

The Wisebag Pilot Study: Feasibility, Acceptability and Performance of an Electronic Event-based Monitoring System (Wisebag)

This document describes study-specific procedures for **The Wisebag Pilot Study: Feasibility, Acceptability and Performance of an Electronic Event-based Monitoring System (Wisebag)**. The Wisebag Pilot will be conducted at the CAPRISA eThekweni study site in Durban, South Africa. The CAPRISA eThekweni site must maintain this section of the Study-Specific Procedures (SSP) Manual in its entirety. All other VOICE sites not participating in this Pilot are not required to maintain this section of the manual.

1 Introduction

This section specifies the sources of procedural information available to Wisebag Pilot Study staff, the responsibilities of Wisebag Pilot Study Investigators of Record (IoRs), and the process by which the study site is approved to begin implementation of the Wisebag Pilot Study.

1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the Wisebag Pilot Study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please alert the Wisebag Pilot Study Management Team (described below) of any such inconsistencies. Study implementation questions that are not answered by the protocol or this manual should be directed to the Wisebag Pilot Study Management Team. This group consists of representatives of the MTN Coordinating and Operations Center (CORE-PITT and CORE-FHI), RTI International, and the Protocol Chair. This group can be reached using the following email address:

mtnwbmgmt@mtnstopshiv.org

1.2 Investigator Responsibilities

The Wisebag Pilot Study must be conducted in accordance with the United States Code of Federal Regulations and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice. Copies of these regulations and guidelines are referenced in the MTN Manual of Operations (MOP) which can be accessed at:

<http://www.mtnstopshiv.org/node/187>

The DAIDS policies on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* and *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies can be accessed at:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch>

The Wisebag Pilot Study also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all such regulations, policies, and guidelines should be maintained in on-site essential document files. Please refer to Section 3.1 of this manual for more details on essential document files.

The IoR at the site must sign both a protocol signature page and an Investigator Agreement to formally indicate his/her agreement to conduct the Wisebag Pilot Study in accordance with the study protocol and all applicable regulations, policies, and guidelines. This form can be found on page 11 of the Wisebag Pilot Study protocol. The obligations and responsibilities assumed by the IoR when signing the Investigator Agreement are listed on the form. IoRs may delegate their obligations and responsibilities for conducting the Wisebag Pilot Study to other study staff members; however, delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation.

Consistent with the regulations, guidelines, and policies cited above, the IoR at the site must obtain and maintain Institutional Review Board and/or Ethics Committee (IRB/EC) approval of the Wisebag Pilot Study throughout the period of study implementation. See Section 8.4 of the MTN Manual of Operations (MOP) for detailed information on IRB/EC submission, review, approval, and documentation requirements. The site is encouraged to request an acknowledgement of receipt for all documents submitted to their IRBs/ECs and to request that IRBs/ECs note the effective and expiry dates of all approvals. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files.

1.3 Study Activation Process

Prior to undertaking any study procedures, the site must obtain approval to conduct the Wisebag Pilot Study from all responsible regulatory authorities and IRBs/ECs. The site also must complete protocol registration procedures with the DAIDS Regulatory Support Center Protocol Registration Office and study activation procedures with DAIDS and the MTN CORE (FHI). Detailed information on the requirements of these pre-implementation steps can be found in Section 10 of the MTN MOP. The MTN CORE (FHI) will issue a Site-Specific Study Activation Notice when all study activation requirements have been met. No protocol-specified study procedures may be undertaken prior to issuance of the Site-Specific Study Activation Notice.

2 Protocol

A complete reference copy of the Wisebag Pilot Study protocol Version 1.0, dated April 15, 2011, is provided in Appendix 1. The site is required to maintain current and all archived versions of this manual as well as the protocol, including any clarification memos, modifications or protocol amendments, in the essential files.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9.2 of the MTN MOP.

3 Documentation Requirements

Study staff is responsible for proper collection, management, storage, quality control, and quality assurance of all study-related documentation, related to the MTN Wisebag Pilot Study. This section contains information on the essential documents that the study site must maintain throughout the study. It also contains information related to establishing adequate and accurate participant research records — commonly referred to as the “participant file” — for the Wisebag Pilot Study.

3.1 Essential Documents

The DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* specifies the essential documents that study sites must maintain for DAIDS-sponsored studies, including the Wisebag Pilot Study. When required documents are modified or updated, the original and all updated versions must be maintained. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location. In its policy on *Requirements for Manual of Operational Procedures*, DAIDS requires study sites to establish a standard operating procedure (SOP) for maintaining essential documents. This SOP should be established prior to activation of the Wisebag Pilot Study and will be followed for the Wisebag Pilot Study.

Essential documents may be stored in files and/or in binders, which may be further subdivided, consolidated, and/or re-organized if desired.

To preserve blinding, certain documents related to the study products, including the Randomization Code List (provided by RTI) and the Serial Number – Functionality Link Log (provided by Wisepill Technologies) must be stored in the site pharmacy. It is suggested that the Wisebag Pilot Study participant files be stored separately from the other essential documents. Section 3.2 below provides information on the required contents of these files. It is also suggested the Screening and Enrollment Log (described in Section 4.6 of this manual) be stored in the study clinic or data management area, and not necessarily with the other essential documents.

3.2 Participant File Documentation

Study sites must maintain adequate and accurate participant file records containing all information pertinent to the Wisebag Pilot Study for each study participant.

3.2.1 Participant File Contents

Participant files should contain all of the following elements:

- Basic participant identifiers.
- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures

- Note: Any questions the participant asks during the written IC process (and responses to these questions) should be documented in file notes or on the informed consent cover sheet.
- Documentation that the participant met the study's selection (eligibility) criteria.
- A record of the participant's random assignment.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all study activities that take place during the conduct of the study.
- A record of study products dispensed to the participant and returned by the participant.
- Referrals made (if applicable).
- Reason for any deviation from protocol-specified procedures and those outlined in the site's SOPs for the Wisebag Pilot Study.
- Study-related information on the participant's condition before, during, and after the study, including:
 - Data obtained directly from the participant
 - Data obtained by study staff
 - Data obtained from non-study sources as relevant to the Wisebag Pilot study and participant safety (as applicable)

In addition to the above, DAIDS requires that all protocol deviations be documented in participant records, along with reasons for the deviations, efforts made to correct the deviations, and efforts made to prevent similar deviations in the future (see the MTN website at <http://www.mtnstopshiv.org/> for the protocol deviation template used for all MTN studies). The Wisebag Pilot Study site also must report reportable protocol deviations per Section 15.4 of the MTN MOP. It is also recommended that a copy of all protocol deviations recorded at the site be maintained in one central file or sub-file with the Essential Documents.

3.2.2 Concept of Source Data and Source Documentation

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines the terms source data and source documentation. Please refer to the ICH website for more detail

(<http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>).

Source documents are commonly referred to as the documents — paper-based or electronic — upon which source data are first recorded. As a condition for study activation, the study site must establish a Source Documentation SOP that specifies the use of the documents listed below as source documents. Although it is the responsibility of the site to determine the most appropriate source document for each required participant file element, Appendix 2 provides a guide that the site may follow.

