

MTN-003-P01

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

Microbicide Trials Network

Sponsored by:

**Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
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MTN-003-P01

Wisebag Pilot Study

LIST OF ABBREVIATIONS AND ACRONYMS.....	4
PROTOCOL TEAM ROSTER	5
INVESTIGATOR SIGNATURE FORM	11
PROTOCOL SUMMARY	12
1 KEY ROLES	14
1.1 Protocol Identification.....	14
1.2 Sponsor and Monitor Identification.....	14
1.3 Medical Officer	14
1.4 Data Center.....	14
1.5 Study Operations	14
2 BACKGROUND and INTRODUCTION.....	15
2.1 Oral Pre-Exposure Prophylaxis and Microbicide Adherence in HIV Prevention Trials.....	15
2.2 The MTN-003 (VOICE) Study	15
2.3 Objective Measures of Product Adherence.....	16
2.4 Wisepill/Wisebag Technology	17
2.5 Wisebag Pilot Study	18
2.6 Study Hypotheses and Rationale for Study Design.....	19
3 OBJECTIVES	19
3.1 Primary Objectives	19
3.2 Secondary Objective	19
4 STUDY DESIGN	20
4.1 Identification of Study Design.....	20
4.2 Summary of Major Endpoints	20
4.3 Description of Study Population	20
4.4 Time to Complete Accrual.....	21
4.5 Study Groups:	21
4.6 Expected Duration of Participation	21
4.7 Sites	21
5 STUDY POPULATION.....	21
5.1 Selection of the Study Population and Recruitment	21
5.2 Inclusion Criteria	21
5.3 Exclusion Criteria	22
6 STUDY PRODUCT	22
6.1 Supply and Dispensation of Wisebag.....	22
7 STUDY PROCEDURES	22
7.1 Screening and Enrollment.....	22
7.2 Exit Visit: End of Week 2	23
7.3 Interim Visits:.....	23
7.4 Behavioral Evaluations.....	24
7.5 Blinding Evaluations.....	24
8 ASSESSMENT OF SAFETY	24

8.1	Safety Monitoring	24
8.2	Social Harms Reporting	25
9	CLINICAL MANAGEMENT	25
10	ANALYTICAL CONSIDERATIONS.....	25
10.1	Overview and Summary of Design.....	25
10.2	Study Endpoints.....	25
10.3	Primary Study Hypotheses.....	25
10.4	Number of Participants.....	26
10.5	Data, Study Monitoring and Analysis	26
11	DATA HANDLING AND RECORDKEEPING	27
11.1	Data Management Responsibilities.....	27
11.2	Source Documents and Access to Source Data/Documents	27
11.3	Quality Control (QC) and Quality Assurance.....	27
12	CLINICAL SITE MONITORING	27
13	HUMAN SUBJECTS PROTECTIONS	28
13.1	Institutional Review Boards/Ethics Committees	28
13.2	Protocol Registration.....	28
13.3	Study Coordination.....	29
13.4	Risk Benefit Statement.....	29
13.5	Informed Consent Process.....	29
13.6	Participant Confidentiality.....	30
13.7	Special Populations.....	30
13.8	Compensation	30
13.9	Study Discontinuation	31
14	PUBLICATION POLICY.....	31
	APPENDIX I: Sample Informed Consent Document	32
	REFERENCES.....	36

List of Tables

Table 1:	Screening and Enrollment	23
Table 2:	Exit Visit: End of Week 2	23
Table 3:	Approximate Number of Participants per Group.....	26

Wisebag Pilot Study

LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	Audio-Computer Assisted Self Interviewing
AIDS	Acquired Immunodeficiency Syndrome
BRWG	Behavioral Research Working Group
CAB	community advisory board
CORE	Coordinating and Operations Center
CRF	case report form
CRS	clinical research site
CWG	Community Working Group
DAIDS	Division of AIDS
DOT	Directly Observed Therapy
EC	Executive Committee
EMS	Electronic Monitoring System
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
HIV	human immunodeficiency virus
ICF	Informed Consent Form
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
IT	information technology
MEMS	Medication Event Monitoring System
MTN	Microbicide Trials Network
MO	Medical Officer
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases
NIMH	National Institute of Mental Health
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
QC	quality control
RE	regulatory entity
RSC	Regulatory Support Center
SMC	Study Monitoring Committee
SSP	study specific procedures
TDF	tenofovir disoproxil fumarate
VOICE	Vaginal and Oral Interventions to Control the Epidemic

MTN-003-P01

Wisebag Pilot Study

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

INVESTIGATOR SIGNATURE FORM

**Version 1.0
April 15, 2011**

A Study of the Microbicide Trials Network

**Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health**

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the US Division of Acquired Immunodeficiency Syndrome (DAIDS), unless otherwise specified by DAIDS or the Microbicide Trials Network (MTN) Coordinating and Operations Center. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, and made available to NIMH and DAIDS, for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record _____
Date

