STUDY TITLE: SteadyRx: Smartphone ART Adherence Intervention for Drug Users

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DATE: July 17, 2017

ABSTRACT

Purpose

The primary purpose of the "SteadyRx" protocol is to evaluate the SteadyRx Smartphone-based intervention as a means of promoting and maintaining antiretroviral adherence in people living with HIV who are struggling with addiction.

Participants & Inclusion/Exclusion Criteria

Study participants will be selected from adults who are receiving care at the Comprehensive Care Practice on the Johns Hopkins Bayview Medical Campus. Applicants will be eligible to participate in the study if they: a) are 18 to 100 years old; are HIV positive; c) have a primary care physician who is providing their HIV-related care including prescribed ART; d) meet criteria for substance use disorder; e) speak fluent English; f) can operate a smartphone. Applicants will be excluded if they a) report current suicidal or homicidal ideation; b) report active hallucinations; or c) are enrolled in another HIV/AIDS-related or medication adherence-related study.

Design

This randomized controlled pilot study features a parallel group design. Participants (N = 50) will be randomly assigned to one of the two groups: Treatment as usual (TAU) or the SteadyRx-supported antiretroviral adherence group (SteadyRx). We will randomize using urn stratification to promote equal numbers of individuals in each group and balanced distributions within a dichotomized covariate expected to be associated with the outcome. Stratification variables are current depression (Y/N); self-report of problem drug use in the last 30 days (Y/N); and TOFHLA score ≤ the rolling median (Y/N). Study participation will last for six months from the date of randomization.

Standard Services

Participants will be receiving care for their HIV at CCP. This will include ART.

Assessments

An intake assessment (e.g., ASI-Lite) will be collected prior to randomization. Additional assessments will be conducted at 30-day intervals throughout the 6-month intervention period. All assessment forms are listed in the List of Manual Forms. Complete descriptions of each assessment and the schedule of delivery for each assessment is provided below.

Primary Outcome Variable

The primary outcome measures for intervention effectiveness will be (1) the percent of participants who take 95% of prescribed doses of their antiretroviral medication(s) within three hours of their scheduled dosing time each month as measured by MEMS, and (2) the percent of participants who achieve a viral load <400 HIV-RNA/mL at each of the two assessments collected during the active intervention period.

Secondary Outcome Variables

Secondary Measures. (1) Monthly percentage of on-time (i.e., within three hours of the scheduled time set by patient-physician agreement) bottle openings as measured by MEMS and self-report, respectively. Note that this is different from the primary measure which dichotomizes adherence (Y/N) with a 95% threshold. The primary measure is the measure of greatest clinical significance. The secondary measure is more sensitive to changes in behavior; (2) CD4 counts and HIV-1 RNA levels obtained at primary care visits.

Exploratory Measures. (1) MOS-HIV physical health and mental health summary scores (0-100) across the study period; (2) self-reported days of opiate and cocaine use.

Usage, Acceptability, and Cost Measures. Outcomes related to the usage and acceptability of the Smartphone application will include Acceptability Questionnaire total score, SUMI global scale score, average uses per day, and average duration of use per day. Outcomes related to the cost of the intervention will include total cost of the intervention per person, and the incremental cost-effectiveness ratio (ICER). To calculate ICER, we will divide the costs of the intervention by the difference between the two groups in terms of the percent of participants who take 95% of prescribed doses of their antiretroviral medication. The ICER can be interpreted as dollars spent per unit of desired outcomes gained. In addition, a more complete cost/benefit analysis conducted by academic economists will be included in a future large-scale study.

INVESTIGATORS

The following is a list of the responsible investigators for the study and their contact information.

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RECRUITMENT

Responsible Staff

The Outreach Coordinator and Student Investigators will be responsible for conducting the screening interviews. Only approved staff members will be responsible for obtaining informed consent to participate in this research. The Outreach Coordinator will coordinate the recruitment process and will supervise all recruitment activities. All aspects of the recruitment process are detailed in the Intake Assessment Checklist, which should be used to guide the entire process from the first time we are introduced to a potential participant to the time when they are randomly assigned to a study condition.

Rate of Recruitment

We will need to randomly assign five people per month to the study conditions. This may require obtaining consent for more than five people per month. We can begin by obtaining initial consent from a minimum of two people per week, and then reducing this number if the rate of random assignment greatly exceeds our target. It is acceptable to have a rate of recruitment that is higher than the target, but it is a problem to have a rate of recruitment that is lower than the target for an extended period of time.

Identifying Participants

Overview of initial screening procedures. It is possible that all participants will be patients at the Comprehensive Care Practice (CCP). CCP is located in the Mason F. Lord Building at the Johns Hopkins Bayview Medical Center in Baltimore, MD. CCP provides primary medical care to ~450 HIV+ adults and will serve as the primary recruitment site. However, over the course of this research we will attempt to identify possible recruitment sites within the State of Michigan. If we identify sites within Michigan, we will seek WMU IRB approval for those sites prior to initiating recruitment from those sites. Recruitment procedures across the sites will be as similar as possible given local resource constraints. Any differences will be specified concurrently with seeking approval for the new site(s).

Participants will be recruited from their regularly scheduled HIV care appointments at which current viral load and CD4 counts are evaluated. Anyone who is HIV positive who meets the criteria for substance use disorder will be told by their doctor about our research study and given a recruitment flyer that explains the nature of participation.