For Wisebag Pilot Study, participant files contain several source documents:

- **Narrative participant file notes:** file notes should be used to communicate any deviations from SOPs, any protocol deviations that are not recorded on other source documents, any referrals made that were not documented elsewhere. The participant file notes should also document any contacts with participants including counseling sessions, questions from the participant (at any point in the study visit) as well as answers provided by the study staff, if this information is not documented elsewhere.
- **Case Report Forms (CRFs) and non-CRF forms:** The case report forms for this study are designed for use with the RTI data management system described in Section 10 of this manual. RTI will provide the master versions of these forms to the site, and printing will be coordinated locally. RTI will also provide several additional study-specific forms (non-CRFs) to the site. See Appendix 2 for a listing of all forms for this study. All CRFs and other forms used in this study can be found on the MTN Wisebag Pilot Study website (www.mtnstopshiv.org/node/3227).
- **In-depth interviews:** Additional notes taken during in-depth interviews are source documents and must be kept in the participant file.
- Visit Checklists and/ or other site-specific flowsheets
- Randomization slips documenting participants' randomization number
- Other source documents (e.g., site-specific worksheets) as identified in the site Source Documentation SOP.

3.2.3 Document Organization

Study staff must make every effort to store all study records securely and confidentially. Participant files must be stored in the same manner for all participants, in areas with access limited to authorized study staff only. Study staff is responsible for purchasing file folders, binders, storage cabinets, and any other equipment or supplies needed to properly store all records.

Study-related documentation collected during the screening process should be stored in file folders (flat files) or thin folders for each potential participant. All screening documentation — for potential participants who eventually enroll in the study as well as for those who do not enroll — must be maintained and available for monitoring throughout the study. Flat files may be maintained for participants who enroll, if the files have some kind of secure mechanism (i.e. rings, clasps) to hold papers. Otherwise, documentation should be transferred to files that have secure mechanisms for holding papers. Pocket files are not adequate as loose papers may still fall out.

All documents contained in participant files must bear a participant identifier, which generally will consist of either the participant identification number (PTID) or the participant name. To maximize participant confidentiality, the PTID should be used whenever possible, and records that bear names or other personal identifiers, such as locator forms and informed consent forms, must be stored separately from records identified by PTID. Any documents transferred or transmitted to a non-study site location — including RTI or a local data management center— must be identified by PTID only. Table 1 gives a list of documents developed for the Wisebag Pilot Study and whether name, PTID and/ or randomization number are recorded used.

Table 1- Listing of Wisebag Pilot Study CRFs and Logs

Document name	Name/ Initials	PTID	Randomization Number
Screening and Enrollment Log	X	X	X
Randomization Log (in clinic)		X	X
Randomization Code List (in pharmacy)		X	X
Enrollment Status Form		X	X
Locator form	X		
Informed Consent Form	X		
Diary Card		X	
Case Report Forms		X	
Visit Checklists		X	

Visit Checklists: The sample checklists in Appendix 4 of this manual provide an example of convenient tools to fulfill the requirement of documenting all study activities that take place at each visit with study participants. Every item in the left column of each checklist should be initialed or marked 'NA'. If the visit procedures deviate from what is outlined in the checklist, documentation of this should be in the participant file notes or at the bottom of the checklist. Visit checklists may be considered source documentation for completing protocol-specified procedures, as well as the order of procedures, per the site Source Documentation SOP.

All on-site databases must be secured with password-protected access systems. When in use, documents that link PTIDs to other participant identifiers should not be left unattended or otherwise accessible to study participants, other study clinic patients, or any other unauthorized persons.

As a condition for study activation, each study site must establish an SOP for Data Management. This SOP minimally should contain the following elements:

- Procedures for assigning PTIDs, and linking PTIDs to participant names
- Procedures for establishing participant files
- During-visit participant file and CRF review procedures
- Post-visit participant file and CRF review procedures and timeframes
- CRF data entry procedures, including timeframes, CRF storage locations before and after data entry, and mechanisms for identifying when forms have been entered
- Procedures and timeline for resolving data quality control notes from RTI
- Storage locations for blank CRFs and guides

- Storage locations for documents identified by participant names or other personal identifiers
- Storage locations for documents identified by PTID
- Confidentiality protections
- Other ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3 Record Retention Requirements

Study records must be maintained on site for the entire period of study implementation, and (at least) two years after study close-out, per ICH guidance. Thereafter, guidance for long-term record storage will be provided by the MTN CORE (FHI) in consultation with DAIDS. No records are permitted to be relocated off site, discarded, or destroyed without prior written authorization from DAIDS.

4 Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and enrolling participants in the Wisebag Pilot Study. Informed consent considerations are provided in Section 5 below.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

Approximately 50 participants are targeted to be enrolled in the Wisebag Pilot Study. This is anticipated to take place over a period of approximately 8 weeks.

Wisebag Pilot Study Participant Accrual Plan

The site is responsible for developing its own accrual plan that can be described in the site Accrual SOP. However, as accrual of participants is dependent on having unsuccessfully screened for the VOICE study, it is recommended that the section of the accrual plan addressing Wisebag Pilot Study accrual is developed in collaboration with relevant VOICE staff.

The accrual plan should minimally contain the following elements:

- Site-specific accrual targets
- Methods for tracking actual accrual versus accrual targets
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures (if not specified elsewhere)

Study staff is responsible for updating this accrual plan if needed to meet site-specific accrual goals.

4.2 Assignment of Participant ID Numbers

RTI will provide Wisebag Pilot Study participant ID numbers (PTIDs) to the site. The site will assign one PTID to each participant after written informed consent to participate in the study has been obtained (see Section 4.3 Screening Definition and Eligibility Criteria). PTIDs are assigned in sequential order as provided on the Screening and Enrollment Log. Once a participant has received a PTID, she will maintain that same PTID throughout the entire study.

The PTID will be written in the boxes located near the upper left corner of each CRF page. The PTIDs used for this study are four digits long and are formatted as "XYYY." The two parts of the PTID are: the site number (X) and the participant number (YYY).

For CAPRISA eThekwini participants, the range of IDs will be: 1001 - 1999

4.3 Screening Definition and Eligibility Criteria

The term "screening" refers to all procedures performed to determine whether a potential participant is eligible to take part in the MTN-003-P01 study. The screening process is formally documented on the Inclusion/Exclusion Criteria form, the Enrollment Status Form CRF, and in participant file notes as appropriate. Any contact made with potential participants for screening and/or screening procedures should be documented in the Participant Contact Log and/or participant file notes.

Eligibility for the Wisebag study is documented on the Inclusion and Exclusion (IE) CRF, and in chart notes as appropriate. VOICE CRFs (Screening documents and Screening Laboratory results) must be reviewed to ensure eligibility for Wisebag Pilot Study participants. The process for retrieving this information must be outlined in the site Eligibility Determination SOP (further specified below). These CRFs from the VOICE study will be used as source documents for determining eligibility per the site Source Documentation SOP and certified copies of the VOICE CRFs needed to document eligibility must be maintained in the Wisebag Pilot Study participant file. There will not be multiple screening attempts for potential participants who are found to be ineligible.

If eligible per the IE form, study staff should collect locator information, administer the Demographics Form and then randomize the participant into the study by selection of the next sequential randomization envelope.