MTN-003-P01

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

PROTOCOL SUMMARY

- Short Title:** Wisebag Pilot Study
- Protocol Chair:** Ariane van der Straten, PhD, MPH
- Sample Size:** Approximately 50 women
- Study Population:** Women who meet the MTN-003-P01 eligibility criteria, who screened out of a MTN-003 (VOICE) screening
- Study Site:** Site(s) in sub-Saharan Africa as designated by the MTN Executive Committee
- Study Design:** Three-arm, randomized, placebo-controlled, double-blinded pilot study of Wisebag for daily use. Women will be randomly assigned (1:2:2 ratio) to:
- Placebo Wisebag
 - Online device Wisebag
 - Offline device Wisebag
- Study Duration:** Approximately 10 weeks total: accrual will require approximately 8 weeks. Additionally, the follow-up period will take approximately 2 weeks. Each participant will have 2 visits, 2 weeks apart.
- Study Product:** N/A
- Study Regimen:** Study stickers will be stored in the Wisebag and used in lieu of actual products for this pilot. In all three groups, participants will be asked to open their assigned Wisebag daily, peel off a sticker, and place it on a study-provided diary card.

Primary Objectives:

- To compare the on-site technical performance of the “offline” and “online” functionalities of Wisebag
- To assess the success of attempted blinding of the “dummy” vs. active (“online” or “offline”) Wisebag
- To measure the concordance between Wisebag opening-event data (both “online” and “offline”) and self-reported data.

- To explore the feasibility and acceptability of Wisebag use by participants

Primary Endpoints:

- **Technical Performance**
 - Staff-reported and participant-reported technical and user-related problems with device and bag; diary card and signal data from device (“heart beat” and participant-initiated opening-events)
- **Ability to Identify Randomization Arm**
 - Participants’ self-evaluation of their arm assignment and their ability to detect (at study exit) whether a bag is an active or non-active bag
- **Concordance with Self-Report**
 - Opening-event data (downloaded from device at the clinic or sent wireless to server) compared with self-reported diary card and questionnaire data
- **Feasibility and Acceptability**
 - Participant attitudes and experiences with Wisebag assessed through questionnaire and open-ended interview data at study exit

Secondary Objective:

- To assess the appropriateness of educational materials/instruction sheets for Wisebag use

Secondary Endpoint:

- Appropriateness of educational materials will be assessed through questionnaire and open-ended interview data at study exit.

1 KEY ROLES

1.1 Protocol Identification

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

Protocol Number: MTN-003-P01

Short Title: Wisebag Pilot Study

Date: April 15, 2011

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2 BACKGROUND and INTRODUCTION

2.1 Oral Pre-Exposure Prophylaxis and Microbicide Adherence in HIV Prevention Trials

Biomedical HIV prevention research is at a critical juncture. Two trials have recently reported effectiveness; CAPRISA 004, which evaluated 1% tenofovir gel (TFV gel) used pericoitally in women, and iPrEX, which evaluated oral Pre-exposure Prophylaxis (PrEP) of Truvada® in men who have sex with men. In both trials effectiveness was correlated with adherence level in a dose-response relationship, demonstrating the central importance of maintaining high product adherence to minimize the efficacy-effectiveness gap.^[1, 2] Indeed, lower-than-anticipated product adherence is believed to have contributed to efficacy dilution in several randomized controlled trials of *female-initiated* biomedical HIV prevention methods.^[3-5]

The CAPRISA 004 trial reported a marked decline in the observed effectiveness of TFV gel as adherence decreased: 54% amongst “high (>80%) adherers” vs. 38% and 28% amongst “medium (50%-80%)” and “low (<50%)” adherers, respectively.^[1] Furthermore, assignment to active product did not appear to be protective in the latter two sub-groups.^[1] A similar pattern was reported by the iPrEX study.^[2] Thus, accurately measuring product adherence is critical to minimize potential distortion of results and erroneous interpretations of study findings, such as concluding that a product is safe when actually it was not used at all or at the exposure level required, incorrect attribution of side effects, or perceived lack of efficacy of a truly efficacious product because of suboptimal adherence^[6].

2.2 The MTN-003 (VOICE) Study

MTN-003, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study is designed to assess the safety and efficacy of daily dose oral and vaginal formulations of tenofovir and oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in preventing HIV acquisition. The VOICE study is a Phase 2B, five-arm, multi-site, randomized, placebo-controlled trial that is double-blinded within each mode of administration, but open-label with respect to the randomly assigned mode of administration (vaginal or oral). Approximately 5000 participants will be randomized to the five study arms in a 1:1:1:1:1 ratio. The VOICE study is being implemented in sub-Saharan Africa.

A secondary objective of the VOICE study includes the evaluation of adherence to daily regimens of vaginal gel (tenofovir 1% gel and placebo) vs. oral tablets (TDF, FTC/TDF, and placebos) used to prevent HIV infection.

This adherence objective will be assessed using indirect self-reported measures, including study product counts at the sites' pharmacy, as well as face-to-face interviewing with responses collected via Case Report Forms (CRFs), and Audio-Computer Assisted Self Interviewing (ACASI). It is widely accepted that self-report of study product adherence by participants is inflated^[7]. Similar to self-report, product count estimates are also likely to be inflated if participants forget to return their products or “dump” them (non-returned products can be reported as used by participants). The study design of VOICE also allows limited comparisons of effectiveness, safety, adherence, and associated frequency of viral resistance among HIV seroconverters across formulations. Currently planned biological measures (e.g., drug level in plasma at all VOICE sites; and in Peripheral Blood Mononuclear Cell (PBMC), which is being

considered at some VOICE sites) will only be informative for participants in the VOICE oral group. No biomarkers are currently available for assessing product use in the VOICE vaginal group.