> **Script for physician:** *I am conducting a research study with my colleagues that may be of interest to you. The research study is testing a way to help people living with HIV take their antiretroviral medicines according to their prescriptions. The study provides $50 per month for participating in an interview and showing the interviewer your pill bottle. Some people in the study will also get money for taking their medication. Here is a flyer about the research study. If it seems like something that might interest you, then you can talk to the outreach coordinator today. She can tell you more about the study and will ask you a few questions to determine if the study is right for you. I want to stress that participating in this*

research is optional, and that your care at Johns Hopkins will not be affected in any way by your decision to participate or not participate. Would you like to talk to the outreach coordinator to learn more about it?

If they express interest in learning more, the doctor will contact the staff member at the doctor's office who is in charge of study recruitment and assessment (hereafter, outreach coordinator). The person who is currently serving in this role is Tyesha Karume. Tyesha has a bachelor's of science in nursing and a masters of education. She regularly consults with Comprehensive Care Practice patients regarding the importance of medication adherence and helps them address barriers to adherence and access to care. Tyesha is a JHU employee who is listed on the JHU IRB protocol as a study team member, has completed all training required by the JHU IRB, and is approved by the JHU IRB as a consent designee for this study. The outreach coordinator will go upstairs to CCP and wait for the patient to finish their appointment. Once the appointment is complete, the outreach coordinator will escort the patient to their office. The outreach coordinator will briefly explain the intake interview process and basic purpose of the study.

Script for outreach coordinator: *As you know, I am recruiting participants for a research study. This study is about a smartphone-based intervention for medication adherence that makes it easier for users to contact their care providers, provides users with reminders to take their medicine, and pays users money when they submit videos of themselves taking their pills each day. Half of the people who join this study will be randomly selected to receive the smartphone-based intervention, which we call SteadyRx. All of the people who join this study will get paid $30 per month for participating in interviews and $20 for bringing me a special electronic pill bottle that we will use to hold your medicine that tracks when you open the bottle, a total of $50 per month. If you are interested in joining this study, then I will help you to do that. We will need to schedule another appointment in order to move forward. During this appointment, we will go through a study consent form together that explains the study in detail. Then I will ask you questions that will allow me to assess whether you qualify to take part in this study. The whole process will take about two hours. Since it includes an interview, you will be paid $50 if you complete this process, whether or not it turns out you qualify for the study. Would you like to proceed?*

If the patient agrees to move forward they will schedule an appointment for 10:00 AM or 1:00 PM on the next day or as soon as possible. Participants will be instructed to bring their pill bottles to the appointment.

Intake Interview

Reminder Calls Participants who have not returned for their assessment will be given reminder calls related to their scheduled intake interview by the student investigators. They will also receive follow up calls if they fail to show up for their

scheduled appointment time. Reminder calls will be given one day before their scheduled appointment. The calls will be between 10AM – 6PM Monday through Thursday and 1PM – 5PM on Sunday.

If the participant does not answer, the student investigator will wait one hour and then call again. This process is repeated if they do not answer again. If they do not answer a third time, the student investigator will leave the following voicemail:

> *"Hi (PERSON's NAME), my name is *First Name* and I am calling on behalf of Tyesha Karume at the Comprehensive Care Practice at Johns Hopkins Bayview. I just wanted to remind you that you have an appointment scheduled for (APPOINTMENT TIME) tomorrow and confirm that you will be coming. Thank you and have a nice day."*

If someone other than the participant answers the phone, follow the following script:

> *"Hi, I'd like to speak to (PERSON'S NAME)."* If the person on the phone asks who you are or why you are calling then say, *"My name is *First Name* and I am calling to remind them about an appointment they have at Johns Hopkins tomorrow."* If they ask for further details tell them *"I'm sorry, but I am only allowed to discuss details with (PERSON'S NAME)."*

Once the participant is one the phone, follow the following script:

> *"Hi (PERSON'S NAME), my name is *First Name* and I am calling on behalf of Tyesha Karume at the Comprehensive Care Practice at Johns Hopkins Bayview. I just wanted to remind you that you have an appointment scheduled for (APPOINTMENT TIME) tomorrow and confirm that you will be coming."* If they say yes, say *"Okay, great, remember that your appointment is at (APPOINTMENT TIME) and that you need to bring your pill bottle and will be paid $30 for completing the interview and if you qualify for the study, then you will receive an additional $20 for bringing your pill bottle. That means you will be paid up to $50 tomorrow for bringing your pill bottle and completing the interview."* Once they respond, then say *"Okay, see you at (APPOINTMENT TIME) tomorrow, have a great day, Bye."*

If they indicate that they are unsure, or do not know what you are talking about, follow the following script:

> *"Tyesha asked me to call you because I am helping her recruit participants for a research study and you are scheduled for an appointment with her tomorrow. If you'd like, I can remind you what the study is all about."*

If they wish to be reminded, follow the following script:

> *"This study is about a smartphone-based intervention for medication adherence that makes it easier for users to contact their care providers, provides users with reminders to take their medicine, and pays users money when they submit videos of themselves taking their pills each day. Half of the people who join this study will be randomly selected to receive the smartphone-based intervention, which we call SteadyRx. All of the people who join this study will get paid $30 per month for participating in interviews and $20 for bringing me a special electronic pill bottle that we will use to hold your medicine that tracks when you open the bottle, a total of $50 per month. The whole process will take about two hours. Since it includes an interview, you will be paid $30 if you complete this process tomorrow, whether or not it turns out you qualify for the study, and $20 for bringing your pill bottle if you qualify for the study."*

Reminder calls will be discontinued immediately upon request of the participant, will not exceed three per week, and will be discontinued after one month from the originally scheduled intake interview or appointment time.