Inclusion and exclusion criteria for participants are as follows:

Inclusion Criteria

Potential participants must meet all of the following criteria to be eligible for inclusion in the study:

- 1) Age 18 – 45 years, inclusive at screening
- 2) Presented and screened out of the VOICE trial
- 3) Able and willing to perform the study procedures

- 4) Able and willing to provide informed consent for study participation
- 5) Has tested HIV-negative within 90 days of enrollment, per VOICE screening laboratory results
- 6) Is currently not pregnant, per VOICE laboratory results or self-report
- 7) Willing and able to provide locator information to the research team

Exclusion Criteria

Potential participants who meet the following criteria will be excluded from the study:

- 1) Has any condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.
- 2) Screened out of VOICE for any clinical condition, that in the opinion of the IoR, may require monitoring or care beyond the scope of this pilot study.

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the Wisebag Pilot Study. The site must establish a SOP for Eligibility Determination that describes how study staff will fulfill this responsibility. This SOP minimally should contain eligibility determination procedures, eligibility verification procedures for each inclusion/exclusion criteria, QC/QA procedures, and staff responsibilities. Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the Wisebag Pilot Study management team (mtnwbmgmt@mtnstopshiv.org) immediately.

4.4 Definition of Enrollment & Randomization Process

Participants will be considered enrolled in Wisebag Pilot Study after they have been randomly assigned to a Wisebag device group.

Randomization Process

In the Wisebag Pilot Study participants will be randomized to a Wisebag device group on the day of Enrollment. The randomization scheme is based on a 1:2:2 allocation to dummy Wisebag, online device Wisebag and offline device Wisebag, respectively. Prior to the start of the study, the RTI statistician will establish the randomization scheme and provide the site with the Randomization Code List, which will link a participant's randomization number with her randomized Wisebag device assignment. This statistician, the onsite pharmacist, and the data manager (or designee) are the only individuals who will know the participant's randomization assignment. Upon enrollment, participants will receive the next sequential randomization number listed on the Randomization Log in the clinic. The clinic staff will complete the MTN-003-P01 Study Wisebag Request Slip indicating an initial supply of the wisebagWisebag. The participant will take this slip, containing her randomization number and PTID to take to the pharmacy, where the pharmacist will dispense the appropriate Wisebag and 16 stickers. The pharmacist will consult the Device Functionality – Serial Number Link Log to ensure the correct Wisebag is dispensed, and document the information on the Product Dispensing Log and the Randomization Code List. The pharmacist will sign the Request Slip and retain the original in the pharmacy. A copy will be given to the participant to return to the clinic and filed in the participant files..

4.5 Screening and Enrollment Timeframe

Recruitment, accrual, and screening/ enrollment procedures for the Wisebag Pilot Study will begin upon study activation and continue for approximately 10 weeks until the estimated 50 participants are enrolled.

4.6 Screening and Enrollment Logs

The *DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on a Screening and Enrollment Log. The Screening and Enrollment Log will provide a comprehensive picture of all participants screened, and enrolled in the study. Each participant logged should also have a completed Enrollment Status form, which will indicate enrollment into the Wisebag Pilot Study or reasons for ineligibility. Each person who provides informed consent and meets inclusion and exclusion criteria is provided with the next chronological PTID; those who do not meet the criteria are provided with a PTID of '0000'. This log will include Wisebag Pilot Study PTID, the screening date, participant's name, if the participant met all eligibility criteria, if the participant was randomized/ enrolled, or the reason for not enrolling (if applicable).

An example of a Screening and Enrollment Log can be found on the Wisebag Pilot Study website (www.mtnstopshiv.org/node/3227). The site is encouraged to modify this as needed.

4.7 Weekly Wisebag Pilot Study Progress Reports

Once the Wisebag Pilot Study accrual is initiated, study staff will report the number of participants screened and enrolled to the Wisebag Pilot Study management team on a weekly basis, along with other key progress indicators as requested by the management team.

5 Informed Consent

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons, and a process, involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the process is described in greater detail below. Please also refer to Section 4.8 of the *International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP)* and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further guidance on the informed consent process and documentation requirements.

US regulations (45 CFR 46) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to potential study participants
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the participant comprehends the information
- Document the process

As a condition for study activation, the study site must establish an SOP for obtaining informed consent from potential study participants that ensures that all of the requirements listed in Section 5 of this Manual are met. The SOP must be consistent with the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. It is recommended that the SOP contain the following elements (listed below) and that the site seek IRB/EC review and approval of the SOP:

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for determining participant identity and age
- Procedures for determining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for determining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Considerations and requirements for illiterate participants, including specification of who may serve as a witness to the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the many different study informed consent forms are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form used
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

There will be one informed consent form for both screening and enrollment into the Wisebag Pilot Study. Potential study participants must provide written informed consent in order to undergo protocol-specified screening, eligibility determination, and enrollment procedures. Written informed consent must be obtained and documented per the site Informed Consent SOP and Informed Consent coversheet. The participant must be provided with an opportunity to ask any questions she has. Any questions the potential participants may have regarding consent and responses to these questions must be documented in file notes and per site Informed Consent SOP.

Language of informed consent: All consent procedures should be conducted in the primary language of the participant. If the written informed consent form is requested in a language that is *different* from the language the procedure was conducted in, this discrepancy should be documented on the informed consent cover sheet or in the participant file notes.

Documentation of informed consent:

US regulations require that informed consent be documented by “the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent.”

To fulfill this requirement, complete all signature and date lines on the informed consent form in ink. Full legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant’s full surname, and it is strongly recommended that initials not be used in place of a participant’s full first name. However, if a participant commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

An informed consent cover sheet will be used with the informed consent form as a way to document informed consent procedures. Per DAIDS policy, each step must be documented, either using this cover sheet or an alternate method as described in the site Informed Consent SOP.

Comprehension of informed consent: Comprehension of the informed consent process must also be documented per the site Informed Consent SOP. For participants who do not consent, no Wisebag Pilot Study procedures will be performed.

5.1 Informed Consent Procedures for Illiterate Participants

If a participant is not literate in English or Zulu, an impartial literate witness must be present during the entire informed consent process/discussion with the participant. The impartial witness will be asked to sign and date the informed consent form to attest that the information in the informed consent form was accurately explained to and apparently understood by the participant. When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, as an agent of the study per se. Refer to Appendix 3 for a summary of considerations for obtaining informed consent from illiterate participants. The process for consenting illiterate participants for the Wisebag Pilot Study will be conducted per site Informed Consent SOP.

6 Visit Procedures

This section provides information on requirements and procedures for Wisebag Pilot Study visits.

6.1 Visit Scheduling & Timing

There are two scheduled visits for this study: the Screening and Enrollment visit (Day 0), and the Exit visit, which is targeted to occur 2 weeks later (Day 14). At the end of the Enrollment visit, the participant should be scheduled to return 2 weeks later for her second and final visit.

During the Screening and Enrollment visit, the participant will undergo screening procedures (see Section 4 above), and randomization. Upon completing the randomization procedures (see Section 4.4 above), the participant will return to the clinic for Wisebag use instructions, protocol adherence counseling, and the first observed opening event. The counseling session is further detailed below in Section 6.3, and Table 2 in Section 10.3 outlines the CRF completion schedule for all scheduled visits.

