Trial number: NCT03086655

Tel-Me-Box:

Testing a New, Real-time Strategies for Monitoring HIV Medication Adherence in India

PROTOCOL

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SECTION 1: OVERVIEW

1.1 Aim 3

To perform a pilot RCT to estimate the effect of real-time adherence feedback delivered wirelessly through the Tel-Me-Box on hair ARV concentrations, device-monitored adherence and viral load suppression in adherence-challenged patients. Among adherence challenged-patients at SJRI without virologic resistance, this pilot will produce a preliminary estimate of the effect of real-time, wireless adherence feedback delivered in a tailored fashion via Tel-Me-Box on hair ARV concentrations, device-monitored adherence and virologic suppression compared to patients (60 in each arm) using Tel-Me-Box without real-time feedback.

1.2 Eligibility

Potential participants must meet the following inclusion criteria to be considered:

- 18 years of age or older
- HIV-positive
- Currently on ART
- Speak one of the local languages
- Able and willing to participate in the study, provide informed consent, contact information, and express a willingness to return for follow-up visits as per the study schedule for the next 12 months.
- Adherence-challenged per self-report, i.e. report of <90% ART adherence or >2 ART treatment interruptions of at least 2 days in the past 3 months.
- Not used or participated in one of our previous studies, using AMD/TMB
- Live within 100 km of study site

1.3 Recruitment, Screening and Enrollment

1.3.1 Enrollment Overview

A total of 120 participants will be enrolled with 60 in the intervention arm and 60 in the control arm from our Bangalore and Mysore sites.

1.3.2 Referral procedures

- Referrals by ART center staff as well as patient self-referrals are encouraged.
- A study team member will station him/herself at the ART center from 9am to 1pm.
- The study team member will meet the Medical Officer or person in charge at the recruitment site and inform him/her about the team's presence at the venue.
- Counsellors at KC General ART Center, Bangalore, and KR Hospital ART Center, Mysore, will introduce the study to potentially eligible participants, hand them a referral card with the study's phone number, and refer them to the assessment team member present at the venue.

- The designated staff member at each site will meet with the referred patients and give a brief summary of the study
- If an individual indicates interest in the project to team member and has time to talk on the same day, the team member will screen the participant to determine eligibility. See 1.3.3. below.
- If the participant indicates lack of time and wants to meet us on another day, their contact information will be recorded by the assessment team member on the "Basic Contact Information" form, and they will be informed by the team member that someone from the study will contact them for screening to determine eligibility.

1.3.3 Screening Procedures:

- The participant may be screened in person at the time of referral at the ART center, or in person during a later scheduled visit.

- The assessment team member will first screen the participants for eligibility and adherence levels using the Screening and Basic Assessment Form (see Appendix).. The form will include a dummy ID and no other personal information will be collected on this form.

- The participant is screened in order to determine eligibility as per section 1.2 above and also to assess adherence
- If the participant is not eligible to participate, the team member will let them know that they are not eligible and will thank them for their time.

- After the screening is complete and if the potential participant is eligible, the assessment staff will explain the study in detail and ask if the person is interested in enrolling. The assessment staff will explain the study schedule, i.e. questionnaire assessments every 3 months for 12 months, plus blood samples will be collected during the BL, 6M and 12M assessments, and hair samples will be collected at BL and 12M. If the person indicates interest and willingness to enroll in the study, consent (section 1.3.4) and enrollment (section 1.3.5) must be completed in-person in a private room and may be completed at the time of referral.

- Name and ART numbers of all persons referred will be entered in a register on a daily basis. The assessment coordinator will check the screening book and sign off. At this point, the assessment team members will share any field notes from the ART Center on a daily basis with the Assessment Coordinator.

- The Assessment coordinators will assign a team member to enter the information from the screening register to the screening database on a daily basis.

1.3.4 Consent Procedures

- At the referral site or in the office, the assessment staff will talk to the eligible potential participant in a private space (i.e. interview room) and carefully go over the Informed Consent Form.
- The assessment staff member will offer to answer any additional questions the potential participant may have.
- The assessment staff will ensure the potential participant that his/her HIV status will not be disclosed to anyone outside the study and will emphasize that no identifying information will be shared with non-study staff.
- If a potential participant is non-literate, the consent is read and explained by a study staff in the presence of a witness who can be a relative or another study staff. Once the potential participant has indicated that he / she has understood and agrees to the consent, he/she will sign the consent form using a thumb print.
- The study staff will also offer a copy of the information sheet to for the participant to keep.

1.3.5 Enrollment Procedures

- If the potential participant agrees to participate in the study, use the TMB device and sign the consent form then s/he is considered enrolled in the study.

- The assessment team members will issue a study card which will have office contact information and dates of the follow up assessments.

- The assessment team member will collect detailed contact information for the tracking form, including phone numbers (primary and secondary contact number), Whatsapp number, street address, information about landmarks, the name and phone number of someone who knows how to reach the participant, and ART number.

- TMB landline number (at Mysore site) and TMB mobile number are the primary means of contacting the study staff by telephone. (Assessment team members are not encouraged to provide any personal mobile numbers to the participants as it may cause problems if any staff leaves the project or is doing an assessment when a participant wants to contact them).

- The enrollment process ends with the administration of the baseline interview (see section 2.3) and randomization of the participant into one of the intervention arms.

1.4 Randomization To Intervention Or Control Arm

At the completion of baseline (see 2.3 for details), participants will be randomized to intervention or control arm. At each site, half of the participants will form the intervention group and the remaining participants will form the control group. The UCSF statistician will use a random number generator (https://www.randomizer.org/) to randomly pick half of the 60 ID numbers from one site and put them into one group. The 30 non-chosen numbers will form a second group, The statistician will then randomly decide which group will be assigned to the control group and which one to the intervention group. The process will be repeated for the other site.

This randomized set of ID numbers will be shared with the intervention team (tech team) at each site and they will assign the next available ID on the list, thereby randomizing the participant, at the time of completion of baseline. The tech team will prepare the TMB device according to the intervention arm allocated and give the participant the TMB device (see section 7.1.4 for details below). The assessment team will be blinded to the allocation.

SECTION 2: ASSESSMENT: BASELINE AND FOLLOW-UP

2.1 Introduction

The assessments are performed by the trained assessment team. Following are the different data collection components:

- Screening and eligibility assessment (Section 1.3.3)
- Questionnaires: Baseline, 3 month, 6 month, 9 month and 12 month follow-up
- Phlebotomy at BL, 6 months and 12 months, hair at BL and 12 months
- Electronic adherence monitoring devices
- Field notes (Maintained by assessment coordinators with details of challenges faced in the field. This can be related to recruitment, assessment, ART centers or any other part of assessment process.)

The table below outlines the assessment schedule for baseline and follow-up assessments:

Assessment	Questionnaire	Phlebotomy	Hair collection
Baseline	**X**	**X**	**X**
3M Follow-up	**X**		
6M Follow-up	**X**	**X**	
9M Follow-up	**X**		
12M Follow-up	**X**	**X**	**X**

The baseline assessment will be conducted on the same day the participant was screened and signs the consent. The baseline assessment will not be considered complete, and the person will not be considered enrolled until s/he has completed the questionnaire, phlebotomy, and hair sample collection. (Interview procedure detailed in section 2.4)
At baseline, all the participants will be provided a card with their assigned ID number. They will be informed to identify themselves according to ID numbers provided to them when they are calling the office phone numbers

Follow up dates are determined based on the baseline interview date. The interview can take place during a window of 15 days before and four weeks after this date, but the aim is to get the interview done as close to the target date as possible. If the interview cannot be completed within four weeks post the target date, the participant is considered lost to follow-up for that wave.

2.2. Pre-Interview Procedures for All Waves

Questionnaire sets will be photocopied, arranged, and stocked in the project offices. Assessment coordinators will assign staffs on a rotational basis for highlighting the interviewer instructions and skips in different colors. The highlighting helps the interviewers pay attention to the skips and instructions while conducting the interviews. Assessment staff who travel away from the project office will take questionnaires, tracking forms, and other required forms documents from the inventory which is managed by the Administration manager.