The proposed study, MTN-003-P01 aims to pilot test the feasibility of using Wisebag, a novel event-based electronic monitoring system, as an indirect objective measure of adherence to daily product use. This pilot study will inform the feasibility of including Wisebag in the design of a future VOICE ancillary study on objective measures of adherence.

2.3 Objective Measures of Product Adherence

Aside from Directly Observed Therapy (DOT), there is presently no validated objective method available to measure participants' adherence to vaginal study product use in HIV prevention trials. Furthermore, DOT is not a logistically practical option in studies of vaginally applied products. Because of the lack of accurate adherence measurement capabilities in HIV prevention (as well as treatment) trials, there has been an indeterminate amount of product non-adherence that may, in turn, preclude researchers' ability to accurately measure the safety or efficacy of a novel vaginally applied intervention technology. The methods commonly used for measuring adherence in HIV prevention (and treatment) research studies include self-report, electronic pill cap monitoring, pill or applicator counts, and application insertion indicators (e.g., mucin test). Each of these methods has strengths and limitations, thereby precluding any of them from serving as a universal "gold standard."

This lack of a gold standard to measure product adherence has challenged the microbicide field, and measurement has typically relied on self-report, which suffers from several biases, including recall and social desirability.^[7, 8] Over-reporting of product use using self-reported measures is notorious, and prevents accurate estimation of the effectiveness or safety of an intervention.^[3, 4] Findings from prevention trials that have measured adherence using both self-report and more objective measures have highlighted discrepancies by mode of data collection.^[2, 9-12] More objective measures of adherence such as applicator stain tests have been used in some microbicide trials^[9, 10], but they have several limitations: They are assessor dependant, and will not work with all types of applicators.^[8, 12-14]

For their Phase 3 Carraguard trial, the Population Council used an applicator staining technique as a surrogate marker for use of a vaginal microbicide. Preliminary results suggest substantial over-report of product use by self-report compared with the applicator staining technique.^[6] The test involves spraying a dye on all used applicators and then rinsing. If mucin is present, the dye "sticks" and is visible as a color changes. As mentioned above, these applicator assays are also time-consuming to process and difficult to reproduce on various applicator types.^[13, 14]

Medication Event Monitoring System (MEMS) caps, an electronic measure of pill bottle opening events, has been successfully used in HIV treatment adherence research and programs for several years, and more recently in an oral PrEP trial (J. Baeten, personal communication). In fact, use of MEMS to monitor HIV treatment adherence has become widespread^[15-17]. In one study, treatment adherence was measured through self-report compared to MEMS in different time increments (3 day, 7 day and 1 month)^[16]. Findings indicated that self-report often resulted in inflated levels of adherence compared to MEMS, which consistently provided more conservative adherence levels over all time periods. Finally, a recent pilot in Uganda^[15] conducted a HIV treatment adherence comparison through MEMS, Wisepill, unannounced home visits and self-report. The results revealed that adherence levels as measured by MEMS as well as Wisepill were lower than similar data from other studies as well as lower than levels

from unannounced pill counts and self-report. In the absence of a gold standard for adherence measurement, MEMS and Wisepill are making gains at determining more accurate levels of adherence. However, in the context of HIV *prevention* adherence, these findings are only directly applicable to tablet adherence and thus still leaves a gap in *vaginal* gel adherence monitoring.

2.4 Wisepill/Wisebag Technology

Wisebag™ (Wisepill Technologies Adherence Management Solutions, South Africa) is a portable, lunch-bag size container, which can contain approximately 30 individually wrapped gel applicators or more, closes with a zipper, and has a self-contained battery-operated electronic device that includes a chip which provides an electronic signal each time an opening event occurs, and counts and records any opening events, as well as a daily control signal ('heart beat') to signify proper battery functioning. Wisebag event monitoring system can be set-up such that all data are stored in the device until the information is downloaded at the clinic at follow-up visits (offline modality) or, each time an event occurs, a signal is sent to the central management system in real-time through a wireless system (online modality). Through this latter modality, it is possible to monitor adherence on an ongoing, 'real time' basis. The real time data capture and monitoring, although more expensive, allows up to the minute insight on patterns of use and non-use as well as the ability, where appropriate, to follow up with participants when non-adherent.

In recent HIV treatment studies, as described above, the Wisepill, a similar device using wireless technology to monitor tablet use, has allowed assessment of tablet-taking opening events in real time, and in combination with cell-phone reminders.^[15] In another recent study, Wisebag was piloted among 10 participants in the CAPRISA 004 trial, and this was the first application of such a technology to the microbicide context^[11]. Another pilot study currently being conducted in Uganda among 50 caretaker/infant pairs is using Wisebag for pediatric liquid HIV treatment in Uganda (Jessica Haberer, personal communication).