Calling No-Shows. Any participant who does not show up for the randomization appointment at their scheduled time should be contacted via phone by outreach staff, reminded of their appointment, reminded of the possibility of entering the study, and rescheduled if necessary. A record of all attempts to call no-shows should be kept on a separate contact log.

Transportation to the Intake Appointment. Should the participant be unable to immediately attend the intake appointment following the initial screening, the participant should be assisted in developing a plan to attend the appointment. We cannot provide financial assistance to make this happen, but we do provide a reloadable gift card with an initial value of $50 to everyone who completes their intake interview, independent of whether they qualify or choose to continue and be randomly assigned to one of the study groups. If a participant is unable to complete the intake assessment through no fault of their own (e.g., technical malfunction) and must return, they will be compensated $20 for the return trip.

Procedures for Initiating the Intake Assessment. Once the participant has arrived for the intake assessment, the outreach coordinator will obtain the CD4/RNA counts, substance abuse history, and depression diagnosis from the participant's primary physician. The outreach coordinator will print out the following materials:
1) Inclusion/Exclusion Checklist; 2) Smartphone Assessment; 3) Study Consent Form; 4) HIPAA form; and 5) Material Acknowledgement Form. The outreach coordinator will contact the WMU staff to inform them that the participant has arrived and give them the CD4/RNA counts, the substance abuse history, and depression diagnosis of the participant. The outreach coordinator will then

initiate the Smartphone Assessment. If the participant meets inclusion criteria, the outreach coordinator will escort him/her to the assessment station on the second floor of CLH. If the participant is excluded, the outreach coordinator should ask if the participant needs bus tokens and dismiss them. The outreach coordinator will set the participant up at the assessment computer to begin the informed consent process. The assessment computer is under the control of the WMU staff using TeamViewer remote control software.

Informed Consent Process. The consent process will require that participants are seated at a computer that will run a presentation that plays a recording of staff reading the consent form aloud and also displays the corresponding consent form text on the screen. Participants will be given their own paper copy of the consent form, and a staff member will then begin the computerized presentation. If the computerized presentation is not available, a study team member will read the consent form aloud to the subject. The study team member will answer any questions posed by the participant during the reading of the consent form. At the end the study team member will ask, "Do you have any questions?" or if the participant asked questions during the reading, "Do you have any more questions?" If the participant asks a question that is directly related to the consent process or the intake interview that cannot be answered by referencing the consent form, then the study team member should immediately call the principal investigator and consult with him prior to answering the question. After the consent form has been presented to the participant, they will be given a brief quiz that will address the major points of the consent form to ensure that they understand the details of the consent form. Any errors will be explained and corrected by the study team member. An investigator will be consulted if a person scores less than 70% correct, or if the subject has any questions that the person administering the consent cannot address. If the participant scores more than 70%, the study team member will ask, "Would you like to participate in the interview?" Participants will be given as much time as they need to give initial consent. If the participant declines, the study team member will thank them for their time and see the participant out of the research space. If the participant accepts, the study team member say, "Please sign and date the initial consent form," and indicate where to do so on the form. The staff member should also sign and date the form as indicated. The participant should be told to retain their copy of the consent form. At this point, the initial consenting procedure is complete and the intake interview can begin.

Inclusion/Exclusion Criteria and Checklist. The Inclusion/Exclusion Checklist lists the inclusion/exclusion criteria for the study and the location where the relevant information can be obtained to determine whether or not a participant meets each criterion. At no time should any study team member disclose to the participant the requirements for eligibility into the study. If a participant asks a question related to the eligibility criteria, immediately consult with the principal investigator about what action to take. During the intake interview, the

Inclusion/Exclusion checklist should be updated and reviewed. If the participant has either failed to meet an inclusion criterion or has met an exclusion criterion, then the participant should be dismissed. Of course, participants can stop the interview at any time and for any reason. A participant who chooses to stop the interview permanently prior to the completion of the interview will be considered dismissed and will not be further evaluated for study participation. If a participant is excluded following the informed consent, they should be paid $50 for participating in the intake assessments.

Inclusion/Exclusion Criteria:

Applicants will be eligible to participate in the study if they:

a) Are 18 to 100 years old
b) Are HIV positive
c) Have a primary care physician who is providing their HIV-related care including prescribed ART
d) Meet criteria for substance use disorder
e) Speak fluent English
f) Can operate a smartphone

Applicants will be excluded if they:

a) Report current suicidal ideation. **Immediately initiate suicide prevention protocol in accordance with CCP policy/practices.**
b) Report auditory or visual hallucinations. **Immediately alert study doctor if a participant has active hallucinations.**
c) Are currently participating in any other HIV/AIDS related or medication adherence related research studies.

Informing Participants of Eligibility/Ineligibility. **The applicants should never be told why they are eligible or ineligible.** This policy will prevent the community from learning about the eligibility criteria. This is imperative, since knowledge of the study criteria could result in applicants either falsely self-reporting characteristics in an effort to get admitted to the study. All staff members should be intimately familiar with the policies related to eligibility described in this treatment manual.