Target Days and Visit Windows: The target visit exit date will be 2 weeks (14 days) from the enrollment date, with an allowable visit window of plus or minus 3 days. If the study is still in the accrual phase, participants may return at any time to complete exit visit procedures.

Missed Visits: Participants who present after the close of the exit visit window (Day 18 or later) will complete Exit Visit study procedures, as long as the study is still in the accrual phase. If a participant missed the exit visit window the site is expected to follow-up with the participant in order to retrieve the Wisebag and Diary Card, which may require a visit to the participant's home. After unsuccessful contact attempts, including a home visit, the Exit visit will be considered Missed and the participant will be considered lost to follow-up. Site-specific procedures for participant contact and follow-up are further specified in the site Retention SOP.

Home Visits: Any home visit will be for purposes of participant follow-up and retrieval of the Wisebag and Diary Card only. No study procedures will be conducted outside of the study clinic. Study staff as designated by the IoR or Study coordinator may conduct the home visit, and upon returning to the clinic the Wisebag will be given to the pharmacist along with the participant's PTID., and the pharmacist will complete the PDL CRF. The Diary Card will be transcribed onto the Diary Card Log (DCL) form with a notation that the participant did not complete the Exit visit then filed in the participant's file. Additionally, notation about the participant's circumstances and the Wisebag retrieval should be made in the comments section of the Termination Form.

Interim Visits: Enrolled participants who come to the clinic prior to the start of the Exit Visit window (see above) will have an Interim Visit. The Interim Visit Checklist (see Section 7 below) should be followed, and reason for the visit documented in the participant file notes. Procedures will depend on the nature of the visit.

6.2 Data Collection Procedures

All interviewer-administered CRFs should be administered in the primary language of the participant. Any deviation from this should be documented in the participant file notes. Visit checklists should guide the order of procedures for each visit. See Section 7 for more information on the visit checklists, and Section 10 for more information on the CRFs.

6.3 Protocol Adherence Counseling, Wisebag Instructions and First Observed Opening Event

After a participant receives her randomization number, she will go to the pharmacy where she will receive her assigned Wisebag and stickers. The pharmacist will complete the Product Dispensation and Accountability Log.

Following this, the participant will meet with a Wisebag Pilot Study staff member for Protocol Adherence counseling and Wisebag instructions. This counseling session will describe the study procedures each participant is to follow while at home. The participant will be given her diary cards (bound in an A3-size booklet), and the staff member will describe how to use the study products and the diary cards. The staff member should use the Wisebag Product Counseling Checklist, and ensure that the following key messages and instructions are explained to the participant:

Every day the participant is instructed to do the following:

Open the Wisebag (one time only). Remove one sticker and place it on the diary card in the box that corresponds to the correct day and time quadrant the sticker is removed.

Close the Wisebag.

Additional notes for participants:

1. Try to remember to open the bag and remove the sticker at approximately the same time every day. However, if this is not done, that is OK. **Put a sticker on the card only on days when the bag is opened**
2. If a planned time slot or an entire day is missed, do not go back and add stickers to the card for that time or day.
3. If the bag is opened more than once on a day, put only 1 sticker on the card. You will be asked about these other openings at the Exit Visit – you can make notes on the diary cards if that will help you remember them.
4. With each Wisebag opening and closing, make sure the zip is all the way open and all the way closed.
5. The Wisebag is valuable and should be transported and stored safely. It must be returned to the study clinic when you come back for your Exit visit.
6. The device must not be tampered with or removed from the bag.

First Observed Opening Event

Following the Wisebag instructions and protocol adherence counseling, study staff will ask participants to do their first opening and calendar entry under direct observation. The participant should do the the first opening and closing of the Wisebag, as well as the placing of the sticker on the Diary Card, but staff members may assist her if needed. The counseling session and the first product use should be documented and summarized in the

participant file notes. The first opening event at the clinic will be documented later (at the Exit visit) as the first opening event on the DCL CRF.

6.4 Exit Visit

At the Exit Visit (Day 14, ± 3 days), procedures will follow the Exit Visit Checklist (see Section 7 below). If the study is still accruing participants, an Exit Visit may be conducted later than 3 days following Day 14. The key procedures that will take place are as follows :

- 1) A staff member will review the diary cards with the participant, count the returned stickers, and complete the Diary Card Log to record the number of self-reported opening events associated and non-associated with sticker retrievals.
- 2) The participant will return her Wisebag to the pharmacy, and the data manager will download the data off of the device (if applicable) and complete the Product Dispensation and Accountability Log (see Section 10.10 below). For active devices, all data will be “cleared” off of the device prior to dispensing to another participant.
- 3) Finally, a staff member will administer the Acceptability and Use Questionnaire, followed by the IDI. The participant should then be thanked and reimbursed for her time.

7 Visit Checklists

Appendix 4 contains examples of checklists detailing the protocol-specified procedures that must be completed at Wisebag Pilot Study visits. These checklists should be modified as needed to ensure they fit with systems at the site, and subsequently reviewed by the MTN CORE (FHI) for approval prior to implementation. The checklists also specify the data collection forms that must be completed at each visit. The checklists may be source documentation for completing the protocol-specified procedures, as well as the order of procedures, per the site Source Documentation SOP. See Section 3 for more information on Source Documentation.

8 Participant Retention

The Wisebag Pilot Study has only one follow-up visit, and is short in total duration (2 weeks), therefore required retention efforts are limited. Detailed locator information will be collected at the screening and enrollment visit, and site staff should develop and use appropriate strategies for maximizing participant retention. Site staff is responsible for establishing a standard operating procedure (SOP) for participant retention, and for updating the SOP and retention efforts undertaken. The SOP should minimally contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals
- Procedures for completing and updating participant locator information
- Site-specific definition of “adequate” locator information (for purposes of determining participant eligibility)
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods, including what outreach/locator efforts are taken within 24 hours, 1-2 days after the missed visit
- Methods for timely evaluation of the utility of retention methods

- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

Participants will be considered “retained” if they complete their Exit visit. Participants will be classified as “withdrawn” if they are withdrawn from the study by the IoR, or withdraw themselves from the study, prior to the Exit visit. Participants will be classified as lost to follow up if they missed the exit visit window (± 3 days or until the end of the accrual period) and there were 3 unsuccessful contact attempts including at least one Home Visit (see section 6.1 above).

9 Reporting of Social Harms

Social Harms

The Wisebag Pilot Study is a minimal risk study with no clinical procedures and no investigational products. Social harms (SH) are considered to be non-clinical adverse consequences that may occur as a result of study participation. For example, although the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants’ involvement in the study could become known to others and this may cause physical, emotional or psychological problems for the participants.

Additionally, the site will develop a Participant Safety Monitoring SOP for emergency procedures to be used in situations of social harm and when situations that require immediate attention are identified, including but not limited to domestic violence, suicidal ideation or behavior. The procedures will provide clear guidelines for Wisebag Pilot Study researchers to refer participants in these situations to the relevant institution/body.