To ensure that the interview rooms are ready and equipped to conduct interviews without any delays, the Assessment coordinators will assign assessment staff on a rotational basis to have the Interview rooms ready with questionnaires and forms of the scheduled IDs for the particular day.

The project manager will coordinate the pre interview procedures when on site and assessment coordinators are unavailable.

2.3. Baseline Interview Procedures:

The baseline assessment will be conducted on the same day the participant was screened and signs the consent (see enrollment above).

2.3.1 Complete the Tracking Form

Assessment staff will complete a tracking form (see appendix) with contact information for the participant during the baseline assessment. They will review this contact information and complete an updated tracking form if necessary, at every follow-up visit.

- The tracking form should be completed accurately and with every available detail. At least three means of contacting the participant for follow-up need to be obtained including the correct address, contact numbers, persons to contact, and places to contact. The tracking form must include a secondary contact to be considered complete. The primary number has to be verified on the spot using the office phone during the enrollment process. During baseline and other follow up interviews, along with the primary number, the secondary number should be verified on spot as well and noted in the tracking form. Restricting details to a single mobile number on the tracking form to contact participant will be considered incomplete. If the participant is not willing to provide tracking information or provides insufficient tracking information at baseline, the participant will not be enrolled in the study.

- Completed tracking forms will be reviewed by the Assessment Coordinator to ensure necessary information is collected and verify all tracking forms have at least three means of contacting participants and a secondary contact person. The Assessment Coordinator will then submit the tracking form to the data coordinator for cross-checking and filing in the office.

- Tracking forms will be stored securely in the project offices and the contact details will only be made available as needed to the assessment team to maintain confidentiality.

Once the tracking form is complete, the interviewer will administer the questionnaire, per study protocol below, and collect hair samples (in case the lab team is not available) (section 6) and arrange phlebotomy (section 5) according to the assessment schedule. After the baseline questionnaire, the participant also meets with the intervention (tech) team to receive a TMB device (section 7.1.4)

2.3.2. Administration Of Baseline Questionnaire

Following the completion of the tracking form, the assessment staff will administer the questionnaire. Each question in the questionnaire will be available in Kannada and English. Interviewers will ask all applicable questions verbatim and mark an answer for each question. If a respondent declines to answer a question, or does not know what to answer, the interviewers first try to reassure the participant all answers are confidential, there are no right or wrong answers, and if the participant is not sure, to please give a best guess. If participant still refuses or doesn't know, interviewers are to circle the question number and write 'DN' for 'don't know' responses and 'R' for when the participants refuses to answer the question. Interviewers then use the 'Notes' following each instrument to explain why the participant did not answer the question.

1. After completing the assessment interview, the interviewer will review the completed questionnaire in the presence of the participant before concluding the appointment to make sure there are no missing responses. The interviewer will place a checkmark in the margin after each question, to confirm an answer has been marked.
2. The interviewer will schedule a date with the participant for the next follow-up interview based on the follow-up date chart made available to them and filed in their interviewer files. Each interviewer has participant IDs assigned to him/her and follow up of these IDs is the responsibility of that interviewer. The follow up chart is also printed and displayed on the notice board in the office. Each week the Assessment Coordinators send the updated follow up chart to the Data Associate at SJRI. The whiteboard in the SJRI office and Mysore site office are updated on a weekly basis. The follow-up date is calculated based on the baseline interview date. Interviewers are to encourage participants to come for follow-up interviews on the calculated dates (refer to section 3.1 for identifying and scheduling participants for follow-up).
3. The assessment staff will inform the participant that they will be contacted well in advance to remind the participant about the date and time for the next assessment date.
4. Before concluding the appointment, the interviewer will make sure that the participant has been handed over the TMB, and study card, that lab and hair samples have been collected, refreshment (provided after blood draw) and reimbursement have been provided, and thank the participants for their time. At this time the interviewer will also verify the primary and secondary numbers (if possible) by calling from the office number. The interviewer will let the participant know to expect the blood report within 30 days (to account for any delays in the process)
5. Further quality control will be performed on each completed questionnaire prior to the data entry. Any missed items or questionable data entries on the questionnaire will be verified with the assessment staff by the assessment coordinator while the participant is still in the office, to ensure accuracy of the data. In the absence of the assessment coordinator, one of the senior interviewers will be assigned by the coordinator to conduct reviews.

2.3.3. Handing Out The TMB Device

All participants will receive a TMB device during the baseline interview session. The participants assigned to the intervention group will meet with intervention team member (tech team) to go over their pill taking schedule, and to work out a plan for tailored reminders (vibration, beep or LED light). The participants assigned to the control arm will be handed a Tel Me Box without

reminders. All will receive instructions on how the device works. See section 7.1.4 for details about the procedure. This will be handled by tech team staff, as the interviewers are blinded to what intervention arm the participant belongs to.

Interview general notes:

1. Total number of slots available for assessments is dependent upon the availability of assessment staff members and should not exceed 3 assessment interviews per assessment staff per day. E.g. if there are 5 assessment staff with full availability, the total number of slots available for that day is 15.
2. In the event that a potential participant drops in without any indication, or that a participant presents at a time other than the one for which s/he was scheduled, the assessment team will consult with the assessment coordinator or the study project manager (if the assessment coordinator is not available) to determine the most appropriate course of action. If the participant is within the interview window of the wave to be completed, and there is an assessment team member available who does not have 3 scheduled assessments that day, this interviewer will accommodate the participant and complete the assessment. If no assessment team member is available, or the participant is not within the window for a follow-up interview, a team member will try to convince the participant to come at the originally scheduled time, or reschedule for another date.

2.4. Interview Procedures for 3m, 6m, 9m and 12m

Once the participant arrives at the site office, participant meets the tech team member first, to hand over the TMB device. The tech team member addresses any concerns with the device, and completes TMB related task as necessary (troubleshoot, SD card back up). Participant is then directed to the assessment team, where the interviewer will collect the study card. The study card is handed over to the data coordinator / data associate for verification.

Before administering the follow-up questionnaire, the interviewer will review tracking information with the participant to check if there are any changes in address and/or contact numbers since the last interview. If there are any changes in the tracking information a new tracking form will be filled. If there is no new information, the interviewer will make a note on the tracking form that the tracking form was reviewed and there are no changes.

After verifying and updating the tracking form, the interviewer will administer the follow-up interview the same way as outlined for the baseline questionnaire above. The 3 and 9 month follow-up visits, however, do not include blood sample collection. Hair sample collection is not to be included at 3, 6 and 9 month follow-up visits.

SECTION 3: FOLLOW-UP, TRACKING, AND WITHDRAWAL

3.1. Identifying and Scheduling Participants for Follow-Up

1. The Assessment Coordinator, referring to the follow-up tracker, will list participants due for 3M, 6M, 9M and 12M follow-up and share the list with the data associate who will then update the follow-up tracker on the follow-up board at SJRI. These participants will be identified according to the Bangalore and Mysore study sites. This f/u list will be generated every week and will be shared with the assessment team and the data team. The data team will cross check the follow up chart with the interview log and revert back to the assessment coordinator on the same day.
2. These numbers will be then handed over to the assessment team. Assessment coordinator will assign the IDs equally among the team members on a monthly basis, Interviewers will be responsible for assigned IDs until follow up is completed.
3. Over the course of the next 4-6 days, the team will contact each participant individually and schedule the participants for the interview (i.e. for 3M, 6M, 9M and 12M follow-up) using the procedure for follow-up calls. These calls will start 15 days before the actual interview date. The team members will call the participants on the mobile phone numbers documented in the Tracking form (refer section3.2.1).
4. The team should not schedule more than 3 interviews per assessment staff based on the number of staff available in a given day taking into account team members who have applied for leave.
5. As a standard rule, the follow-up assessments should be scheduled as close to the assessment due date as possible. But in cases when the participant is not available for the interview, it may happen till 4 weeks after the due date before the participant is considered lost to f/u for that assessment (3M, 6M, 9M or 12M from the date of baseline assessment).
6. After the follow-up calls are completed, the assessment team will update the interview schedule and hand over the list of scheduled participants to the assessment coordinator for supervision and filing. The assessment coordinator will be in charge of handling the schedule of the participants.