The Intake Interview. The interview will be conducted by using the SteadyRx Intake Assessment Checklist – Outreach Coordinator and the Intake Assessment Checklist – WMU Staff. This interview includes the Smartphone Assessment Protocol, the Testing of Functional Health Literacy in Adults (TOFHLA), the Beck Depression Inventory (BDI-II), the Visual Analog Scale for self-reporting ART adherence, the Medical Outcomes Study HIV Health Survey, Addiction Severity Index – Lite (ASI- Lite), and the Patient Reactions Assessment.

The Smartphone Assessment Protocol assesses whether participants can operate a smartphone.

The Test of Functional Health Literacy in Adults (TOFHLA) – a standard measure of health literacy which has been shown to predict ART adherence.

The Visual Analog Scale for self-reporting ART adherence which has been recommended as providing the highest quality self-reports of ART adherence in several recent studies.

The Medical Outcomes Study HIV Health Survey is a widely used assessment of quality of life for HIV/AIDS patients that assesses perceived physical and mental health.

The Addiction Severity Index-Lite which assesses drug use and related problem severity

The Patient Reactions Assessment is a 15-item validated instrument for assessing a patient's perceived ability to initiate communication about their illness. This will allow us to determine whether the consult element of SteadyRx has an effect on patient's perceptions of the quality of their communication with their provider.

After the intake interview is completed, the staff member should review and complete the Inclusion/Exclusion checklist. If the participant is eligible, then he/she should be informed that he/she is a candidate for diversion to treatment and he/she is invited to participate in a research study.

Any participant who is ineligible should be informed that they are not eligible to participate in the study. Upon notification of ineligibility, some participants may be saddened or angered. See the section on study eligibility for further details describing how to handle ineligible participants. Be sure to retain all completed assessments, independent of whether a participant was eligible for the study. Assessments completed by ineligible participants will be collected and stored separately from assessments completed by eligible participants.

CD4 counts and HIV-1 RNA levels. The participants will sign a separate consent form granting their care provider (i.e., Comprehensive Care Practice) permission to share their test results with the study team. Thus, we anticipate that we will have a baseline measure and two study period measures of CD4 and HIV-1 RNA levels for pilot study participants. We will also maintain a record of scheduled appointments and whether the participant attended each appointment (Y/N; coded yes for any appointment attended within one week of the originally scheduled date). Importantly, we will be collecting our monthly assessments on the same day as the patient is scheduled to have their CD4 and HIV-1 RNA levels checked in the same building. Note that we do not plan to interface directly with

the existing medical records systems used by care providers. Instead, care providers will submit the information to the outreach coordinator, who will relay the information to the study team in Kalamazoo via the phone.

RANDOM ASSIGNMENT TO STUDY CONDITIONS

Overview

The random assignment process is the collective responsibility of student investigators and the outreach coordinator. The separate roles of these staff members in this process are described in separate sections below. The day of random assignment must occur within two weeks of the first meeting. If a participant has not completed the necessary procedures for randomization by the two-week time point, then that participant should be permanently discharged from the study.

Procedures

Overview. All staff will be prepared for the intake assessment. After the informed consent is signed by the participant, the Outreach Coordinator notifies the WMU staff and brings the participant to the computer terminal. Student investigators will have the primary responsibility for randomly assigning participants to one of the two study conditions. After completing the randomization procedure, the Outreach Coordinator and WMU staff should train participants how to use the SteadyRx app and PillWatch function (if in SteadyRx group), distribute CTPayer card, and update relevant data logs.

Randomization Variables. The proposed pilot study will feature a 2 group, randomized controlled, parallel group design. In order to assess the effectiveness of the proposed intervention as a whole, participants will be assigned to receive usual care (Control Group) or the SteadyRx smartphone intervention. A computerized urn randomization procedure will be used to randomize participants and balance groups on three baseline characteristics that may independently influence the main outcome measures of ART adherence and viral load. Specifically, depression, active drug use, and low health literacy have all been shown to be associated with reductions in ART adherence. Thus, we will use presence of current depression (Y/N); self-reported recent Cocaine or Opiate use (Y/N); and TOFHLA (a health literacy measure; see Assessments) score ≤ the rolling median (Y/N) as the stratification variables in the present study. While it might be desirable to stratify on additional variables, increasing the number of variables is not practical given the study's sample size.

Procedure. After obtaining informed consent, the student investigator will complete the intake interview. First, the ASI-Lite will be administered to finish determining eligibility. If the participant is eligible for the study, the TOFHLA will be administered. While the participant is completing the ASI-Lite and the TOFHLA, the student investigator will call the Outreach Coordinator to obtain depression status, CD4 count, HIV-1 RNA levels, and drugs of abuse history information. Once the participant has completed the TOFHLA and information regarding recent drug use and depression status, group assignment can be determined. The student investigator will then call the principal investigator,

Anthony DeFulio, and give the answers to the stratification variables. The principal investigator will then run the urn randomization procedure and relay the group assignment to the student investigator. The participant will then complete the rest of the surveys (Visual Analog Scale for self-reporting ART adherence, MOS-HIV, Patient Reactions Assessment, SteadyRx Reminder Enrollment Form, and Contact Information Sheet).

Notifying Outreach Coordinator. After the participant has been randomized and is completing the rest of the assessments (see above), the student investigator will inform the Outreach Coordinator of the group assignment. The Outreach Coordinator will bring the necessary materials to complete the intake to the participant (MEMS cap, CT Payer card, and smartphone (if in SteadyRx group). After the Outreach Coordinator is notified of study condition, and the assessments are finished, the student investigator will inform the participant of study condition.

Notifying Participant of Study Condition. The student investigator will notify the participant of the result of the randomization procedure.