If any SH are reported by participants, the SH should be fully documented in participant file notes. Study staff should use as much detail as possible to describe the event, including a full description of the event, severity of the event, action taken, approximate onset and resolution dates. Every effort will be made by study staff to provide appropriate referrals (including counseling referrals to the participant, and/or referral to appropriate outside resources as needed) per the site Safety Monitoring SOP.

All social harms reported by study participants will be reported to the Wisebag Management Team every 2 weeks, and to responsible site IRBs according to their individual requirements. Upon review of the social harms report event, the Wisebag Management Team will forward the report to the DAIDS MO.

10 Data Collection

For questions about this section or about general data collection policies, procedures, or materials for Wisebag Pilot Study, please contact Liz Montgomery (emontgomery@rti.org) or Helen Cheng (hcheng@rti.org).

10.1 PTIDs

For more information on assigning PTIDs for the Wisebag Pilot Study, please refer to Section 4.2 of this manual.

10.2 Visit Codes

In the Wisebag Pilot Study, visit codes will be assigned for each visit and recorded on the corresponding checklist, CRFs and file notes.

The visit code for the screening and enrollment visit is 1.0. The visit code for the Exit visit is 2.0. Interim visits should be coded sequentially from 1.1 upwards.

10.3 Case Report Form Completion Schedule

Table 2 lists the case report forms that are required to be completed at Wisebag Pilot Study visits.

Table 2
Wisebag Pilot Study Case Report Form Completion Schedule

Form Acronym	Form Name	Completion Schedule
DEM	Demographic Form	During screening and enrollment
ESF	Enrollment Status Form	During screening and enrollment
PDL	Product Dispensation and Accountability Log	At enrollment, after randomization and at Exit.
IDI	In Depth Interview Guide	At Exit
ACC	Acceptability and Use form	At Exit
DCL	Diary Card Log	At Exit
TF	Termination Form	At end of study completion

10.4 Form Supply

All master case report forms and guides needed for Wisebag Pilot Study will be supplied by RTI and should be printed locally. The site is responsible for maintaining an adequate supply of the current version of CRFs (blank) and guides in all languages. One copy of previous versions of CRFs and guides should be maintained in an archive, and all other copies destroyed.

10.5 Form Storage

Form storage will be detailed in the site Data Management SOP. It is recommended that for each participant, study forms be stored in a flat file with either secure closures or a hard-cover binder (see also Section 3.2.3).

10.6 How to Complete Interviewer-Administered Forms

For the Wisebag Pilot Study, the Demographic Form, Acceptability Form and IDI guide are interviewer-administered. The following are general guidelines for capturing interviewer-administered CRF data.

1. CRF General Guidelines for Capturing Data

Based on Good Clinical Practices (GCP), follow the guidelines below when completing CRFs:

- Read carefully and follow all the form instructions printed on the back of each form;
- Press firmly when recording data or writing comments;
- Print all data and comments legibly by hand.
- Do not use cursive or script writing as it can be difficult to read;
- Write numbers as large as possible while staying within the boundaries of the boxes;
- Record data on the front of the CRFs only;
- Record written text responses on the lines provided. If additional space is needed, continue writing the response in the margin;
- Mark only one response except when given explicit instructions to **mark all that apply**;
- A response is required for every item unless instructed otherwise by a skip pattern.
- Note: The site staff member who initially completes the form must record his/her initials and date in the space provided at the bottom right-hand corner of the forms.

2. Recording Categorical responses on the CRF:

Mark the appropriate box with an X. Only record one response per question. For example, on the DEM Form, for item 7 which asks, 'What is his highest level of education', if the participant reports that it is "Primary school, not complete" mark the corresponding box with an X.

Primary school, not complete

3. Recording Numerical responses on the CRF:

Some questions include boxes for recording a numeric response. The following instructions should be followed when recording numeric responses:

Right justify all numbers and fill in any boxes with leading zeroes.

The following example shows how a value of 7 is recorded when two response boxes are provided:

Correct:

0 7

Incorrect:

7

Write the number(s) as large as possible while staying within the boundaries of the box on the CRF hardcopy.

4. How to Record Dates on the CRF

All dates are recorded in the format ddMMMy, where dd is the day, yy is the year, and MMM is the month. The dd and yy are numeric and MMM is alphabetic.

5. Recording responses to Multiple-Answer Questions on the CRF:

When instructed, the participant can provide multiple answers to a specific question. Mark all the appropriate boxes with an X. These items will be identified with a 'mark all that apply' instruction.

For example, on the DEM, item 15, the participant is asked what her ethnic group or tribe is and the instructions indicate 'mark all that apply.'" The participant will then be prompted to

answer all languages. If needed, the Interviewer will provide the participant with the response options: Zulu, Sotho, Xhosa, Other (specify). The Interviewer should mark an X next to every response the participant provides. If she lists 1 or more ethnic groups not listed as an option, mark the **Other, specify** box with an X and list ALL other groups, i.e. "Tsonga".

6. Recording textual responses on the CRF:

Some questions are open-ended or require the interviewer to specify a response. The interviewer should write the participant's response verbatim, if possible. If the response is too long, the interviewer should summarize the response.

7. How to Handle Missing and Unknown Data

If the answer to an item is missing (MSG), not applicable (NA), or if the participant refuses to answer (REF), the interviewer should make a written notation corresponding to the codes above (MSG, NA, REF) in the margin next to the item on the CRF and the response boxes should be left blank. This procedure should be followed for any type of question on the CRF forms. A skip pattern is the **only** valid reason to leave a response blank without any margin notation on the CRF.

8. Correcting Data on the CRF form

Once all data has been written, the CRF should undergo a review process. Immediately following the completion of the form, the Interviewer checks the form to make sure it is complete and accurately entered. Then, the form is given for review to a second staff member (according to the site's internal QC process and Data Management SOP). This second reviewer then reviews the form to check for inconsistencies or incomplete information prior to data entry. If anything is incomplete, the designated staff reviews the form with the Interviewer to fill out the information and document a brief explanation in the comment's section of the form as to why something wasn't filled out. All comments should be documented with staff initials and date.

In-depth interviews (IDIs)

The IDIs for this study will be conducted in a semi-structured format, and data recorded directly on a CRF. Staff should record responses in English on the form, to avoid the need for lengthy translation services. However, staff may record notes in other languages and extrapolate and translate responses immediately following the interview if needed. Staff should attempt to translate the participant responses verbatim, but may summarize if needed. The following additional information is provided as general information about the collection of data in in-depth interviews.

IDI and Qualitative Interview Techniques¹

- **Maintain Confidentiality.** Respect confidentiality at all times. Be careful not to comment to other family members or neighbors about anything that you learned the interview. This is especially important when interviewing people about their sexual behaviors.

¹ The Qualitative Interview Techniques section is adapted from the following reference: Mack, Natasha, Cynthia Woodson, Kathleen MacQueen, Greg Guest and Emily Namey. Qualitative Research Methods: A Data Collector's Field Guide. RTP, NC: Family Health International, 2005.