Like Wisepill and MEMS caps, the Wisebag electronic device monitors each opening event of the bag, and provides a date and time stamp of when these occurred. This non-invasive indirect objective approach to monitor adherence, has thus been adapted to monitor gel applicator use.

Potential Use of Wisebag in VOICE: For women in the VOICE vaginal groups, use of the Wisebag would provide an objective measure of adherence that does not rely on participant self-report. A benefit of an electronic event-based monitoring system (as opposed to a low-tech, cross-sectional or serial cross-sectional approach such as unannounced product counts through home visits), is that it generates precise and detailed information on date and time of each event, allowing the research team to examine patterns of product use, product "holidays" etc. in addition to overall product adherence level. As described above, the technology was originally designed to serve two functions: a wireless opening-event monitoring system and an adherence intervention tool. The latter function, used in the 2 initial pilot studies from CAPRISA and in Uganda^[11, 15], uses a wireless cell phone technology to send a signal to a server when the bags are opened and send a real-time reminder to participants if events are not recorded within an expected timeframe. Additionally, the online functionality provides daily data on women, even if they forget to bring back their Wisebag at the next study visit. Given the wireless reporting capability of Wisebag, site staff will not be affected. Nevertheless, a simpler, cheaper version of the device is currently being developed for "offline" event monitoring (all opening signal events would be stored on the device's electronic chip and downloaded on a local server at study visits), providing only the assessment component (similar to a MEMS cap) which is the

functionality needed in VOICE. Furthermore, because of the relatively high cost of the current “active device” Wisebag (approximately \$200/bag), the Wisepill company can produce a “dummy” Wisebag which is identical looking, but has no recording system inside the device, in order to provide similar looking bags to all vaginal group women at a VOICE site, while collecting data only on a smaller subset.

In this Wisebag Pilot Study, we will test several of its new functionalities that will determine whether and how to scale up its implementation as part of a larger VOICE ancillary study on objective measures of product use. The new features tested in this pilot study will include: a) use of the “offline” monitoring functionality, b) use of a “dummy” Wisebag in a blinded fashion and c) monitoring of **daily** product use among ~ 50 South African women at a site determined by the EC, in a population similar to that enrolled in VOICE, using study stickers stored in the Wisebag.

2.5 Wisebag Pilot Study

Wisebag Pretest Phase

Wisebag will first go through a pretest phase in the US and at a selected study site, with members of the research team, prior to implantation of the Wisebag pilot study. The pretest activities will include:

- Pre-testing the offline functionality and performance of Wisebag in a “controlled” setting;
- Adapt an algorithm for identifying “curiosity events” (i.e. openings without taking any products);
- Monitor the temperature level inside the Wisebag under different ambient temperature conditions anticipated at the study site;
- Develop and pretest with staff the educational materials and instruction sheets, to ensure it is suitable for use in sub-Saharan Africa.

Wisebag Pilot Study

The overall goal of this pilot study is to determine if Wisebag is suitable for use in sub-Saharan Africa and to assess its utility in providing adherence monitoring data among women who present and screen for participation in a HIV prevention trial. Findings from this Wisebag pilot study will help determine the feasibility of including Wisebag in the final design of a larger VOICE ancillary study of objective measures of adherence. Considerations for using an electronic events monitoring systems (EMS) for the vaginal group in VOICE include:

- a) the current absence of any validated biomarkers as surrogates of vaginal gel adherence;
- b) the provision of a noninvasive indirect objective measure of applicator use that can accurately measure opening events from an applicator storage bag, and;
- c) the potential relative logistical simplicity of deploying this monitoring tool at a subset of VOICE sites.

This new technology may provide critically needed information to VOICE investigators in order to understand pattern of use and adherence levels of the vaginal gel among VOICE vaginal group participants.

In summary, this Wisebag pilot is a randomized pilot study (1:2:2 ratio) assessing three Wisebag functionalities (‘dummy’, online and offline), described herein. Approximately 50 HIV-uninfected women, who screen out of VOICE for administrative, clinical or laboratory reasons,

will be enrolled at one or more sites in sub-Saharan Africa, as designated by the MTN EC Committee.

2.6 Study Hypotheses and Rationale for Study Design

2.6.1 Study Hypothesis

This is primarily an exploratory descriptive study that is not designed to test a hypothesis. However, the objectives of the study are based on the assumption that the “active” Wisebags will successfully and accurately record opening events, and will be acceptable for use by women in the study, and that women will not be able to distinguish between an active and dummy Wisebag.

2.6.2 Rationale for Study Design

The proposed Wisebag pilot study is a critical step to informing the development of a larger ancillary study for VOICE to objectively measure study product adherence. It is widely accepted that self-reporting of adherence yields inaccurate results, most often inflation, of product use. Adherence, however, is one of the most important components of testing whether or not a study product is effective. Wisebag, an opening event-monitoring bag, is a promising technology that could provide objective measures of the days and times that women may retrieve gel applicators for use. However, the functionality of Wisebag when used daily and in “offline” mode has never been tested, and requires piloting prior to larger-scale deployment in VOICE.