3.2. Procedures for Making Follow-Up Calls

3.2.1. Calling Participants for Follow-Up

1. All calls will be made using the office mobile phone numbers depending on participant's availability as per the best time to call, communicated by the participant in the tracking form.
2. If possible, participants will be contacted on their mobile phones. If mobile numbers are not available, then follow the instructions provided in the tracking form by the participant during the screening, baseline or most recent follow up visit can be used which are stored in the study office cabinets.
3. Interviewers will follow instructions written in the contact sheet on how to identify themselves when contacting the participant or the secondary contact mentioned in the contact sheet. (e.g: call from St John's hospital, KR Hospital, friend, insurance agent…)

4. Team will send a reminder message via whatsapp to those participants who use the app, are willing to be contacted over whatsapp and are not available over phone (not answering calls, number switched off/not reachable).

5. The assessment staff will remind the participants due for 6M interview that during their upcoming visit, phlebotomy will also take place. And remind those participants due for 12M that phlebotomy **and** hair sample collection will take place.

6. The assessment team will remind the participants to bring their Tel-me-boxes, current medicines and medical records (ART booklets) for verifying their medications and ART numbers.. If the participant is unable to make a visit or forgets to bring their TMB when coming for the interview, then a home visit can be scheduled (refer 3.4.2). If the participant forgets to bring the medical records, the interviewer will request the participant to send us a picture of the medical record once they reach home and send it by Whatsapp to the study tablet device.

3.2.2. Timeline for Making Follow-Up And Reminder Calls

1. The interview window is 15 days before due date to 4 weeks after the interview date. After this participant is considered lost to follow up

2. The interviewers will start making follow-up calls 15 days before the participant is due for a follow-up visit. In cases when the participants indicate they may not be available during the next assessment interview date during their current interview, the interviewer will need to let the assessment coordinator know who will then note this in follow up chart. Interviewers will try to contact participant three weeks before the interview due date to check if there have been any changes to participant's plans and ask if they are available for interview.

3. Two more reminder calls will be placed prior to the scheduled assessment i.e. one call three days prior and one call a day prior to the scheduled assessment.

3.2.3. Tracking for Non-Responsive Participants

1. Number of tracking attempts: The tracking attempts will continue on a daily basis until the participant has been seen for their follow-up visit. A minimum of 10 attempted contacts must be logged before the participant can be declared as "lost to follow up" *with regard to that visit* (not in terms of the entire study). These will be recorded in the tracking attempt sheet.

2. Tracking via ART Center ART dates of participants are collected from contact list at the beginning of follow up. Each participant is tracked via ART three days prior to their ART visit date to ensure that the team does not miss a follow-up in case the participant is not in touch, yet visits the ARTC. The assessment coordinators remain in touch with ART Center staff via Whatsapp/phone call. ART number of participants who are required to be tracked will be shared by the interviewer in the Whatsapp group, requesting the assessment team coordinators at each site to track visits. Assessment team coordinators in turn will enquire with ART Center staff if the participant has visited ARTC on a given date. The updates from ARTC will be posted in the Whatsapp group for the interviewers and tech team members.

3. If the participant cannot be reached through phone calls and through the ART Center, a tracking visit to participant's residence or work place can be conducted after 15 days of due date, if the

participant has permitted a tracking visit to either of these places during enrollment. The purpose of the visit is to get in touch with the participant and inform them about the assessment follow-up date, time and venue. The team also should use this visit as opportunity to collect new contact details if they have changed. If the participant is willing and gives permission, the due assessment may be administered at the time of tracking.

4. If the participant is in touch, but has failed to meet the interviewer 15 days after the due date for interview due to a busy schedule, the team will conduct a home visit, if the participant agrees (section 3.3).

5. Interviewers will share their tracking and interview challenges with the team each week during the assessment team meeting held once a week, so that the team can learn from each other and help problem solve difficult situations.

3.2.4. Handling Calls from Participants Calling the Office Mobile Numbers:

When a participant calls the office number, the person answering the phone will respond to the request as appropriate. If the caller needs to be referred to a specific member of the team, then the person answering the phone should obtain the caller's contact information and say that the interviewer will return the call as soon as possible. If a specific interviewer needs to be reached quickly, the person answering the office phone should attempt to contact that interviewer to relay a message or inform the Assessment Coordinator immediately

**Participants need to be given the office phone number only as the primary way to contact the study.

3.3. Home and Workplace Tracking and Assessment Visits:

NOTE: 'Home' in the sections described below can also refer to a mutually agreed upon convenient and safe location that is not actually the person's residence.

3.3.1. Conditions for Home and Workplace Tracking Visits for Participants Out of Contact

When the participant is not reachable over the phone (at least 10 attempts), has not responded to any messages on mobile or tracking through the ART centers, and the participant has failed to meet the interviewer for 15 days after the due date of the interview, the tracking team should plan a tracking visit.

The purpose of the visit is to get in touch with the participant and inform about the assessment follow-up date, time and venue. The team also should use this visit as opportunity to collect new contact details if they have changed. If the participant is willing and gives permission, the due assessment may be administered.

3.3.2. Conditions for Home and Work Place Visits for Assessment and/or to Exchange TMB

A home visit will be done in the following circumstances; (1) to complete a follow- up assessment when a participant reports his or her inability to come for the follow-up assessment interview and/or (2) to exchange a non-functional TMB when the participant is unable to come to the study

site. The assessment team will visit the home or appropriate place indicated in the tracking form at the discretion of the participant to complete the assessment, and/or TMB exchange. The following are examples of when a home visit will occur:

- *Ill health*: Participant is too ill to attend the assessment
- *Personal issues*: Participant reports personal issues that interfere with attending, such as depression, work, family functions, religious functions etc.
- *Financial issues*: Participant reports that he or she doesn't have money to travel to the assessment venue.
- *Transport related*: Participant reports that he or she has no transport available or very limited public transport services available to travel or has no transport available at the time the participant has to travel to the assessment venue.
- *TMB*: The TMB is not sending a signal or the participant has reported technical issues with the TMB and is unable to go to the study site for the exchange for the above reasons. Note: Any TMB-related visit needs to be conducted by a tech team member in order to keep assessment staff blinded to the assigned arm

This is not an exhaustive list. At any point, if the participant reports any reservations of traveling to the study site, the study team member, in consultation with the assessment coordinator, may go ahead and complete the assessment or TMB exchange through a home visit or at any specific place which the participant chooses.

3.3.3. Procedure for Home and Workplace Visits

Before starting with a home or workplace visit, the assessment team (or tech team, in case of a device-related visit) should check the previous tracking form to see if home/work place visits are allowed and if yes, follow any instructions noted there for the team to follow at the time of such a visit.