- **Influencing Responses.** It is especially important to be on guard against asking leading questions. Leading questions are those that imply a value judgment on your part. This can bias the responses that you will obtain because if the participant disagrees with you, they may be reluctant to state it.
 - *biased question: "I know that most smart people in this community always use condoms, don't they?"*
 - *Better phrasing: "I have heard some people in this community say that most smart people use a condom, and others say that they know smart people who don't use condoms. What do you think?"*

- **Probe for Depth.** As much as possible ask follow up questions and probe for a deeper understanding of what the participant is saying. Examples of probing phrases might be: "Why?" "How did you feel when that happened?" "Did you do that?" "What do you think?" "What happened then?" "Can you tell me more?" "I'm not sure I understand." Such probing also may require extra patience on the part of the interviewer.
 - *Example: Can you tell me more about why you didn't feel you could tell your partner about using the Wisebag?*

- **If Uncertain, Verify Responses.** When you want to be sure that you have heard clearly what the participant said or that the information is accurate, rather than asking them to repeat their response, you can reflect the answer back to the participant.
 - *Example: So your sister was curious and you told her that only you could open and close the Wisebag?*

- **Do Not Respond to Questions.** If the participant asks you questions that are the focus of the interview, do not answer them. Your answers might influence how the participant will answer the rest of the questions. Instead, turn the question around and ask them what they think.
 - *Example: Well, I was hoping you could help me understand what people in this community say about how you catch the HIV virus.*

- **Be Patient.** It is not necessary to be asking questions every minute. Creating pauses can permit the participant to think more deeply about the topic. Don't be afraid to wait quietly while they think about a response or further probe, but be reassuring in your body language so the participant knows you are genuinely interested in what she/he has to say.

- **Do Not Interrupt Participant's Work.** The participant is doing a favor to answer the questions. If the participant must interrupt the interview to attend to a child, a customer, a neighbor, use this time productively to review your notes and think about what else you would like to ask.

- **Handle Time Wisely.** Always note the time when the interview begins and ends. As you begin the interview, evaluate how much time you may have with this participant and what are realistic goals for asking questions from the interview guide. Ideally, the interview will flow like a conversation rather than a series of questions and answers.

- **Be Truthful.** In responding to questions from participants during the interview, provide brief, truthful answers such as about the objectives of the study, or the likely benefit to the community.
- **Moderate Tone of Voice.** During the interview, use a moderate, friendly tone of voice.
- **Moderate Body Language.** Be sensitive to your participant's body language and aware of your own. Avoid body language that may send the signal that they are giving "correct" answers, or are wasting your time.

10.7 Form Completion Instructions

Detailed form completion instructions are provided on the back of each form page. These instructions include the purpose of each form as well as how each form should be completed. Some items on forms are straightforward and do not require specific instructions. Therefore, instructions for all form items are not listed on the back of each form; rather, instructions are provided only for those items needing a detailed explanation. For the Wisebag Pilot Study interviewer-administered forms instructions on how to probe for participant responses are included in the instructions on the back of each form page.

10.8 Case Report Forms

The current version of all case report forms (English and local language) will be kept on the MTN Wisebag Pilot Study website: www.mtnstopshiv.org/node/3227

10.9 Downloading and Transmitting Wisebag Data

At the Exit visit, Wisebags will be collected in the pharmacy and then transferred to the IT department for an unblinded data staff member to complete the following procedures to capture any information stored on the device. The following procedures should be followed for all active (offline and online) devices.

At the end of a participant's study participation period, the data must be downloaded to the local machine and uploaded to the RTI FTP site. It is important to perform the procedure in the specified order; otherwise, the Wiselogger application may stall or crash. Opening more than one Wiselogger session may also cause the application to crash and is not recommended.

To download the files, the designated staff member in the IT department will perform the following steps:

- 1) The staff member will first open the Wiselogger application.
- 2) After opening the application, the device will be connected to the computer using a micro-USB to USB cable. After a few seconds, the read-out screen in the bottom left-hand corner will read 'OK', which indicates that the data has been received by the Wiselogger application. If the application does not read the device for any reason, without closing the application, disconnect the device and plug it in again.
- 3) Next, all text files must be downloaded to the local machine. To do this, the staff member will select each file in the right-hand window and click on the 'Download' button. These files contain the opening event times (medeventX.txt) as well as

heartbeat times (heartbeatX.txt) and are numbered consecutively. All files will be named according to the device's long serial number and date. Although the same device may be dispensed to multiple participants, the download date embedded in the filenames will clarify the PTID with whom the data is associated.

- 4) Next, the device should be disconnected from the computer.
- 5) Lastly, the Wiselogger application may be closed.

All downloading activities will be recorded in the Device Data Download Log (Appendix 6).

These exported files will be zipped together (named according to long serial number and date of download) and, along with the updated Device Data Download Log, uploaded to the FTP server within one day of downloading. An email will also be sent to the RTI-SF Data Manager informing her that files have been uploaded to the FTP site.

To upload data, open a Client window and connect to RTI FTP server using the following information:

- Host: ftp.rti.org
- Username: Wisebag
- Password: j3Vld2HJ
- Port: 990

Zipped data files will be uploaded to the **/Data/Device** directory while logs will be stored in the **/Data/Device/Log** directory.

If the site experiences any problems downloading data files or uploading to the FTP site, the RTI-SF Data Manager should be emailed (hcheng@rti.org) to resolve issues.

10.10 Erasing Offline Devices After a Participant's Study Completion

For the offline device, the participant data files (opening event data file and heartbeat data file) must be erased before the next participant may use the device. If any files are found on online device, they must be erased as well.

1. RTI-SF Data Manager (DM) will email site confirming that new files have been received. Site staff will confirm will confirm with DM before erasing any data from device.
2. To erase data from device, open the Wiselogger application and plug in the device. Once all files appear in the right-hand window (there should be at least one file named medeventX.txt and one file named heartbeatX.txt), click on the 'Delete all'.

If the site experiences any problems erasing data files, the RTI-SF Data Manager should be emailed (hcheng@rti.org) to resolve issues.

10.11 Monitoring Battery of Active Devices

At the start of the study, the manufacturer of the active devices will supply devices with a full battery providing a minimum of four months of usage; recharge of batteries should not be required. RTI-SF Data Manager will monitor voltage of offline devices via downloaded data received from the site and will monitor voltage of online devices via online reports. If recharge of a device battery is required, sites will follow procedures as outlined by device manufacturer.

10.12 Entering and Transmitting CRF Data

Overview of Data Entry

Data for quantitative analysis will be collected manually on CRFs at the site. Data will then be double entered at the site per site Data Management SOP, using a CPro database (which allows for double data entry). Following data entry on a weekly basis, the site will generate a discrepancy report to check consistency between the two entries as well as other designated consistency checks. Once the reports are run, they should be printed and used to document the corrections that are made to the main database by site data entry personnel. A written note on the original discrepancy report documenting the changes made, staff initials and date should be provided for each finding listed on the on the discrepancy report and then the report filed.

Once data entry discrepancies have been resolved at the site, data should be uploaded to and encrypted FTP server weekly and sent to RTI.

Encrypted FTP is set by RTI's FTP department with encryption security settings dictated by Wisebag Pilot Study compliance regulations. FTP use is account, username and password protected with access granted only to designated team members from RTI and the site. The encrypted FTP site tracks user activity and file uploads making it easy to manage precisely whom and when new files are updated, what changes are made, and what versions are most current.