3 OBJECTIVES

3.1 Primary Objectives

- To compare the on-site technical performance of the “offline” and “online” functionalities of Wisebag
- To assess the success of attempted blinding of the “dummy” vs. active (“online” or “offline”) Wisebag
- To measure the concordance between Wisebag opening-event data (both “online” and “offline”) and self-reported data.
- To explore the feasibility and acceptability of Wisebag use by participants

3.2 Secondary Objective

- To assess the appropriateness of educational materials/instruction sheets for Wisebag use

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-003-P01 is a three-arm, randomized, placebo-controlled, double-blinded pilot study of Wisebag for monitoring daily product use. The study is double-blinded with respect to participants and investigators, (but not for pharmacy and information technology (IT) staff who will manage the download of the electronic data and the battery charging of Wisebag devices). Approximately 50 participants will be randomized to the 3 study arms in a 1:2:2 ratio. The 3 groups will be “dummy” Wisebag (n~10) “Online device” Wisebag (n~20), or “Offline device” Wisebag (n~20).

There will be two study visits: an enrollment visit and one follow-up/exit visit, two weeks after enrollment. During study participation, participants will be asked to open their assigned Wisebag at approximately the same specified time daily, to peel off one sticker from a set of study stickers inside the bag, and place the sticker on the appropriate day of the week on a study provided diary card. After two weeks of daily openings, participants will be asked to return to the study clinic for an exit visit with their Wisebag and diary card.

4.2 Summary of Major Endpoints

Primary Endpoints:

- **Technical Performance**
 - Staff-reported and participant-reported technical and user-related problems with device and bag; diary card and signal data from device (“heart beat” and participant-initiated opening-events)
- **Ability to Identify Randomization Arm**
 - Participants’ self-evaluation of their arm assignment and their ability to detect (at study exit) whether a bag is an active or non-active bag
- **Concordance with Self-Report**
 - Opening-event data (downloaded from device at the clinic or sent wireless to server) compared with self-reported diary card and questionnaire data
- **Feasibility and acceptability**
 - Participant attitudes and experiences with Wisebag assessed through questionnaire and open-ended interview data at study exit

Secondary Endpoint:

- Appropriateness of educational materials will be assessed through questionnaire and open-ended interview data at study exit.

4.3 Description of Study Population

This Wisebag Pilot Study will enroll women who are not pregnant, HIV-uninfected, who have screened out of VOICE for administrative or other clinical and/or laboratory reasons, and meet the eligibility criteria outlined in Section 5. Furthermore, HIV-positive women will not be invited

for participation because this small pilot study is unable to provide the clinical care or psychological support services that these participants may require, particularly if they are newly diagnosed.

4.4 Time to Complete Accrual

The accrual period is targeted over approximately 8 weeks.

4.5 Study Groups:

The three study groups are as follows:

- "Dummy" or placebo Wisebag group: this group will receive a Wisebag which looks and feels identical to an active-device Wisebag, but has no battery or electronic recording system inside the device.
- "Online device" Wisebag: Active-device Wisebag with wireless component and SIM card for sending in real-time all opening events to a central server, in addition to a battery.
- "Offline device" Wisebag: Active-device Wisebag without the wireless component and the SIM card, and with battery and electronic recording system to store all opening events, which are then downloaded to a server at the clinic site.

4.6 Expected Duration of Participation

Once enrolled, each participant is expected to complete approximately 2 weeks (14 days \pm 3 days) on the study.

4.7 Sites

The study site(s) will be located in sub-Saharan Africa and will be selected by the MTN Executive Committee. The site(s) will be selected based on participation in VOICE as well as capacity.

5 STUDY POPULATION

5.1 Selection of the Study Population and Recruitment

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be utilized to ensure the appropriate selection of study participants.

5.2 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

5.3 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.

6 STUDY PRODUCT

The Wisebag pilot study will not involve the administration of any study product. In lieu of study products, participants will be provided with peel-off stickers that will be dispensed in the Wisebag.

6.1 Supply and Dispensation of Wisebag

All three types of Wisebag containers will be manufactured and supplied by Wisepill Technologies. Wisebags and study stickers will be dispensed only to enrolled participants, following Informed Consent and randomization. Each participant will receive one type of Wisebag, based on the randomization scheme. Dispensing will take place on the day of enrollment.

7 STUDY PROCEDURES

Additional information on visit-specific study procedures are presented in this section. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-003-P01 SSP Manual located at <http://www.mtnstopshiv.org>.

7.1 Screening and Enrollment

The Screening and Enrollment Visit for the Wisebag pilot should take place within approximately 4 weeks of the last VOICE Screening Visit; however participants may be enrolled up to 90 days after the date of the last VOICE Screening Visit. Screening for all data collection activities will include oral or written confirmation that participants meet the inclusion and exclusion criteria. Study staff will create checklists to ensure this is consistently documented.

Table 1: Screening and Enrollment

Screening and Enrollment	
Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> • Obtain informed consent • Confirm eligibility • Obtain locator information • Randomization • Schedule next (exit) visit • Provide counseling regarding protocol adherence • Provide reimbursement for study visit
Behavioral	<ul style="list-style-type: none"> • Conduct demographic and brief behavioral assessment • Dispense (2) weekly diary cards as well as the Wisebag along with instructions on use. • Practice opening/closing the bag and placing a study sticker on their diary card

7.2 Exit Visit: End of Week 2

Visit window at target exit visit date: The target visit exit date will be 2 weeks (14 days) from the enrolment date, with an allowable visit window of plus or minus 3 days. Participants who present late for their exit visit (Day 18 or later) will complete study procedures, as long as the study is still in the accrual phase. Otherwise, the participant will be classified as lost to follow up if they missed the exit visit window and there were 3 unsuccessful contact attempts.