If the result is the SteadyRx group, the student investigator will say the following:

> "You have been assigned to the SteadyRx group. This means that you are able to be paid $30 each month for coming here and completing an interview with our outreach staff. This also means that you will be provided with a cell phone for 6 months. You will be provided with a medicine cap that will go on top of your prescription HIV medication bottle. You are responsible for keeping track of both of these items. If either of these items are lost, stolen, or sold, you will be penalized. If you keep your cell phone for the whole study, you will receive $100 at the end of the study. Instead of receiving $100 for returning the cellphone, you may choose to keep it. Each time you bring your medicine cap back to an interview, you will receive $20. On the cell phone, you will find an app called SteadyRx, which we will teach you how to use now. Do you have any questions?"

If the result is the control group, then the student investigator will say the following:

> "You have been assigned to the control group. This means that you are able to be paid $30 each month for coming here and completing an interview with our outreach staff. Each month, we'll set up an appointment for the following month and our outreach staff will be calling you from time to time to remind you about your appointments and the money you can make. You will be provided with a medicine cap that will go on top of your prescription HIV medication. Each time you bring the medicine cap to an assessment interview, we will pay you $20. We will make an appointment with you for our next meeting today before you leave. I'd also like to provide you with $50 for coming here today, and you may also have two bus tokens if you'd like. Do you have any questions?"

If the participant was found ineligible for the study due to answers given in the ASI-Lite, then the student investigator will read the following script:

> "Unfortunately, you did not qualify for the study. The good news is that we are paying you $50 for your time today. Tyesha should be down any moment with the card. We want to emphasize that we thank you for coming out and taking time to complete these assessments. This also is a very important part of our study. We also wanted to note that this will not change your care at the CCP or at Johns Hopkins. Thank you again for your time."

MEMS Cap. All participants will receive a MEMS cap which is to be placed on the cap of their prescription HIV medication. The intake assessment cannot take place if the participant did not bring their pill bottle. The student investigator is responsible for initiating a participant into the MEMS database located at http://www.mwvaardex.com/. The student investigator should use their own personal login information to access the database.

Assigning Materials. All participants will be assigned a CTPayer card which will be loaded with $50 for completing the intake assessment, regardless of study group assignment. All participants will sign a SteadyRx Material Acknowledgement Form that specifies what materials they received. A log will also be updated with this information.

CT Payer. All debit cards will be issued and loaded through CTPayer. The outreach coordinator will be responsible for issuing the debit card. Prior to giving the debit card to the participant, the outreach coordinator will call the student investigator in Kalamazoo and inform them of the specific card being issued to the participant. The principal investigator and student investigators will be responsible for assigning the debit card to participants and paying participants through the CTPayer system. Immediately after being informed of the debit card information, the student investigator will login to the CTPayer system with the lab account through their website https://partners.payoneer.com/ and change the Payee ID of the specific debit card to the participant's assigned participant ID.

SteadyRx Group Only. Participants in the SteadyRx group will receive a Smartphone with the SteadyRx application downloaded onto it. Participants will be required to complete PillWatch protocol.

Creating Participant SteadyRx accounts. The responsibility of creating Motiv8 Systems accounts for participants in the SteadyRx group will be the student investigators' in Kalamazoo. In order to access the backend of the SteadyRx, the student investigators will create an admin account for themselves using the credentials given by the principal investigator. The student investigators will then navigate to the following URL: http://steadyrx.red5hift.com.

The Clients tab should be the default start page. Click "Add Client" in order to begin the process. Both their login and their alternate ID will be the participants' PTID. The password will be selected from the list of passwords created by the principal investigator on the shared Google Drive. Once a password has been assigned to a participant, cross that password out on the list. After creating the account, the student investigator must then assign participant to either the OnePerDay or TwoPerDay program. This will correspond to whether the participant must take their antiretroviral medication once or twice per day. The student investigator will create either one or two dose windows accordingly entering the participants' cellphone number followed by "@myboostmobile.com" where it asks for an email address. Finally, the student investigator will add the participants' healthcare contacts to the InTouch contacts.

Preparation for the First 30-Day Assessment and Participant Departure. After the participant has been informed of their study condition, outreach staff should then set up the first 30-day assessment appointment, provide the participant with an appointment card, confirm their contact information and release the participant. The student investigator should make a $50 payment to the participant, update the Materials Assignment records, and set up a new data sheet.

GENERAL PROCEDURES

Overview

The rest of the study manual from this point onward describes how participants who have been randomly assigned to one of the two study conditions (i.e., Control or SteadyRx) are handled throughout the main portion of the study (i.e., the post- randomization period). This section on general procedures covers procedures that are applied to all randomized participants, independent of their group assignment. The subsequent sections apply only to participants who have been assigned to the SteadyRx group. Thus, the focus of this section is on the monthly assessments.

Monthly Assessments

Reminder Calls. Participants will be given reminder calls related to their scheduled monthly assessment by the student investigators. They will also receive follow up calls if they fail to show up for their scheduled appointment time. Reminder calls will be given one day before their scheduled appointment. The calls will be between 10AM – 6PM Monday through Thursday and 1PM – 5PM on Sunday.