1. When scheduling the home visit assessment interviews or TMB exchange, the team member should discuss the place of the interview and privacy in the house or the place chosen by the participant.
2. A team of two staff members will do the tracking visits. In the case of tracking a female participant, the team will include at least one female team member.
3. A phlebotomist will also join the assessment staff for assessment and tracking visits for 6M and 12M follow-up.
4. Before going for the visit, the team member should plan the route map to reach the participant place as given in the postal address (that is available in the previous tracking forms).
5. The staff will carry the following required materials for the visit:

- For all visits: Route map, contact details, address, and tracking form
- TMB exchange visits: replacement TMB
- Assessment and tracking visits: Cash for reimbursement, participant reimbursement vouchers, and the assessment questionnaire appropriate for the wave.
- 6M follow-up assessment and tracking visits: phlebotomy supplies(section 6)
- 12M follow-up assessment and tracking visits: phlebotomy (section 6) and hair collection supplies (section 7)

6. The staff will update in the whatsapp group while starting to the destination and once they reach the destination, staff will update on details of tracking done. When the staff reaches the participant's place, they will identify themselves as instructed by the participant in the tracking form (i.e. addressing oneself as an insurance agent, friend, relative, or from St. Johns, KR Hospital, KC General, TMB Study). All home/work place visits will be done with the permission of the participant.
7. Meet the participant and complete the tracking form, follow-up assessment (including phlebotomy for the 6M follow-up and hair sample collection & phlebotomy for the 12M follow-up). If the visit was a tracking visit, and if the participant agrees to be interviewed, then the assessment should be completed. If the TMB needs to be exchanged, then that too needs to be done during this visit by a tech team member.
8. If the staff is unable to meet the participant, then the staff can pass on the information to the family member **only if the family member is aware of the participant's HIV status and study participation.** If not, staff will hand a contact number to the family member and ask them to tell the participant to call back, using whatever script that has been approved by the participant.
9. Once the visit is complete, the assessment staff member will seal the questionnaire, tracking form, and all related documents in an envelope and transport them to the office safely on the same day. Procedures for transporting lab samples will follow the procedures outlined in section 5 and 6 of the protocol. Upon arrival at the project office, staff will hand over the documents to the assessment coordinator for quality checking procedures. Once the documents are verified, they will be handed over to the data coordinator for cross checking and secure storage.
10. A report of the tracking visit will be compiled by the assessment staff member who conducted the tracking visit and inform the assessment coordinator about the tracking visit after completing it.

3.4 Participant Withdrawal, Loss to Follow Up or Death

3.4.1 Participant Withdrawal

When a participant withdraws from the study, the team should follow the following procedures:

1. When a participant expresses that he/she wants to withdraw from the study to an assessment team member, the information is immediately passed on to the Assessment Coordinator for further action.
2. The Assessment coordinator will call the participant and probe and note down the reasons for the withdrawal and the date of the withdrawal. During this conversation the assessment coordinator will also find out from the participant a convenient date and time for handing back the TMB.
3. If the participant mentions that the reason for her / his withdrawal is due to the challenges of using the device, an exit interview will be conducted to record all the challenges the participant faced due to the device.
4. All this information along with withdrawn status is communicated to the Study Managers and copied to the Data Coordinator and Project Engineer via email.
5. The Assessment Coordinator will write a note on the Tracking form as 'withdrawn from the study' and also update in the tracker

3.4.2 Reconsidering Decision to Withdraw

In the event a participant would like to re-consider her/his decision to withdraw from the study, s/he may do so, provided that this is any time before completion of the 12M follow up date.
Please follow the following procedures in the event of such a situation:

1. Check if the participant is still under follow- up (i.e: before the 12M follow up date.)
2. Inform study managers and data coordinator, Project Engineer about the participant's wish to reenter the study.
3. The Assessment coordinator will mark the tracking forms as "rejoined" and remove the status "withdrawn from the study". And also make a change in the tracker.
4. In an email to the Study Managers, Data Coordinator and Project Engineer, the assessment coordinator will note the time period the participant was withdrawn, date of reinstatement, and reasons why he or she reconsidered his or her decision.
5. This information should be forwarded to UCSF for assisting in the data analysis and IRB renewals.

3.4.3. **Death of a Participant**

When a participant's death is reported, please follow the following procedure:

1. Please make sure by referring to tracking form whether participant's HIV status was disclosed to the family or the person who reported the participant's death.

2. If unsure, or if you know that the participant's HIV status was never disclosed to the person who reported the death, do not disclose anything about the status or participant's participation in the program. Empathize with the person who reported about the death.

3. If it is sure that the family of the participant knows about participant's status and participation in the study, empathize with the family of the participant and acknowledge participant's help in the study.

4. The Assessment Coordinator will inform the Onsite PI, Project Manager, data coordinator, project engineer and Project Administrator immediately via email. The assessment coordinator will complete the death report form available in the office. The Assessment Coordinator will make a note of the participant's date of death, cause of death (if available), person who passed on the information and the relationship with the participant. In case of unnatural death, collect information about how the person died (suicide, murder, accident), when the death occurred, and any additional information available.

5. The Assessment Coordinator will mark the tracking forms as "participant expired" and write appropriate note on the time period when the participant's death was reported, date of the actual event and who reported the death of the participant (relationship of that person to the deceased participant).

6. The Assessment Coordinator will gather all the verified information related to the death & send across to the Data Coordinator. The Data Coordinator will verify all the information and send the detailed death report form to UCSF.

7. Simultaneously, the Death Report Form for the IEC will be completed by the Assessment Coordinator and sent to the Project Administrator and copy the Project Manager, Data Coordinator. The Project Administrator will need to inform the St John's IEC about the death by submitting the completed "adverse events form" within 24 hours of receiving information on the death. (This is the only form available to inform the St John's IEC of all kinds of participant deaths, even if they are not necessarily of adverse nature.)

SECTION 4: DATA MANAGEMENT

The following is for St John's, Bangalore site. The same procedures will be followed for the Project office in Bangalore and Project office in Mysore.

4.1 Data Entry Procedures

Prior to the start of data collection, the Data Coordinator designs a database for each data form that needs to be entered so that all data recorded can be entered accurately and in a way that makes manipulation of these data to prepare them for analysis as efficient as possible. This is sent to the Statistician at UCSF for validation.

Before the interviewer starts the entry, he/she will 1) Keep their personal phones in the mobile box in silent or vibration mode 2) Wear headphones throughout the entry. This will help them listen to the "speak cells" feature on excel that helps in cross checking the entries made, hence helping in reducing data errors.

Primary Entry Procedures:

After the completion of the pre-data review, questionnaire ID number will be mentioned on the white board in the column under the initials of designated assessment staff, indicating the questionnaire is ready for primary data entry.

1. The Interviewer who had interviewed the participant has to complete the primary data entry of the interview. The interviewers will enter the data & the necessary notes pertaining to responses collected from the participants in the database as in the questionnaire. For responses marked DN, -888 will be entered and for responses marked R -999 will be entered in the database.
2. In the case of breakdown of the office network connections or the computers the entries may delay but need to resume with immediate effect from the time all the technical issues related to network or computer are resolved.
3. In case the interviewer is not in office (s/he is in the field doing more interviews or on leave) then the primary entry should be done as soon as s/he is back in office. If the interviewer is away for a long time then another interviewer available in office should be doing the primary entries.
4. After primary data entry, the ID number on the office white board will be underlined using a green whiteboard marker by the interviewer (who has entered the questionnaires in the database), indicating the completion of the primary data entry for that specific number.

Secondary Entry Procedures:

1. The secondary entry is done by a different interviewer than the one who did primary entry and once s/he completes the entry the ID number on the white board should be underlined with a red whiteboard marker.
2. The secondary data entry should be completed within two working days of the completion of the primary data entry.
3. Once the ID's are underlined on the whiteboard indicating the completion of the primary and secondary entries the data is available for verification by the Data Coordinator (.)

4.2 Data Entry Verification

Post-interview procedures for Data Coordinator:
On a monthly basis, the Data Coordinator and Data Associate (In Mysore) will do the data verification as follows:

1. Once the primary entry and secondary entry for a set of ID numbers is complete (for a site) the data manager creates a save as copy of the PE file in Excel and deletes the data for all the IDs except the ones that need to be verified.
2. To this file the data from the secondary entry file is pasted
3. The data is sorted by selecting the ID number column heading (Data/Sort A to Z) and the workbook is unshared.
4. Then the data is verified by using the formula below for each ID (by selecting the Primary data for an ID and Secondary data for the same ID) in the first (demo) sheet. Cntrl+G →Alt+S → M → Enter→ Select a color to highlight the column difference
5. The formula is applied after the macro record option (in view) is turned on and once it is completed for the first sheet the record option is stopped. From the second sheet onward, the process is repeated by simply running this macro.
6. Then the errors are identified (the highlighted cells after applying the formula), and an error list is created in a set format and the errors are checked against the questionnaire to check if they occurred in PE or SE. Errors in the SE can be ignored. Errors in the PE need to be corrected. The entry person who did the error corrects the errors and the DM says the errors and monitors their correction.