Table 2: Exit Visit: End of Week 2

Week 3	
Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> • Collect Wisebag from participant. • Download data from the 2 week period from all “active” Wisebags • Provide reimbursement for study visit • Debrief on the full purpose of the research
Behavioral	<ul style="list-style-type: none"> • Conduct behavioral and acceptability assessment • Collect and review diary card • Semi-structured brief qualitative interview • Perceived Wisebag product

7.3 Interim Visits:

Interim visits may be performed at any time from enrollment to Day 10 for the reasons listed below. Interim visits after Day 10 (and before Day 14) will be in the Exit visit window and an Exit visit will be conducted in lieu of an interim visit. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit.

- For Wisebag use or data collection related reasons, e.g., a participant may need additional stickers, a new diary card or a replacement Wisebag because of malfunction (e.g. the zipper is broken), loss or theft.
- In response to social harm or safety concerns. Although this is not expected to happen, given the minimal risk associated with this study, participants will be told to come to the study in case such an unexpected event happens. In such occasion, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical or psychological care as required.
- For other reasons at participant request.

7.4 Behavioral Evaluations

Using electronic monitoring event opening signals, diary cards and/or interview-administered questionnaires, the following behaviors will be assessed:

- Adherence to daily opening events of the Wisebag
- Technical problems and user related issues with Wisebag, including ease/difficulty of use, storage, curiosity events (by self or others), disclosure/secretcy, sharing or theft of Wisebag or stickers, etc.
- Use of Wisebag for non-study purposes (e.g. to store food, personal items etc.)
- Acceptability of use of Wisebag

To ensure that study participants understand how to use the Wisebag and stickers, and how to complete the daily diary card on their own, study staff will guide each participant through a practice session at the enrolment visit.

7.5 Blinding Evaluations

At the exit visit, women will be asked by an interviewer if they believe they were assigned to a dummy or an active device Wisebag. Following completion of the behavioral assessments, each participant will be shown two demonstration Wisebags, one dummy and one active, and will ask to indicate to the interviewer which one she believes is the active and which one she believes is the dummy. Data will be recorded on an appropriate CRF.

8 ASSESSMENT OF SAFETY

The Wisebag pilot study will involve minimum risk: it does not involve ingesting or topically applying a study product and does not involve any clinical, laboratory or other procedures associated with risk to participants. Therefore, few safety concerns are expected as a result of study participation. The study site IoR is responsible for continuous monitoring of all study participants and for alerting the protocol team if unexpected concerns arise. Study sites will have written procedures for ensuring prompt reporting to the Institutional Review Board (IRB)/Ethics Committees (EC), of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database.

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. Since the safety risks are minimal in

this pilot study, if any such unexpected concerns arise, the team will notify an appropriate on-site staff member (Site Clinician, Counselor, Nurse) affiliated with the CRS for follow-up.

The Manual for Expedited Reporting of Adverse Events to Division of AIDS (DAIDS) will not be used for this study for the following reasons: 1) this study does not involve a study drug and is non-invasive; 2) adverse events are not primary or secondary objectives of the study. Untoward clinical or medical occurrences reported by study participants to have been experienced during study participation will be recorded in participant file notes.

8.2 Social Harms Reporting

Social harms 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. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the DAIDS MO and responsible site IRBs according to their individual requirements.

9 CLINICAL MANAGEMENT

There are no additional clinical management considerations for participants enrolled in the Wisebag pilot. Participants who express concerns with social, psychological or clinical issues will be referred for appropriate care to services available at the CRS, or at nearby partnering facilities.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

The Wisebag pilot study is an exploratory study using quantitative and qualitative data collection methods. It involves electronic event monitoring signal data, sent over wireless phone or directly downloaded from the Wisebag devices onto a server, self-collected diary data, and interviewer collected survey data, and qualitative open-ended textual data.

10.2 Study Endpoints

The main outcomes of interest in the Wisebag pilot will be 1) technical and user-related performance of the Wisebag in the online modality versus the offline modality 2) success of attempted blinding, 3) signal accuracy of the events monitoring in the online modality versus the offline modality as compared to the diaries provided by participants, and 4) participant attitudes and experiences with Wisebag.

10.3 Primary Study Hypotheses

This is primarily an exploratory descriptive study that is not designed to test a hypothesis. However, the objectives of the study are based on the assumption that the "active" Wisebags will successfully and accurately record opening events, and will be acceptable for use by

women in the study, and that women will not be able to distinguish between an active and dummy Wisebag.

10.4 Number of Participants

The approximate sample size per site is estimated in Table 3.

Table 3: Approximate Number of Participants per Group

Device Group	Number of Participants
Dummy	10
Online	20
Offline	20
TOTAL	50

10.5 Data, Study Monitoring and Analysis

10.5.1 Study Monitoring Committee (SMC)

This is a brief pilot study, and no SMC review will be performed for this study.