If the participant does not answer, the student investigator will wait one hour and then call again. This process is repeated if they do not answer again. If they do not answer a third time, the student investigator will leave the following voicemail:

> *"Hi (PERSON's NAME), my name is *First Name* and I am calling on behalf of the SteadyRx research team. I just wanted to remind you that you have your monthly assessment scheduled for (APPOINTMENT TIME) tomorrow and confirm that you will be coming. Thank you and have a nice day."*

If someone other than the participant answers the phone, follow the following script:

> *"Hi, I'd like to speak to (PERSON'S NAME)."* If the person on the phone asks who you are or why you are calling then say, *"My name is *First Name* and I am calling to remind them about an appointment they have at Johns Hopkins tomorrow."* If they ask for further details tell them *"I'm sorry, but I am only allowed to discuss details with (PERSON'S NAME)."*

Once the participant is one the phone, follow the following script:

> *"Hi (PERSON'S NAME), my name is *First Name* and I am calling on behalf of the SteadyRx research team. I just wanted to remind you that you have a monthly assessment scheduled for (APPOINTMENT TIME) tomorrow and confirm that you will be coming."* If they say yes, say *"Okay, great, remember that your appointment is at (APPOINTMENT TIME) and that you need to*

bring your pill bottle and will be paid $30 for completing the interview and you will receive an additional $20 for bringing your pill bottle. That means you will be paid up to $50 tomorrow for bringing your pill bottle and completing the interview." Once they respond, then say *"Okay, see you at (APPOINTMENT TIME) tomorrow, have a great day, Bye."*

If they indicate that they are unsure, or do not know what you are talking about, follow the following script:

"Tyesha asked me to call you because you are scheduled to come in for your monthly assessment interview tomorrow for the SteadyRx research study you are participating in."

Reminder calls will be discontinued immediately upon request of the participant, will not exceed three per week, and will be discontinued after one month from the originally scheduled intake interview or appointment time.

Collection Schedule. Scheduling monthly assessments is the responsibility of the outreach coordinator and the student investigators in Kalamazoo. Both are responsible for different aspects of the monthly assessment protocol. Monthly assessments should be scheduled to occur every 30 days over the course of 180 days (for a total of six monthly assessments after random assignment). The first monthly assessment is scheduled for 30 days after the day of random assignment. During the Monthly Assessment Interview, the outreach coordinator should review and update the **Monthly Assessment Checklist-Outreach Coordinator,** and the student investigator should update the Monthly Assessment Checklist-WMU staff. The outreach coordinator should keep a record of all scheduled assessments, which should include their PTID, the scheduled date for all assessments, whether or not the assessment was collected for all planned assessments to date, the date that each collected assessment was actually conducted, the number of days that passed between the planned collection date and the actual collection date, and summary data indicating the overall percentage of planned assessments that have been collected to date and the average days from planned collection to actual collection for all collected assessments to date.

Contacting No-Shows. The student investigators are responsible for contacting participants who do not show up for monthly assessments. Any participant who does not show up for a monthly assessment at their scheduled time should be contacted via phone by student investigators reminded of their appointment, reminded of the $50 they can earn, and rescheduled if necessary. Participants can also be contacted by using the information on the participant contact information sheet that was completed as part of the intake or most recent monthly assessment. Any updates that occur to the contact information should be noted on the most recent contact sheet. If necessary and if time allows, then the outreach coordinator can travel to the participant's residence to conduct the monthly assessment. A

record of all attempts to call no-shows should be kept on a separate log.

Elements of the monthly assessments. The outreach coordinator will be responsible for:

- Attaching the MEMS reader to the assessment computer
- Obtaining CD4 and HIV-1 RNA levels from medical record
- Scheduling the next monthly assessment

Reading a participant's MEMS cap. Upon a participant's arrival, the outreach coordinator will place the MEMS cap on the reader and initiate the reading. Tutorials for reading a MEMS cap will be made available to the outreach coordinator from the student investigators as well as from the help section located within the database. They will obtain CD4 and HIV-1 RNA levels from the medical record or from printed labs given by the participants. The outreach coordinator will inform WMU staff of the participant's arrival and any new lab information.

Conducting Monthly Assessments. The remainder of the monthly assessment will take place over the phone with one of the student investigators located in Kalamazoo. The student investigator is responsible for reading each assessment question aloud to the participant and filling in the answers accordingly. Upon the completion of both the MEMS reading and phone assessments, the participant should be paid $50. If the participant brought in recent CD4 and RNA lab readings and have an undetectable viral load, they should be paid $100, up to twice during the study. All relevant data logs should be updated (see Monthly Assessment Checklist – WMU Staff).

The student investigator is solely responsible for conducting the following assessments:

- Visual Analog Scale for self-reporting ART adherence
- Medical Outcomes Study HIV Health Survey
- Addiction Severity Index-Lite
- Patient Reactions Assessment

In addition to the previous assessments, student investigators are also responsible for conducting the following assessments for participants in the SteadyRx group:

- SteadyRx Satisfaction Questionnaire
- Software Usability Measurement Inventory

MAIN STUDY: STEADYRX PROCEDURES

Overview

The SteadyRx procedures are the primary responsibility of the student investigators in Kalamazoo, who will be overseen by the principal investigator. It is critical that all student investigators are familiar with the SteadyRx Treatment Manual in addition to the policies and procedures specified in this study manual.

Assessing Videos in SteadyRx

The responsibility of assessing the videos submitted by participants to PillWatch will be the student investigators' in Kalamazoo. Videos will be assessed once per day for all participants by one of the student investigators. The student investigators will create a schedule to equally share this task over the course of the entire study. The student investigators will only use the computers whose IP addresses have been approved by the CTPayer system.