   The format for the error list is as follows;

Sl.no.	ID	PE	SE	Section	Question number	Errors in PE	Errors in SE	Errors corrected	Errors corrected by
1	B xxxx								

****Once data verification is complete the Data coordinator will sign on the front sheet of the questionnaire and enter the date on which the data was verified**

4.3 Data Upload Procedure and UCSF Review:

1. Once the data verification is completed, the database will be uploaded on every first workday of the month to the UCSF box. (If the UCSF box is not working, the Data Coordinator and UCSF team will decide upon a workable alternative procedure for transfer of the data).
2. The Data Coordinator will send the UCSF team a report via email of any inconsistencies, missing data, etc. that could not be resolved and hence remain in the questionnaire and database.
3. The statistician at UCSF will review data received on monthly basis, within a week after the upload. If the statistician observes any errors or inconsistencies that warrant clarification (other

than the ones mentioned in point above), they will be communicated to the UCSF and to the TMB team via email.
4. The UCSF team will determine how best to address needed clarifications, which will be communicated to the Data Coordinator and the Project Manager.

4.4. Data Storage / Maintaining Confidentiality

Hard copies of study documents will be filed in designated folders in designated storage spaces. Soft copies will be stored & password protected on secure servers and UCSF Box and a given folder will be accessible only to staff whose job responsibilities require access. via SJRI one drive only.

All forms transported across sites must be carried out in sealed files and the team member who carry forms and files need to email their respective coordinators and copy the Data Coordinator, Project Manager.

4.5. Data Backups

1. Data will be backed up daily via the automatic OneDrive saves at both sites.
2. Data will be backed up weekly via manual One Drive saves, and data will also be backed up *at least* bi-weekly via USB port to an external hard drive. The external hard drive will be stored in a secured drawer/cabinet.
3. In addition, data will be uploaded to a password-protected UCSF cloud space (UCSF Box) by the study Data Coordinator on a specified day each week per study protocols.

4.6 Data from TMB (Devices)

The data will be available on a secure website, and downloaded and uploaded by the Project Engineer which will be reviewed monthly by the UCSF statistician.

4.7 Data for Phlebotomy Lab Samples from RLS

SJRI Procedures for lab report download and handover:

- The lab team visits the RLS website every day and downloads lab reports when they arrive.
- An Excel file is maintained in which details of lab report downloads are recorded along with other details as mentioned in the picture below. This is reviewed by the Lab coordinator on a daily basis

Serial number	*Participant IDs*	*Accession number*	*Wave*	*Status of Report download*	*Print out*	*Report handed over to (Interviewer initial)*	*Date of report handover*	*Lab values entry*	*Lab values entry-check*	*Lab report handover reciept received*	*Lab report handover reciept received-Date*

- Another Excel file is maintained in which the lab values are entered for both CD4 and Viral load and other details like in the picture below. These values are reviewed by the Lab Coordinator and Data Associates at each sites on a daily basis

ID No	Wave	Date of phlebotomy	Date of Reporting (CD4 & CD8)	CD4 Count Ref. Range 400-1610	HIV-1 Qntitative Real Time PCR (viral copies/ml)	Date of Reporting (VL)

- Data coordinator then updates the Lab Value Master File with the reviewed values, shares it with Lab Coordinator for final review. Once reviewed, this master file is uploaded to the box on the 1st of every month by Data Coordinator
- The Lab Coordinator will be responsible for the blood and hair lab data

SECTION 5: PHLEBOTOMY AND LAB PROCEDURES

5.1 Overview

Phlebotomy for the longitudinal cohort is performed as part of the assessment procedures at baseline, 6-month and12-month follow-up assessments. The tests conducted are: viral load, CD4, CD3 and CD8. Blood will be collected in 6.0ml vacutainers (Reliance).

Phlebotomy procedures at Baseline, 6M, 12M will take place on the same day as the scheduled interview.

Participants have the right to refuse to provide blood samples at assessment visits. If a participant refuses to have his or her blood drawn, then the project staff will not draw the blood, but will complete all parts of the interview to which the participant agrees.

5.2 Procedures

a. Whenever phlebotomy is performed, the assessment team member will hand over the tracking form to the lab technicians.
b. Using the information on the tracking form, the lab tech will fill out a Test Requisition Form (TRF). The TRF, along with the carbon copies provided by 'M/S Reliance Care' are available with the project lab personnel. The TRF will include the following information:
    - Participant Number and wave number
    - Date & time
    - Gender of the participant
    - Age
    - Type of test (Please check the column against specific tests)
    - Accession number (number already on the tube)
    - Name and Signature of the Authorizing personnel (In this case the lab tech)
c. The lab tech will enter the above information using a **black ink ball pen**
d. The Participant ID number should be written on the tubes manually.
e. Please ensure to note down the wave number in the brackets i.e. (BL) for baseline, (6M) for 6 Month assessment, and (12M) for 12 Month assessment.
f. Please write the participant ID and the wave number on the orange color and pink color labels. Make sure to paste the barcode label on the vacutainer as shown in picture below:

g. The project lab personnel will keep the original Test Requisition Form along with the Sample to be picked up by the reliance lab personnel either from the St Johns Office or other project sites. The project lab personnel will file the carbon copy in the project office appropriately.

h. The assessment team will inform the participants well in advance that the cut-off time for collecting samples is 3:30pm from Monday to Friday and 12pm on Saturdays and that they need to be at the site before these times at all assessments that involve drawing blood samples.
i. Please write all necessary details within the specified boxes.

5.2.1 Stock Requirements

The following items need to be in stock:

- Latex gloves
- Tourniquets
- 70% isopropyl alcohol (Spirit)
- Plastic vacutainers-K2 EDTA 6ml. blood collection tubes-with access numbers and labels (Pink or Orange color).
- TRF forms
- Disposable sterile Vacutainer needles
- Coolant gel packs-200gms.-minimum 4 to be kept in freezer compartment of refrigerator
- 5ML syringes (for patients with difficulty to draw sample due to thin veins)
- Butterfly needles (for patients with difficulty to draw sample due to thin veins)
- Cotton
- Bandages
- Sample carrying bags
- Thermocol racks for keeping the tubes upright after collecting samples.

5.2.2 Procedures for Blood Collection

****Universal precautions are to be followed throughout the procedure****

SELECTING VENIPUNCTURE SITE:

i. Place all equipment within easy reach.
ii. Identify patients by name and check particulars on request form.
iii. Please verify all particulars entered on the TRF and Vacutainer by referring to the tracking form prior to collection of blood.
iv. Allow the patient to be comfortably seated on a chair.
v. Explain procedure to allay apprehension.
vi. Choose the median cubital, aphasic or basilic veins in the antecubital fossa.

TOURNIQUET APPLICATION:

i. Apply tourniquet moderately tightly 3 – 4 inches above the venipuncture site.

CLEANING THE VENIPUNCTURE SITE:

i. Use 70% Isopropyl alcohol (Spirit).
ii. Clean the site using a circular motion, inside outward starting at the center of the site.
iii. Allow the site to dry for 30 – 60 seconds.

STEPS IN BLOOD COLLECTION USING VACUTAINER SYSTEM:

i. Hold the colored section of the needle shield in one hand, twist and remove the white section with the other hand.
ii. Screw needle into holder, leave color shield on the needle.
iii. Remove the colored cover of the needle.
iv. Ask the patient to firmly fold the fingers.
v. Perform Venipuncture with aim in downward direction.
vi. Introduce the tube into the holder placing the forefinger and middle finger on the flange of holder and thumb on the bottom of the tube, puncturing the diaphragm of the stopper.
vii. Release the tourniquet as soon as blood begins to flow into the tube and ask the patient to relax the fingers to normal position.
viii. Avoid under/over filling the collection tube (i.e. with 4ml collection tube, do not collect more/less than 4 ml of blood).
ix. Once blood flow ceases, apply soft pressure with the thumb against the flange of the holder to disengage the stopper from the needle and remove the tube from the holder.
x. Gently invert the tube 8 – 10 times to ensure proper mixing of blood and anticoagulant.
xi. Remove needle, place dry cotton on the punctured site, ask the patient to fold the arm till bleeding stops.
xii. Inspect the site to ensure the bandage (circular one) to the pricked site, before allowing the subject to leave.