Once data is transferred to RTI via the FTP site, RTI performs additional cleaning checks using SAS. RTI will send QC reports to site staff by email. Corrections should then be made to the databases. Data is then re-transmitted to RTI as described above. All QC reports received from RTI should be filed at the site. Changes made to the CPro database should be documented on the QC report, as done for the site's internal discrepancy report (described above).

Specific Instructions for Data Entry

1. CRF Data Entry Instructions for CPro Database

Once CRF data have been internally QC'ed at the site, they should be double data-entered into a CPro database by the designated site staff. Instructions for running the CPro software system and beginning the data entry process can be found in Appendix 5. Staff should enter data from CRFs into the CPro database that corresponds to that form. If the response type is categorical, numeric (including dates), or multiple answers, a numeric value should be entered into the database. If the response type is open-ended or textual, text should be entered verbatim in the corresponding database field, as described below.

a. How to Enter a Categorical Response

When entering a categorical response into the CSPro database, look at the subscript next to the box marked with the X on the CRF. Enter the corresponding subscript number into the CSPro database.

For example, on the DEM Form, for item 7 which asks ‘what is his highest level of education’, if the participant reports that it is “Primary school, not complete”, record 2 into the CSPro database (as 2 is the response’s corresponding subscript).

₂ Primary school, not complete

b. How to Enter a Numeric Response

Some questions include boxes for recording a numeric response. The following instructions should be followed when entering numeric responses into the CSPro database:

Right justify all numbers when entering numeric responses in the database, and fill in any boxes with leading zeroes. If boxes are left blank, a QC note will be applied asking for the boxes to be filled in.

c. How to Handle Missing and Unknown Data

If the answer to an item on the CRF is missing (MSG), not applicable (NA), or if the participant refuses to answer (REF), the interviewer will make a written notation as instructed above (MSG, NA, REF) in the margin next to the item on the CRF. The corresponding field should be left blank in the CSPro Database, by keying through with the ‘Enter’ key.

The CSPro database does not have built in skip patterns and therefore, when entering a response which necessitates a skip pattern on the CRF, the data entry staff should manually advance to the appropriate field by pressing the “Enter” key.

For step-by-step instructions on how to enter a data from a CRF into CSPro, refer to Appendix 5.

2. CRF Double Data Entry

CRFs should first be entered manually in a main database called ‘Main’, and then a second time in a verification database called ‘Verify’ by a different staff person. The purpose of double data entry is to minimize data entry errors by verifying the consistency of entries from two individuals entering the same form. See Appendix 5 for detailed instructions on how to enter data in the main and verification database, and run a verification report.

a. Comparing Doubly-entered Data in CSPro

After CRF data has been entered into the corresponding CRF’s two databases (main and verification), a staff member designated by the site (see Data Management SOP) should run an auto-generated verification report which will detail the inconsistencies and errors between the two databases, question by question. For inconsistencies between the two databases, the sites should refer to the hardcopy CRF and determine which database contains the correct response and correct the other manually and re-save. If neither database reflects the response listed on the CRF, both databases need to be manually updated with the correct information and re-saved until all discrepancies are resolved. For instruction on how to make corrections in CSPro, and save the corrections refer to Appendix 5.

Once site verification processes are complete and the main database is considered clean, the Data files should be exported and uploaded to the FTP site as described in Appendix 5.

3. FTP file Transferring, Opening and Modifying

a. Data entry and uploading of files to FTP site

For the above described data entry process, the site should complete the following steps:

- Double data entry of CRF data into CSPro databases;
- Run QC checks through an automated Double Data-Entry Verification process;
- Correct data entry in MAIN or VERIFY database(s) as needed
- Upload the updated data files to the FTP site for RTI review

b. RTI QC and site response and documentation of queries:

Once RTI receives the data Files, an auto-generated SAS report will be run to further detect errors such as out of range data as well as inconsistent PTIDs or missing data. A query report listing all errors will be generated and sent to the site within **1 week** of receipt of the data files. Upon receipt, the sites then have **1 week** to do the following:

- Make necessary data entry corrections/ modifications based on the Query Report to the 1) CSPro database(s) and/or; 2) CRFs;
- Respond item by item in the query report as to how each QC was addressed and resolved and provide staff initials and date for each item on the report. Notation made on the printed QC reports should be clear and conform to GCP standards. Query reports should be printed and filed at the sites.

RTI will verify that each item has been addressed, or will request the site to further follow up with any issue. Once every issue is resolved and the data is considered 'clean' by the sites and RTI, updated/corrected data files should be uploaded to the FTP site.

NOTE: Query notes on weekly Query reports will recur until updated/corrected files are uploaded to the FTP site. Therefore, it is important that the site upload to the FTP site diligently.

Appendix 1

Protocol

Appendix 2
Source Documentation guidance

Guide to Required Case History Elements and Source Documents for MTN-003-P01

Required Case History Element	Source Documents*
Basic participant identifiers.	Locator form, Demographics form.
Documentation that the participant provided written informed consent to screen for and participate in the study.	Signed and dated informed consent form; signed and dated chart notes stating that informed consent was obtained from and fully understood by the participant prior to initiating study procedure; informed consent coversheet.
Documentation that the participant met the study selection (eligibility) criteria.	Inclusion and Exclusion Criteria form; Enrollment Status form; VOICE lab logs and result reports; signed and dated chart notes.
A record of the participant's random assignment.	Randomization number log; pharmacy randomization code list; device functionality-serial number link log.
A record of the participant's exposure to the investigational study product.	Diary card log; product dispensation and accountability log; randomization number wisebag request slip; participant-specific pharmacy dispensing record(s); in-depth interview guide; acceptability and use questionnaire.
A record of all contacts, and all attempted contacts, with the participant.	Signed and dated chart notes and/or other worksheets or site-specific documents if designated in site SOPs.
A record of all procedures performed by study staff.	Completed visit checklists; signed and dated chart notes detailing (i) procedures performed in addition to those contained on the checklist and/or (ii) the reason why procedures contained on the checklist were not performed.
Information on the participant's condition before, during, and after the study.	All documents listed above; all interviewer-administered case report forms; signed and dated chart notes; other designated site-specific source documents.

*Other site-specific source documents also may be used.

MTN-003-P01 Case Report Forms and non-Case Report Forms

CRFs	Non-CRFs
Inclusion and Exclusion Criteria Form (IE)	Diary Card
Enrollment Status Form (ESF)	
Demographics Form (DEM)	
Diary Card Log (DCL)	
Product Dispensation and Accountability Log (PDL)	
Inclusion and Exclusion Criteria Form (IE)	
Termination Form (TF)	
In-Depth Interview Guide	
Acceptability and Use Questionnaire	

Appendix 3

Summary of Considerations for Obtaining Informed Consent from Illiterate Persons

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and must be followed each time informed consent is obtained. It is recommended that each site seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent discussion with an illiterate participant. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process/discussion with the participant should print the participant's name below the "participant's printed name" line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see Figure 5-2 below).
- The participant should make her mark on the "participant's signature" line.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process/discussion with the participant should enter the date upon which the participant made her mark on the informed consent form below the "participant signature date" line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see Figure 5-2).
- Refer to Section 4.8 of the ICH GCP guidance and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials.