The student investigators will then login using the admin account used to create SteadyRx participants' Motiv8 accounts. Then the student investigators will navigate to the videos tab. All videos marked as unattended should be attended to and then either approved or rejected according to the criteria in the PillWatch training module.

Two of the student investigators will assess each video independently. They will be assigned to be the first or the second appraiser. A schedule has been created in order to split this responsibility evenly. The first appraiser will input their decision in the first appraiser's google sheet in the study google drive. They will then notify the second appraiser that they have done so. The second appraiser will then input their decision in the second appraiser's google sheet. This will automatically update the first appraiser's google sheet. The second appraiser will then open the first appraiser's google sheet to check for agreement. If there is agreement, the second appraiser will log in to the Motiv8 systems website and either accept or reject the video submission. If there is not agreement, the second appraiser contacts the first appraiser to deliberate whether or not to accept or reject the video. If they are unable to reach agreement, they ask the third student investigator to independently review the video submission. The team will either accept or reject the video according to the third student investigator's decision.

The first week that the participant is in the study will be considered a training week. During this time, video submissions will be reviewed by the student investigators, who will provide feedback to the participant to insure that they are submitting videos that meet all of the criteria specified in the PillWatch protocol.

Once all videos have either been approved or rejected, the client's account will automatically update with the $2 credit for one day of full medication

adherence. Full medication adherence for the day is defined as one accepted video for the OnePerDay group in the allotted dose time window or two accepted videos for the TwoPerDay group in the allotted dose time windows.

A $6 bonus credit should be given for full medication adherence three days in a row. At the end of every 30-day study period, each participant that has at least 29 days of full medication adherence should be credited $20. The first two times that a participant has an undetectable viral load at their appointment with their primary care physician at CCP, they will receive an incentive bonus of $100. All bonus credits should be manually entered into the client's account information via the client's tab in Motiv8. This includes the intake and monthly assessment payments. The student investigators will specify the reason in addition to the amount in order for the client to have a full record.

Only when the participant is due more than $10 will the student investigators credit their CTPayer card.

SteadyRx Video Submission Feedback

All participants in the SteadyRx group will obtain feedback on their video submissions. The level and detail of feedback is determined by how close the video submissions are to meeting all criteria for acceptance.

Week One Training. Participants will be instructed that the first week of participation is a training week, during which videos may be accepted that do not meet all criteria. Participants will receive feedback the day after their first submission, and every other day after the first submission until the end of training week. Feedback will be given by a student investigator calling the smartphone given to them for the study. Student investigators are to identify specific inadequacies in the submissions (e.g., not opening the pill bottle on screen), explain them to the participant, and check for understanding.

Retraining. If, after feedback has been delivered twice and there has been no improvement, the student investigator will contact the Outreach Coordinator to schedule an appointment for the participant to come in for retraining. At the appointment, the Outreach Coordinator will go through the training materials and instruct the participant on submitting a video that meets all criteria for acceptance. Participants will be compensated $20 for returning to Johns Hopkins for retraining.

Adverse Events & Study Notes

*** Tracking and reporting adverse events is a *** critical responsibility of **all** CLH staff.

The primary policies and procedures on adverse events and study notes are described below. All staff should review the Study Manual to be sure that they are following the procedures appropriately.

Tracking & Reporting Adverse Events. An adverse event is any bad thing that happens to a participant. This could include feeling sick or chronically tired, getting mugged on the streets of Baltimore, or any other bad thing you can imagine, even shark attacks and hang glider accidents.

If any member of the research team learns of an adverse event, it is their responsibility to file an adverse event report and bring the event to the attention of the Outreach coordinator **and** Principal Investigators.

Incarceration. The investigator and outreach coordinators must be immediately notified if a participant becomes jailed or otherwise imprisoned, is enrolled in a halfway house, or enters a constant monitoring procedure managed by any part of a criminal justice system. Under any of these conditions, an Adverse Event Report must be written. The IRB must be notified of any incarcerations at the time of continuing review. In order to avoid a reset, an incarcerated participant must supply a urine sample within two days of release, and then resume a normal testing schedule thereafter. Incarceration will not have any effect on discharge date or any aspect of study procedures except as specified above.

Study Notes. ALL RESEARCH STAFF ARE RESPONSIBLE FOR WRITING STUDY NOTES. Any adverse events should also be entered into the SteadyRx Study Note System. To access this system, open the SteadyRx folder in the BERC folder on Google Drive and click on the Google Sheet with the filename "Study Notes." In addition to writing a study note for any and all adverse events, study notes should be written for ANY deviation from the standard protocol of this study, and for ANY important information not entered elsewhere. If any decision had to be made that was not already specified this Study Manual, then a study note should be made.

The basic rule of creating a study note is this: If you think there is any chance that a study note should be created, then a study note should be created. Specific examples of reasons to write a study note include any study-wide or participant-specific changes in contingencies or policies; any unintentional changes in procedure due to computer or staff error; any alteration in pay not specified in the protocol, or accidental payments or underpayments made to any participant. Once you are done writing the study note, notify the principal investigator.