5.2.3 Procedures for Contacting Reliance to Transport the Samples

The RLS contact person should be informed one day in advance about the samples. On the day of the sample collection, the lab team will coordinate with the RLS person to collect the samples.

Collected samples will be transported by the RLS person as per protocol (*see below*).

- Transportation of the samples is done by the Reliance lab from all the sites as per the protocol. The project lab person will ensure following aspects before the samples are transported:
- Check and verify the TRF form with the corresponding vacutainer for access number, ID number and wave number.
- If any discrepancies found please rectify before the samples are transported.
- Keep the samples and the Original copy of the TRF ready for transportation.
- Give a reminder call to the reliance personnel who are assigned to transport the sample two hours prior to the cut off time (2 PM) to pick the samples.
- If the samples are collected before the cut off time please inform the Reliance staff as soon as the last sample is collected.
- Once the reliance personnel arrives please hand the samples one by one along with the corresponding TRF forms who will then place the samples in the Thermal lab bag with ice packs. Request the sample pick up personnel to sign on the sample handover book.
- When the lab techs are not available due to absence from work or due to field work, all these procedures will be carried out by the Assessment coordinator.
- In cases of emergencies, the lab techs in the ART Center will conduct the blood draw and hair sample either in the site office or at the ART center and will be paid per sample onspot. If the blood draw and hair sample is conducted at the ART Center, the interviewers will carry a kit with all the necessary supplies to carry out a blood and hair sample by the lab techs at the ART center. Once the samples are collected, the interviewers will bring back the samples in a sealed box meant for transporting samples issued by Reliance.
- Sometimes the participants are scheduled for a blood draw at the ART centers and bring it up during the scheduling calls that they would like their blood drawn in the ART Center itself. In such situations, the Assessment coordinators will notify the lab team. In such case the procedure outlined in the previous point will be carried out.

5.2.4 Procedure to Maintain Proper Temperature

While transporting the samples precaution must be taken to avoid direct sunlight on the samples & keep them in a cool place during all months

If outside temperature is expected to be below 30 degrees Celsius:
The whole blood is kept in refrigerator, in 2-8 degrees celsius until such time that the Reliance personnel comes to pick it up either from the site, St John's office, or a venue that is mutually decided upon by a team member and the Reliance personnel.

If outside temperature is expected to be 30 degrees Celsius or above

- The coolant gel packs need to be kept frozen in a freezer until phlebotomy when the packs are moved to an insulated lab bag.
- Then once the phlebotomy is done, the sample is kept in the insulated lab bag until it is picked up by the Reliance personnel.

5.2.5 Procedure for Redraw of Samples

- When a blood sample is rejected the ID number and the wave is informed to the assessment coordinator as well as the phlebotomist to schedule the participant for the re-draw.
- To indicate that there has been a blood redraw the participant ID number is added with a hyphen and the letter A. E.g. the sample for ID B4000 was rejected and so after the redraw the new ID given to this sample would be B4000-A. If the redrawn sample also gets rejected then the new ID for the next redraw would be B4000-B.

5.2.6 Procedures for Issuance of Phlebotomy Lab Reports

1. The lab reports of the participants are handed over to the medical officer of the ART Centers in KCG and KRH on a weekly basis. The assessment coordinators will coordinate with the lab team to ensure that this procedure is carried out.
2. All reports will be sealed in an envelope and handed over the participants.
3. If a participant wants to be a part of the study, but chooses not to have their lab results sent to their doctors, their blood will be drawn and sent to Reliance per normal protocol. However, the results will go only into the study database.

Instructions to the assessment staff:

- Avoid talking to the participants individually or in group about their lab values.
- Encourage participants to consult with their physicians if they have questions about the results
- Any participant who wants to get clarification on the errors (name, ART numbers etc.), should be encouraged to call the designated assessment staff member who is handling the reports. Please assist the participant by providing them with this staff member's phone number or calling him/her from the office mobile.

SECTION 6: HAIR COLLECTION AND LAB PROCEDURES

6.1 Hair Collection and Storage Tasks

All Interviewers are trained in hair collection but the lab team has primary responsibility for the task. The lab team packs the hair in foil, labels them and stores them (separately for each data collection wave) in a container in locked cabinets. The Lab Coordinator oversees the process in both sites and conducts QC once in two weeks to ensure all hair samples are collected and stored as per protocol.

The Lab Coordinator communicates with the Assessment Coordinator on challenges that come up with reference to hair collection and proposes solutions to be executed by the team members. After approval by the Project Manager, the Assessment Coordinators addresses these challenges along with solutions in the weekly team meeting.

6.2 Hair Collection Quality Control Procedures

All collected hair samples will be checked primarily by the Lab Coordinator and the Project Manager on site prior to transportation as follows:

1. One assessment staff member will be present when taping and labelling the hair. The assessment team member who collected the sample will sign off once labelled as a way to keep track.
2. After collection, and before the end of the day, the Assessment Coordinator / Data Coordinator will check if hair has been labelled according to protocol. The hair should be clearly labelled on the distal end and hair should not be shortened from the original length.
3. If hair is not cut and/or labelled correctly, the assessment team member responsible for the collected sample needs to correct the error immediately.
4. Hair taped on the proximal end or in the middle of the sample cannot be analyzed, and hair labelled this way will need to be recollected from that participant as soon as possible.

6.3 Data

The lab team enters information with reference to hair data into the lab log stored on the one drive on a daily basis. The data is overseen by the Data Coordinator.

A master database for lab values will be maintained by Data team with access permission to Data Coordinator, Lab Coordinator, Assistant Project Manager and Project Manager. The values entered in the lab log will be verified by data team and verified values will be copy pasted to the lab master database.

6.4 Hair Sampling: Schedule, Supplies, and Storage

A small sample of hair will be collected at baseline and 12 month follow-up visits

6.4.1 Materials:

- small pair of scissors
- alcohol pad
- aluminum foil (cut into ~4 inches x 4 inches and folded into quarters)
- sealable plastic bag (eg, Ziplock, 3x6”), e.g. Fisher#19240101
- thin adhesive label (for taping hair to tin foil and marking directionality)
- Study label for outside of foil packet
- hair clip (optional)

Hair should be stored at room temperature in a dark location until shipment. Hair is not a biohazardous material and can be handled with bare hands and stored accordingly.

Before sending the samples to UCSF HAL the following process will be carried out by the lab team:

- The ID numbers for which the hair samples are due to be sent to the UCSF HAL will be identified and printed out
- The hair samples will be segregated as per waves for each site and will be packed and sealed in separate envelopes as per the list.
- All the small envelopes will be transferred to a larger envelope.
- The Lab coordinator will write the number of envelopes inside the larger envelopes and sign off.
- The Project Manager cross checks all the details including the packing and after this the envelope is sealed off and handed over to the UCSF team member visiting the India office.

6.4.2 HAIR COLLECTION PROCEDURE

(Detailed Instruction Manual With Pictures Is Available In Appendix)

Small samples of scalp hair are collected in the manner described:

Materials required: Scissors, piece of tin foil, patient labels (2), ziplock bag, alcohol swabs, and desiccant pellet

Suggest making these “hair kits” ahead of time

Step 1: Clean the blades of a pair of scissors with an alcohol pad and allow blades to completely dry

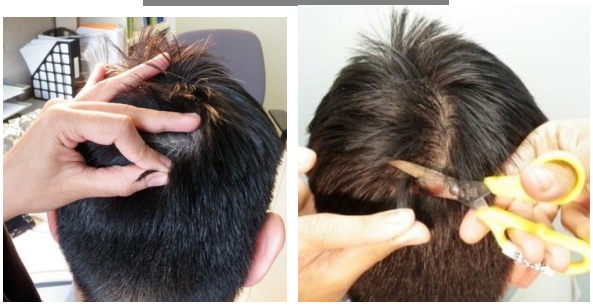
Clean off blades of scissors between patients

Step 2: Lift up the top layer of hair from the occipital region of the scalp. Isolate a small thatch of hair (~100 fibers of hair at the baseline visit; 50 strands of hair for subsequent visits) from *underneath* this top layer of hair from the occipital region. (A hair clip can be used to keep the top layer of hair out of the way).