10.5.2 Data Analysis

Performance endpoint

Performance will be assessed by comparing the number of failures (e.g., difficulties downloading stored data or receiving wireless data, battery- or signal-failures) experienced in each of the active-device groups. Questionnaire data reporting participants' user-related problems with the bag, device and/or battery will be tabulated overall and by randomization assignment. As indicated by the distribution of data, count data may be recoded and analyzed as categorical data. Count data will be compared using Poisson regression while categorical data will be compared using Chi-square tests. In cases of skewed data, alternative regression models may be implemented as appropriate.

Ability to Identify Randomization Arm

To assess blinding, the proportion of participants who are able to accurately identify whether they were randomized to the "dummy" or active-device groups will be reported. The proportion of participants who are able to indicate whether a demonstration bag is "dummy" or active (note that offline and online devices are identical, aside from the SIM card inside the online device), upon visual inspection, will also be reported. A summary statistic, such as the Cohen's kappa coefficient, will be used to summarize a) the level of agreement between the participant's response and the true group assignment and b) the level of agreement between the participant's response and the true bag type.

Concordance endpoint

Concordance between signal data and diary data will be summarized for participants assigned to the active device groups, and analysis will include the following: the proportion of participants whose number of events per signal data equals, exceeds, or is lower than the number of events per diary data. No formal testing will be performed on this endpoint.

Feasibility and acceptability endpoint

Feasibility and acceptability data collected at study exit by questionnaires will be summarized overall and by randomization group. No formal testing will be performed on this endpoint. Open-ended interview data will be tabulated, thematically coded and summarized by randomization group.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by RTI International, who will manage all data for the study. Data capturing of the electronic signal data from Wisebag will be transmitted to a server maintained at Wisepill Technologies, headquartered in Cape Town, and sent weekly to RTI. CRF data will be double-entered at the clinic site and transmitted to RTI via a secure FTP server on a weekly basis. RTI will generate weekly quality control reports and queries for verification and resolution. As part of the study activation process, the study site must identify all CRFs to be used as source documents. A convention for file naming will be developed, and all data will be labeled according to this process. All files sent electronically will be password-protected. RTI will save all versions of all data files on a secure, password-protected server.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. (<http://rsc.tech-res.com/policiesandregulations/>)

For this Wisebag pilot study, source documentation will include recruitment logs, records of attendance, visit checklists, CRFs, diary data, locator forms, interview data and participant file notes. Essential documentation for the study also includes all versions of the protocol, informed consent forms, operating procedures and key communication with the protocol team. In accordance with U.S regulations, each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. Thereafter, instructions for record storage will be provided by DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

11.3 Quality Control (QC) and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies. (<http://rsc.tech-res.com/policiesandregulations/>)

12 CLINICAL SITE MONITORING

RTI International and/or FHI staff will review study records during the course of the study, however no formal clinical monitoring will be conducted.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval. The IoR will permit audits by the NIH or any of their appointed agents, local authorities, site IRBs/ECs, representatives of the MTN, and OHRP.

13.1 Institutional Review Boards/Ethics Committees

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent form, and study-related documents (such as participation education and recruitment materials) are reviewed by an IRB/EC responsible for oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/ECs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs/ECs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office in accordance with the most current DAIDS policies at the time of registration.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent form (ICF) *will not* be reviewed or approved by the DAIDS PRO, and the site will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

13.3 Study Coordination

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS Medical Officer. Study implementation will also be guided by a common SSP manual that provides further instructions and operational guidance on conducting study procedures and associated data processing. Standardized study-specific training will be provided to all sites by RTI, or other designated members of the Protocol Team.

13.4 Risk Benefit Statement

13.4.1 Risks

Participation in research includes the risks of loss of confidentiality and discomfort with the personal nature of questions, although no information on sexual or other private behaviors will be asked to participants in this study. 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 that social harms may result. For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. For example, information learned in this study may contribute to the development of better ways to conduct HIV prevention studies. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to enrollment. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

The Sample Informed Consent does not fully disclose the purpose of the study to participants, in particular participants are not told of the second primary objective to assess the success of the attempted blinding of the “dummy” vs. active Wisebag. **Disclosure of this objective may alter participants behavior toward the Wisebag (i.e., repeated openings of the bag or unintentional damage to the bag may occur because participants are curious about whether they can detect an active Wisebag).** The research could not practicably be carried out if this objective was disclosed to participants as behavior may be modified.

At the end of the study, participants will be notified of the full purpose of the study, including the ability of participants to detect a “dummy” vs. active Wisebag.

Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (<http://rsc.tech-res.com/policiesandregulations/>). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

13.6 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Study staff
- Site IRBs/ECs
- Representatives of the US OHRP, NIH, and/or contractors of the NIH, and other local US regulatory authorities, and representatives of the MTN

13.7 Special Populations

13.7.1 Pregnant Women

Women who are pregnant cannot enroll in MTN-003-P01, in an effort to match Wisebag study participants to that of VOICE.

13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets “Justifications for Exclusion” criteria for younger children as set forth by the NIH. This study does not plan to enroll children under 18 years old.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort.