Appendix 4

Visit Checklists

APPENDIX 5: CPro STEP-BY-STEP DATABASE ENTRY INSTRUCTIONS

The following instructions provide a step-by-step guide to data entry of a CRF into its corresponding CPro database, using the DEM form as an example. If entering data into other CPro databases, substitute the form name for DEM where appropriate below.

Location of files:

All ESF files are located in the folder: **C:\Wisebag\Data\CPro\DEM**.

You can open this folder by clicking on the shortcut on the Desktop named "Shortcut to Wisebag CPro databases" and then opening the DEM folder. The subfolder 'database' contains files that site staff should **not** access. Modifying these files will affect the performance of the databases.

1.1. ENTERING DATA

Data should be entered within one week of form completion.

1.1.1. Data entry into MAIN database.

- Open database by double clicking on the shortcut in the DEM folder named: **DEM_MAIN.pff**
- Type your initials. Click 'OK'.

- Click on 'add' button at the top left side of the screen .
- Enter first form.

- Enter Wisebag Pilot Study PTID as written on the CRF (paper form).
- After entering value, press the Enter or Tab key to proceed to next field. If you would like to move to a previous field, press the Shift and Tab key at the same time.

Note: Do **not** use a mouse to move from field to field.

- If value is blank on form, leave field blank on database by pressing the Enter or Tab key.
- If error message appears, reenter value. If error message instructs you to press F8, do so and then reenter value.
- If you are having difficulty modifying a value in the field, move the cursor to left most position in the box and press delete until all characters have been cleared, then re-enter the correct data.
- Make sure to enter version # of form (including decimal place) at the bottom of every form regardless of whether the form is complete.
- When entering the version number, the decimal place needs to be entered in addition to the numerical values. Therefore, 3 fields must be entered. For example, if the version is 1.0, the "1", "." and "0" all must be entered before saving.
- Press 'Enter' and click on 'Yes' to accept the record. This is an important step because this saves the case and any changes that you have made.

Note: Keying in the version number followed by pressing the Enter key must be completed in order to SAVE all work. This applies to when data is originally entered as well as to when any changes are made.

- Enter all forms.
- Click on 'Stop' button  after entering all forms.
- Close window by clicking on X in top right corner.

1.1.2. Data entry into VERIFY database.

Note: The staff member who enters into the VERIFY database should not be the same person who entered data into the MAIN database.

- Open database by double clicking on the shortcut in the DEM folder named: **DEM_VERIFY.pff**
- Type your initials.
- Click on 'Add' button  at the top left side of the screen.
- Enter all forms (as per instructions for the instructions above for Main database).
- Click on 'Stop' button  after entering all forms.
- Close window by clicking on X in top right corner.

1.2. CHECKING DOUBLE DATA ENTRY

To check on double data entry and resolve discrepancies, compare the MAIN and VERIFY databases by following these steps:

- Produce discrepancy report by double clicking on shortcut in DEM folder named: **DEM.cmp.pff**.
- If discrepancy report is generated, print report.
-> If no discrepancies are found, STOP HERE.
- Close report window by clicking on X in top right corner.
- Open both the MAIN and VERIFY databases.
- For each discrepancy on the list, identify which value has been incorrectly keyed. (Note that "Inp" entries refer to MAIN database values and "Out" entries refer to VERIFY database values.) Correct the value in the appropriate database by double clicking on the relevant PTID in the left column, correcting the field, and saving the changed record. Be sure to check data file name at top of window to ensure that you are correcting the appropriate database (whether MAIN or VERIFY). Mark each item on discrepancy report (e.g., with a check) after resolving in the appropriate database.
- After all discrepancies have been addressed, close both databases.
- Rerun discrepancy report to ensure that discrepancies have been resolved by double clicking on shortcut named **DEM.cmp.pff**. If discrepancy report is generated, print and resolve. Repeat this process until no discrepancy report is generated.

- File discrepancy report(s) in the appropriate binder as specified in site Data Management SOP.

1.3. EXPORTING DATA FROM CSPRO

On the **Thursday** of each week in which data has been entered into the database, export data from the CPro system (specifically the MAIN database) by following these steps:

- Double click on shortcut in DEM folder named: **DEM.exf.pff**.
- Close CPro Text Viewer and CSExport windows by clicking on X in top right corner.
- Two files will be exported to the 'exported files' subfolder in the DEM folder. They are named DEM.sas and DEM.dat and will overwrite the previous .sas and .dat files.

1.4. UPLOADING FILES

1.4.1. Schedule for Uploading

Exported .sas and .dat files should be uploaded to RTI FTP server each Thursday. Site staff should e-mail Helen Cheng (hcheng@rti.org) the weekly FTP report to inform that data has been uploaded. If no records have been entered in a week, site staff should not upload database and should notify Helen Cheng by e-mail message by Friday that no data has been entered that week.

1.4.2. Uploading to FTP Server

- Open FTP window and connect to RTI FTP server using the following information:
 - o Host: ftp.rti.org
 - o Username: Wisebag
 - o Password: j3Vld2HJ
 - o Port: 990
- Click on the QuickConnect button.
- On left-hand window, type location of exported files in 'Local site' box: **C:\Wisebag\Data\CPro\DEM\exported files**. Press Enter key.
- On right-hand window, type location of directory that you will upload to in 'Remote site' box: **/Data/CPro/DEM**. Press Enter key.
- Transfer current version of exported files by dragging DEM.sas and DEM.dat from left-hand window to right-hand window.
- After files have been transferred, right click on file names on the right-hand window and click on 'Rename'. Append today's date to file name such that files are named DEM _ddMMMyy.sas and DEM _ddMMMyy.dat.
- Check that two files have been transferred to FTP server and dated appropriately. If so, you may close the FTP window by clicking on the X in the top right-hand corner.

1.5. QUERY RESOLUTION

A designated site staff person will receive a list of queries by e-mail identifying missing or discrepant data from RTI the week following an FTP upload. Reports will list the Wisebag PTID as well as describe the issue associated with the PTID.

Queries should be resolved within the week and database changes should be made by the end of the week. To address queries:

- Correct error or complete missing information on CRF. Incorrect values (if any) should be crossed out and correct values written beside the erroneous value. Staff member should write initials and date next to the change. (This may be unnecessary if issue is a result of a data entry error.)
- Locate record by opening databases and double clicking on PTID in left-hand column. After making changes to a record, remember to save the change to the record by moving cursor to *version* field, pressing the Enter key, and clicking on 'Yes' to accept changes.
- Follow above instructions to:
 - o Change record in MAIN database
 - o Change record in VERIFY database
 - o Compare two databases and resolve any discrepancies
 - o Export data
 - o Upload exported .sas and .dat files FTP server
- Query List: Complete three columns on the query list indicating action taken, staff initials, and date of action. Query list will be named: QueryList_DEM_ddMMMyy.rtf and will contain the date on which the query list is sent to the site. After query lists have been updated by site, save by appending the site staff initials (e.g. AAA) to the file name such that file will be named: QueryList_DEM_ddMMMyyAAA.rtf. Query lists may be saved in the 'query lists' subfolder in the DEM folder.
- Upload updated query list to FTP for RTI review.