Can use hair clip to keep top layer of hair away if easier

Step 3: Cut the small hair sample as close to the scalp as possible

STRAIGHT HAIR



CURLY HAIR

SHORT HAIR

Can let hair fall directly into piece of tin foil when very short/cropped (no need to label end since too short)

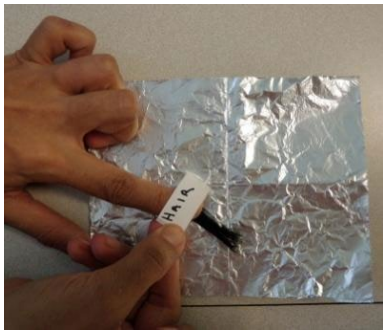
BRAIDED HAIR

Cut hair thatch from in-between braids or dread locks

Step 4: Keep your fingers on the part of the hair that was FURTHEST away from the scalp and put the hair sample down on an unfolded piece of tin foil

Step 5: Put a thin label over the end of the hair sample that was FURTHEST away from the scalp

If hair very short just let it fall into the piece of tin foil and no need to label the distal end



Step 6: Refold the foil over to completely enclose the hair and place a study ID label on the folded piece of foil

Step 7: Place the folded piece of foil inside the plastic (e.g. Ziplock®) bag (desiccant pellet in the bag is optional) and seal the bag;

Good collection: Distal end (side farthest from scalp) labeled

Bad collection: Distal end could have been labeled (long enough) but not

Okay not to label because too short

Hair samples should be kept at room temperature and in a dark place prior to shipment. Hair samples are collected by Principal Investigator (Dr Maria Ekstrand) during her visit to the study site and brought to UCSF.

Once the hair samples have been received by the UCSF project manager, the UCSF statistician prepares a list with the regimens of the corresponding participants. An appointment is made for a representative from the Hair Analysis Lab to come pick up the hair samples in person. The list with the regimens is emailed to this person.

<u>Laboratory assays for hair concentrations conducted at UCSF:</u>
The hair samples are delivered to the UCSF Hair Analytical Laboratory where nevirapine (NVP) and Efavirenz (EVF) is extracted and analyzed with liquid chromatography/tandem mass spectrometry (LC/MS/MS) using validated methods approved by the Division of AIDS' Clinical Pharmacology and Quality Assurance Program.

- The proximal section of the thatch of hair (generally about 1-2cm, depending on duration of exposure to be assessed) is cut down and chopped to 1-2 mm length segments and 5 mg is weighed and processed.
- NVP and EFV are extracted with (methanol : trifluoacetic acid (9:1) for NVP) solution and internal standard in a 37ºC shaking water bath overnight (>12 hours), followed by extraction with 3.00mL methyl *t ert*-butyl ether/ethyl acetate (1:1) under weak alkaline conditions and then analyzed by LC/MS/MS.
- The LC/MS/MS procedure separates NVP And EFV by utilizing a Micromass Quattro LC system equipped with a Hypersil BDS C18 column (4.6 x 100 mm, 5 µm particle size), a mobile phase system consisting of acetonitrile : water : acetic acid (50 : 50 : 0.15) (*v:v:v*) with 4 mM ammonium acetate for NVP and acetonitrile/water (65:35) (v:v) for EFV and mass spectrometric detection with positive ionization for NVP and negative ionization for EFV by ESI (Electrospray Ionization) and mass scanning by MRM (Multiple Reaction Monitoring) analysis.
- Data processing will be performed using Analyst data acquisition software.
- The relative error (%) and precision (coefficients of variation) for spiked quality control hair samples at low, medium and high concentrations are all <15%.
- A detailed methods paper on using LC/MS/MS analysis for EFV on is available at DOI: 10.1002/rcm.3750

SECTION 7:: TEL-ME-BOX PROCEDURES

7.1 TMB Procedures

7.1.1 **Web Login**

The web interface of the device is hosted on a secure webpage. The web interface has two logins: Admin Login and Tech Login.

Admin Login: The Admin Login can be accessed by the UCSF team, onsite Engineer at SJRI and the Data Coordinator using a username and password. The signal provides information on the date and the time the box was opened to remove pills.

Tech Login: The Tech Login can be accessed by the designated team members on the TMB Tech Team including the onsite Engineer. This login will have (de-identified) details on User ID, date, time, phone number of the sim card, IMEI number, last live message received and the status of the box.

7.1.2. Device Preparation:

The Project Engineer will make sure that a minimum of 20 devices – 10 devices with reminder features and 10 without - are with each of the site offices every Monday. The devices will be made to come online during the assembling process and then the battery is disconnected to make sure there is no drainage of battery power.

7.1.3 Device Assembly:

Before handing out the device to participant at the baseline interview, the tech team members will check if the device's electronic circuit is assembled as per procedure by the manufacturer of the circuit board so that the device does not run into issues like a loose electronic circuit, loose charge point etc. Whenever situation permits, the tech coordinator will verify that the device condition is checked and assembled as per procedure before it is handed over to the participant for the first time.

7.1.4 Assigning the Box to the Participant (Baseline)

1. Intervention arm: Once participant is enrolled and assigned to intervention arm, details of pill intake time is collected by tech team member present at the ART center and this is communicated to the tech team coordinator via whatsapp group. Tech coordinator connects the device to the laptop and Tech engineer gains access to the system via TeamViewer (remote desktop viewer) to code the pill intake timing for the device. The device is then tested remotely by tech engineer to make sure the coding for pill intake time is working. The coded device is handed over to the participant by the tech team member at the site office.
2. Control arm: TMB device with no reminders will be handed over to the participant by the tech team member.
3. During the assignment of the device, a small document which describes the usage of the box is handed over to the participant. The participant is free not to carry this document in case they are not comfortable carrying it home. The participant will then be given instructions on how to use the TMB. The tech team (intervention team) staff will need to clarify all queries the participant may have about the TMB. The queries asked here need to be documented and shared with the assessment coordinator and tech coordinator on a daily basis which will be in turn discussed during the upcoming assessment and tech meetings.
4. Once the tech team has assigned the devices to enrolled participants, they will add the device to the website.
5. In the absence of the tech team member, the Project Engineer will carry out this task remotely. A team member will update the device assignment in the whatsapp group before logging out from the site. Tech Team coordinators will add the ID in segregation and keep it updated on a daily basis.
6. The log can be accessed by the Tech team members, Project engineer and study managers. Device related information like sim card, type of network and imei number of device is saved in an excel format and is maintained by the Project Engineer which uploaded to the UCSF box on a weekly basis.

7.1.5 TMB Monitoring

1. **Listing of offline and low battery IDs:** Beginning of the day, the Project Engineer will update the list of offline (More than 24 hours), low battery (Less than 40%) and low battery/offline devices in a WhatsApp group. Once the IDs are listed, the tech team members will make troubleshooting calls for participants who prefer to be called during daytime (office hours). If participants prefer to be contacted over Whatsapp, a whatsapp message is sent from the Study Tablet Device to the participants. All IDs requiring troubleshooting are also listed in the daily logs by the Project Engineer for further recording of the information on the troubleshoot by the team members
2. **Assignment of IDs to Tech Team Members:** At the end of each day, the tech team coordinators will assign IDs to the tech team members to balance the number of IDs each tech team member is responsible for. In the absence of the Tech Team Coordinators, the Project Engineer will carry out the assignment of IDs to the team members.

7.1.6. TMB Box Procedures for Follow-Up Visits

During follow-up visits, the participant meets the tech team member who checks the device for technical issues. The tech team member who has been assigned to collect SD card data and troubleshoot the device for that day completes the task as required (details of troubleshoot and SD card back up in section 7.2)

7.2. TROUBLESHOOTING PARTICIPANTS' TMB BOX PROBLEMS

TMB devices will require troubleshooting in the following circumstances:

1. The device is offline, not sending live messages, or sends messages as 00:00:00 for more than 24 hours (consult offline device flowchart in appendix)
2. The battery level is at or below 35% (consult low battery flowchart in appendix). A detailed supplementary troubleshooting guide is also available and can be found in the box folder and on the office server.

