a Spanish version of the consent form will be used that was translated from the English version and then back translated into English. A bilingual (English and Spanish) study staff will administer the consent process with individuals in the language of their choice. All processes are identical to those described for English speakers.

## 15.5 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals of any gender or racial/ethnic group may participate. Our eligibility criteria include a minimum age of 18 years based on the demographic profile of patients at the community health center adult dental clinics; this also reflects the age of majority in Massachusetts. Some participants enrolled in this research may be between the ages of 18-21, and those individuals will meet the NIH definition of children. We will not seek nor obtain parental consent for these subjects' participation in research, given that they no longer meet the legal definition of minors.

## *15.6* Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without the prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

## 15.7 Certificate of Confidentiality

To further protect the privacy of study subjects, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, civil, criminal, administrative, legislative, or other proceedings, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to the subjects.

# 16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs) and source documentation, in collaboration with Agile Health and Biostatics and Epidemiology Data Analytics Center (BEDAC).

## 16.1 Data Management Responsibilities

BEDAC at Boston University School of Public Health (BUSPH) has been a resource since 1984, providing research services to BU investigators, government, foundations, and industry partners. The BEDAC will provide the following services for this study:

- **Project Management:** Provides the structure through which study operations are planned, tracked, and managed, provides a vehicle to foster effective communication and information exchange, and ensures that project deliverables are completed on-time.

- **Data Management:** Leads the development, implementation, and maintenance of the Data Management Plan (DMP) to ensure that data is traceable and of high quality throughout the entire data life cycle. The DMP provides documentation of data sources, describes the software development life cycle, data collection, and data cleaning procedures, and ensures validation of final datasets to meet Sponsor requirements.

- **Study Monitoring**: Along with the MPIs, provides risk-based approaches to ensure adherence to the protocol, standard operating procedures (SOP), Good Clinical Practice (GCP), and other regulatory requirements.

- **Reporting:** Provides tables, figures, and listing for data management, safety, and statistical findings, using both static and interactive platforms.

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the two PIs. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

## 16.2 Data Capture Methods

Data will be collected using several methods. Signed and dated consent forms will be completed by the participants in the study on REDCap or, in the event of internet interruption, on paper forms and stored at the GSDM offices under secured conditions with a copy uploaded to the participant file on REDCap. Data will also be collected through a secure web-based REDCap database. Paper forms will be used for screeners and questionnaires if they are not entered directly into REDCap. Text message feedback and responses will be collected during the text message program via text

message responses. Only the participant's study identification number will appear on any data. Data collected from research participants will be stored in a secured, password-protected computer file that is separate from identifiers. Any paper data will be placed in a locked file cabinet. A file will be maintained that associates the subject's name with that subject's study identification number. This file will be kept in a secure, password-protected file, separate from the actual study data (e.g., screener and questionnaire data).

## 16.3 Types of Data

Data includes screening forms, informed consent documents, questionnaires, and TM data. Electronic forms of all data forms will be recorded through the secure web-based REDCap database. The Agile Health database will contain the text messaging system, including information on what text messages each participant has received, where they are in the study, and what feedback they have given.

## 16.4 Schedule and Content of Reports

The schedule and content of reports is included in the Data Management Plan.

## 16.5 Study Records Retention

All paper documents will be stored in locked secured cabinets at the offices of GSDM's Department of Health Policy and Health Services Research at 560 Harrison Ave. in Boston, Massachusetts.

The primary databases will reside on a secured server, accessible to appropriate GSDM staff, Agile Health staff, and at the central Coordinating Center at BU School of Public Health.

All study records and computer files will be retained for at least 7 years after the final financial report for the award is filed, or the final study manuscript is published, whichever is later. At each 7-year interval, the necessity of keeping the study records and computer files longer will be reviewed and decided upon.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the

part of the subject, the investigator, or the study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to NIDCR and the local IRB, according to their requirements.

# 17 PUBLICATION/DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry so that the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to err on the side of registration or consult the editorial office of the journal in which they wish to publish."

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## APPENDIX A

**TABLE 1: Schedule of Event (SoE)**

| | SC | BL | D0 | M3 | M6 | WK24 | EoE |
|---|---|---|---|---|---|---|---|
| *Brief screening agreement* | X | | | | | | |
| *Screening* | X | | | | | | |
| *AH phone verification* | X | | | | | | |
| *Eligibility confirmation* | X | | | | | | |
| *Informed Consent Form* | X | | | | | | |
| *Contact Form* | | X | | | | | |
| *Demographics* | | X | | | | | X |
| *GAD-7* | | X | | | | | X |
| *CES-D 20* | | X | | | | | X |
| *HIV/HCV Testing* | | X | | X | X | | X |
| *KAP Survey* | | X | | X | X | | X |
| *PRHS* | | X | | X | X | | X |
| *HIV Testing Self-Efficacy* | | X | | X | X | | X |
| *PrEP Knowledge* | | X | | X | X | | X |
| *PrEP Stigma* | | X | | X | X | | X |
| *PrEP Subjective Norms* | | X | | X | X | | X |
| *PrEP Descriptive Norms* | | X | | X | X | | X |
| *PrEP Experience* | | X | | X | X | | X |
| *PrEP-ASES* | | X | | X | X | | X |
| *IBM Model for PrEP Use* | | X | | X | X | | X |
| *PrEP Intentions* | | X | | X | X | | X |
| *CUSES* | | X | | X | X | | X |
| *ARBA* | | X | | X | X | | X |
| *ASI-Lite* | | X | | | | | X |
| *TCU* | | X | | X | X | | X |
| *SCT Mediators* | | X | | X | X | | X |
| *InDI-A* | | X | | X | X | | X |
| *InDI-D* | | X | | X | X | | X |
| *mMOS-SS* | | X | | X | X | | X |
| *Randomization* | | X | | | | | |
| *Intervention Starting Point* | | | X | | | | |
| *Intervention Ending Point* | | | | | | X | |
| *TM Program Satisfaction* | | | | X | X | | |
| *End of study instructions* | | | | | | | X |

Screening (SC), Baseline (BL), Day 0 (D0), Month-3 (M3), Month-6 (M6), Week 24 (WK24), End of Study (EoE).