13.9 Study Discontinuation

This study may be discontinued at any time by National Institute of Allergy and Infectious Diseases (NIAID), the MTN, the Office for Human Research Protections (OHRP), other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, and NIMH for review prior to submission.

APPENDIX I: Sample Informed Consent Document

SAMPLE INFORMED CONSENT FORM DIVISION OF AIDS, NIAID, NIH

MTN-003-P01

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

Version 1.0
April 15, 2011

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: Wisebag Pilot Study

INFORMED CONSENT

You are being asked to volunteer for the research study named above. This study is for women who have already participated in screening for the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, but who have not enrolled in the VOICE study.

YOUR PARTICIPATION IS VOLUNTARY

Before you decide whether to be in the Wisebag Pilot Study, we would like to explain the purpose of the pilot study, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the pilot study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the pilot study, it is important to know the following:

- If you do not want to, you do not have to join this study
- You may decide to withdraw from the study at anytime
- Some people may not be able to join the research study because of information found out during the screening and enrollment process

PURPOSE OF THE STUDY

The main purpose of the Wisebag Pilot Study is to determine whether the Wisebag, which is a lunchbag-style bag with a zipper, can correctly measure use of a product stored inside the bag, by recording each time the bag is opened to take a product out. We also want to know about your opinion of the Wisebag, and about your experiences using it. The [local authority] has permitted the pilot study to be conducted. The United States National Institutes of Health is funding this pilot study.

Approximately 50 participants will be invited to join the pilot study at this site [insert study site]. The whole pilot study will take about 10 weeks to finish. If you agree to participate, you will take

part in the pilot study for two weeks and have a total of two scheduled visits. Results collected from participants in this study may be used to help researchers develop other studies similar to VOICE, where product use is measured with the Wisebag.

STUDY GROUPS

There are three study groups. If you are confirmed to be eligible and decide to take part in the study, you will be placed in one of the three study groups. Your group will be chosen “by lot” [or other equivalent local term, for example, like flipping a coin or throwing dice] to be in one of these groups. You will not know which group you have been assigned to, nor will the study investigators. You cannot choose your group, and the study staff cannot choose your group for you.

The three study groups are:

- “Dummy” or placebo Wisebag group: this group will receive a Wisebag which looks and feels identical to an active-device Wisebag, but has no battery or electronic recording system inside the device.
- “Online device” Wisebag: Active-device Wisebag with an electronic recording system and a wireless component and SIM card for sending in real-time all opening events to a central computer server, in addition to a battery.
- “Offline device” Wisebag: Active-device Wisebag with an electronic recording system, but without the wireless component, and all opening events are then downloaded to a computer server at the clinic site.

STUDY PROCEDURES

If you decide to join the Wisebag Pilot Study, your visit will start after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- A research study staff member will ask you some basic questions about yourself and your background. You will be shown the Wisebag, with a set of study stickers which will be stored inside the Wisebag, and a study diary card, and be instructed on how to use the study materials.
- You will be asked to remove a sticker from your Wisebag every day for 2 weeks and stick it to your diary card.
- After two weeks you will return to the clinic. You will discuss with study staff about your use of the Wisebag and the stickers. You will be asked a series of questions about your attitudes towards the Wisebag and your experiences using it.

RISKS AND/OR DISCOMFORTS

During the interview we may ask you some questions that may cause you to feel embarrassed or uncomfortable. You can choose not to answer questions in the interview at any time. It is also possible that people or family members may find out that you are participating in this study and as a result, they may ask questions about the Wisebag, treat you unfairly, and you may encounter problems in being accepted by your family and/or community.

NEW INFORMATION

You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

BENEFITS

There are no direct benefits in this pilot study. However, the information that you provide may help health professionals develop better ways to measure whether women are able to use products such as vaginal gels for HIV prevention studies.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT

You may be removed from this pilot study without your consent for the following reasons:

- The pilot study is stopped or canceled
- The study staff feels that staying in the pilot study would be harmful to you
- Other administrative reasons

ALTERNATIVES TO PARTICIPATION

There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

COSTS TO YOU

There is no cost to you for being in this pilot study.

REIMBURSEMENT

[Sites to insert information about local reimbursement:]

You will receive [\$xx] for your time, effort, and travel for your Wisebag Pilot Study visits.

CONFIDENTIALITY

We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this pilot study will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- *[insert names of applicable Institutional Review Boards/Ethics Committees]*
- *[insert applicable local authorities, e.g., Ministry of Health, medicine control authority]*
- Representatives of the US Federal Government, including the US Office for Human Research Protections (OHRP), National Institutes of Health (NIH), and/or contractors of the NIH, and other local and US regulatory authorities

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, you should contact *[insert name of the investigator or other study staff]* at *[insert telephone number and/or physical address]*.

If you have questions about your rights as a research participant, you should contact *[insert name or title of person on the IRB/EC or other organization appropriate for the site]* at *[insert telephone number and/or physical address of above]*.

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or community advisory board (CAB) member [staff will decide which] at [insert telephone number and/or physical address].

SIGNATURES

[Insert signature blocks as required by the local IRB/EC:] If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature or Mark	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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Witness Name	Witness Signature	Date
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