Data Management

Data management is the responsibility of the student investigators and the outreach coordinator. The key outcome measures are all recorded automatically and electronically. This includes pill bottle openings and SteadyRx use measures. All participants will be trained to the point of skill mastery on all aspects of using the electronic pill bottles and the SteadyRx system. The data for all ACASI assessments will be stored in the Qualtrics database. The data for all MEMS caps readings will be stored within the medAmigo database. The data for all PillWatch

assessments will be stored in the backend of the SteadyRx application. All data will be stored on the SteadyRX server. With respect to the SteadyRX system servers, these Servers have been hardened against attack over the network and an intrusion detection system is in place. Administrative access to servers is by encrypted, private key-secured channels only. Servers are physically secured in a locked cabinet in a locked room in a secure facility accessible by photo ID only. The computer services provided under this project include daily system-wide on-site and encrypted offsite backups with incremental database backups in 15 minute intervals. All data transfer will be encrypted using 256- bit SSL encryption, the standard level of encryption used to secure eCommerce and banking transactions on the Internet. HIV serostatus and viral load measures, and drug use history will be provided by the participants' doctor and transmitted over the phone by the outreach coordinator to the WMU staff. A log of the materials assigned to the participants and a discharge log will also be kept on Google Drive.

All video submission data from those in the SteadyRx group will be recorded on individual google sheets. Submissions (y/n), time of submission, submission acceptances, money earned and when payments are made are included in the Google Sheets. Videos are independently accepted or rejected by two student investigators (see Assessing Videos in SteadyRx).

ALL of these databases will be transcribed to a master Google Sheet excel file on a regular basis. In order to ensure accuracy in transcription of paper based data (e.g., HIV serostatus and viral load), two investigators will transcribe the data separately and it will only be recorded on the master data sheet upon agreement. The responsibility of updating these excel files will be shared between the student investigators and the outreach coordinator. Data will be backed up on one of two external hard drives on a weekly basis. Hard drives used will be alternated and the responsibility will be shared across student investigators.

MAIN STUDY DISCHARGE

Main Study Discharge will occur for all participants irrespective of group assignment upon completion of the 6th Main Study Assessment and should be scheduled for study day 180. Outreach staff are responsible for Main Study Discharge and should follow the Discharge Checklist. The Main Study Discharge interview is identical to the monthly assessment interview aside from collecting the participant's smartphone and MEMS cap. The participant is entitled to a $100 incentive for keeping the same smartphone for the entire study period and returning it during this interview. Alternatively, they can forego the $100 and keep the smartphone. They will be told of this choice during the intake interview and reminded at study discharge. If they choose to keep the phone, immediately remove payment and contact information from the Boost Mobile account. Also change the pin to their participant ID and make a note in the phone number records log.

Analytic plan for SteadyRx study

Descriptive statistics (means and standard deviations or proportions) will be calculated for demographics, baseline participant factors (e.g., quality of life, substance use), treatment history, health literacy, and application ratings and engagement. All analyses will be intent to treat; all participants who are randomized will be included. All analyses will be adjusted for the pre-specified covariates used for stratification.[77] All hypothesis tests will be two-sided, α will be set at 0.05, and p-values for secondary analyses will be corrected to maintain α=0.05. Based on our past research and the automated collection of our primary outcome measure, we expect relatively little missing data and little difference in the rates of missing data across groups. We plan to conduct analyses in which missing samples are assumed to represent the adverse outcome (e.g., missing = drug positive) and in which missing data will be ignored (missing = missing). The "missing positive" method is more conservative and will be considered the primary method.

Primary Outcomes. The effects of the intervention relative to the control group on the dichotomous monthly adherence measure will be analyzed with a longitudinal logistic regression model with treatment group and time as covariates. The group term, representing the between-group difference averaged over time, will be the primary coefficient of interest. Correlation among outcomes over time within individuals will be handled using the method of Generalized Estimating Equations (GEE).[78] The dichotomous viral load variable (<400 HIV-RNA/mL, y/n) will be modeled with an analogous model but with only two follow-up measures.

Secondary and Exploratory Analyses. Continuous measures assessed repeatedly over time (bottle openings, CD4, HIV-1 RNA, and MOS-HIV) will be analyzed using a longitudinal linear regression model, analogous to that used for the primary outcomes. We will control for baseline values in the CD4, viral load, and MOS-HIV models. Measures assessed only at intake will be analyzed via linear or logistic regression as appropriate. Baseline predictors of response to treatment, including positive urine screen for cocaine or opioids, health literacy (TOFHLA), depression (BDI), psychological factors (SCL-90), job and educational history (VEA), and executive function (Wisconsin Card Sorting) will be assessed by fitting regression models with interactions between treatment assignment and each predictor variable, to determine if the effect of treatment on outcome varies as a function of each of these predictors. Similar models, with an interaction between treatment group and drug use, adherence to buprenorphine/ methadone, and attendance to primary care, respectively, (as time-varying covariates) will allow us to determine whether these variables affects response to treatment.

Usage, Acceptability, and Cost. Acceptability and SUMI global scale scores, app uses per day, daily duration of use, and cost of the app and incentives and ICER will be summarized via descriptive statistics (mean, SD, medians, histograms).

Data Analysis to be reported in future publication

Groups were compared on intake variables using Fisher's exact tests for dichotomous variables, chi-square tests for categorical variables with more than two categories, and t-tests for continuous variables. Outcome measures were analyzed using generalized estimating equations (GEE) (Zeger, Liang, & Albert, 1988), including and excluding the stratification variables as covariates. GEE results presented use the covariate model unless otherwise specified. Planned comparison t-tests were used to compare between and within groups on outcome measures at time points 1 and 6. Analyses were intent-to-treat and conducted using SAS version 9.3. Missing data were treated as missing-missing. Analyses were two-tailed with statistical significance set at alpha of .05. Due to the error in the collection of biometric data, analyses for these variables are not included.