7.2.1 Troubleshooting Calls

1. Calls to the offline / low battery IDs are listed in the Whatsapp group before 4pm by the Tech Team Members and are assigned to two tech team members as per a schedule created by the Tech Data Associate at beginning of each month. Female team members will be assigned to call female participants and male team members will call male participants. The callers are provided with a "Contact List" which is de-identified. Updated contact lists are provided by the data team to the staff calling in a particular week
2. The assigned callers will make calls as listed as the "Best time to call" by the participants. A contact list is prepared by the data team on a weekly basis and is issued to the team members who are scheduled to be making calling that week. All the identifiers are removed from the contact list and is carried in a sealed folder by the team members. Each week, these forms are collected back, discarded and an updated form is issued
3. Depending on the device issue notified by tech members, the callers will use the offline / low battery flow chart (refer appendix) and

    a. request the participants to either restart the device
    b. open the flap of the device in a network area
    c. charge the device (see troubleshooting flowchart in the appendix)
    d. schedule for a troubleshoot visit.

    Once the calls are made the details are updated in a Whatsapp group.

4. The tech data associate will check the TMB website and compare the IDs that are due for calls for the day and list out the IDs of the devices which are online automatically or which have been charged without our effort. This will help in reducing the number of calls for the day both for the participants and team members. This list will be put up by the tech data associate between 7 and 7:30pm.

Calls will be attempted for primary number, if the primary number does not respond, the secondary number will be attempted. For offline number which are less than 48 hours based on the situation, i.e., if the secondary contacts do not know the status, are far relatives, friends, do not stay with the participants, calls to such numbers can be assigned after 48 hours. Only one call per number will be placed per day. Continued non-responsiveness will result in an unscheduled home visit as per the troubleshoot flowchart (if the team has permission).

7.2.2 Troubleshooting Visits

The logs will have detailed information on attempts made to troubleshoot device issues. All tech team members will follow the troubleshooting flow chart for offline devices and devices with low battery

- **Action Plans:**
  a. Offline devices - If the device is offline for more than 48 hours and is still offline for next day, the tech team member who is in charge for respective ID will plan for a troubleshooting visit as per participant's convenience. The troubleshooting visit needs to be completed within the next 24 hours.
  b. Low battery devices – If the device's battery status falls below 20% (or depending on the situation, like low network strength) the tech team will plan for a troubleshooting visit within the next 12 hours.

- **Planning visit**

  a. Schedule coordination with Assessment Coordinator.
  For devices offline more than 48 hours despite problem-solving with the participant over the phone, Tech Team member contacts Tech Team Coordinator for further action. For male participants, the tech team coordinator overseeing setting up of the visit. However, for female participants, the tech team coordinator contacts the Assessment Coordinator for help coordinating the visit, since it requires the presence of a female interviewer.
  b. Scheduled visit: The tech team member will call the participant to schedule a troubleshooting visit.
  c. Planning unscheduled visit: If the team is not able to establish contact with the participant over the phone via primary number of secondary number and if the participant has given permission for tracking visit, a tracking visit will be conducted.
  As an alternative plan, the tech team members will give the ID to the Assessment Coordinator to find out the participant's next ART Visit date and track accordingly.
  d. The troubleshooting plan will then be updated in the daily log.

- **Conducting troubleshooting visit:**
  a. For a scheduled visit, the tech team members will call and confirm before meeting the participant.
  b. Checklist of items to be carried for Troubleshooting visit
    - Tool kit
    - Diagnostic Box
    - Tablet

- OTG (On the Go device which is used to read the SD card data and copy onto the tablet devices)
- Fevibond
- Extra 2 new device,
- SIM(Vodafone/Idea)
- Power Bank (only carried during troubleshooting visits)
- Troubleshoot register book
- 3M tape

c. Troubleshooting the device- The following procedure will be carried out by the Tech Team member during the troubleshoot of the device.
    - Check the device if it is on ON/OFF mode.
    - Restart the device (3 times)
    - Check if the device is damaged
        - Check the device for outside damages like, locking system, sensor, reed switch holder, battery etc.,
        - If any part of the device is damaged, change the box (during this process team member should call the Project Engineer and update the status.
        - The damaged box will be returned to the Project Engineer the same day.
    - Check for network issues (offline devices only)
        - Shift participant device SIM into diagnostic box to check the network status. If the device is still offline then change the network.
        - If the device is still showing offline, change the box (during this process team member should call the Project Engineer and update the status.
        - If the device is still showing offline mode team will plan to collect SD Card data once in a month and follow up calls should be made once a week to restart the device. This message will be communicated to the participant.
    - Changing the battery (low battery devices only)
        - If the battery in the device has been drained out to non-charging, change the battery (during this process team member should call the Project Engineer and update the status.
        - The old battery has to be returned to the Project Engineer the same day. The Project Engineer will charge the battery to 100% in the office and re-use the same for another device.
d. Before concluding the troubleshooting visit, SD Card data will be collected, and the team member will note down the details of the visit in the trouble shooting field log book and get the participant to sign as acknowledgment.
e. Once the troubleshooting visit is completed, the tech team member will communicate on the Whatsapp group with a short report and a screen shot of the website's dashboard once it is online/charged. The tech team member will leave the site only after the device is online on the dashboard and/or charged and approved by the Project Engineer.
f. After a troubleshoot at office or on site, the tech team member who conducted the troubleshoot will update the troubleshoot log with all the details of the troubleshoot conducted. This document has to be updated on the same day. The document is reviewed by the Tech coordinator and data associate on a daily basis.

g. Possession of study devices : B the End of the day The Tech team members will handover the devices, tablet and power bank to the Data team.
h. The troubleshooting report needs to be updated in the troubleshoot log by end of day or next day by 10.00.am

7.3 Device Return for Withdrawn Participants

If a participant withdraws from the study and needs to return the device, the tech team member will collect the device and check if all the components are intact, especially SD card and sim card. If the device components are found to be damaged, record the damage in log maintained by tech engineer. Once the device is collected, the tech team member will hand over the device to the tech team coordinator. If the participant withdraws from the study but has not returned the device yet the ID will be added to the device tracking excel sheet on the daily logs. The tech team members will contact the withdrawn participant regularly and retrieve the device from the participant as soon as possible.

APPENDIX A: TMB TRACKING FORM

TMB Tracking form

Screener's Initials:		Interviewer / Counselor Initials:	
Participant Number:		Interview Date:	
Hospital No		ART No	
Name (Full):		Spouse's Name	
Father's Name:		Mother's Name	
Age:		Gender:	

Unique Identifier: *(To identify participants when there are more than one participant*

bearing same name) If the participant doesn't have an initial please assign an initial (First letter of participant's child's name, spouse's name etc. For eg: If the participants spouse's name starts with 'K' assign the same letter after the participant's name. Please let the participants know when you do this and tell him or her why you have to do this)

Initials	Initials taken from the name of								
	Spouse	Son	Daughter	Brother	Sister	Father	Mother	Friend	Others
									Specify _____

Contact numbers

Land		Mobile 1:	

line:			
Mobile 2:		Office:	
Address: _____			
Contact person: (if any)	Name:	Relationship:	
		Contact No:	

Special identification /instructions:

House name:		Trade:	
Caste/Sub caste:		Ancestral name:	
Father's Name:		Others:	

Permissions **(Check box if permission granted)**			Instructions
Home visit	☐ Y	☐ N	
Work place visit	☐ Y	☐ N	
Tracking visit	☐ Y	☐ N	

Route map and Land marks: [Mandatory] *Please give reasons if participant doesn't want to provide: Route map includes transport route to be taken from a specified start point, route no (if any), destination, route from alighting point to the participant residence, work place and the land marks near the participants house such as coffee shop, temples, schools etc.*