

Section 4. Informed Consent

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4. Introduction

This section provides information on informed consent procedures for MTN-043. The study protocol includes one informed consent form (ICF) for covering both the mother and infant for screening, enrollment, off-site visits and long-term Storage. This section contains general and MTN-043 specific information and instructions for providing informed consent. In addition, detailed guidance is provided for the standardized approach to the infant and mother informed consenting process that must be followed at all sites.

4.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses a willingness to participate in research, after having been informed of all aspects of the research that are relevant to the decision. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. 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* as well as the DAIDS Policy on *Enrolling Children (Including adolescents) in Clinical Research: Protocol Document Requirements* and DAIDS Policy on *Enrolling Children (Including adolescents) in Clinical Research: Clinical Research Site Requirements* for further guidance on the informed consent process and documentation requirements.

Written informed consent will be obtained from mother study participants per site IRB/EC requirements for her and her breastfed infant to enroll prior to any procedures done at the Screening Visit.

- Sites may be required to obtain consent for the infant from both parents/guardians of the infant based the IRB/IEC's policies or their MTN-043 determination of the DAIDS risk/benefit designation for studies involving children (HHS regulations 45 CFR 46.404, 46.405, or 46.406 or the FDA regulations at 21 CFR 50.51, 50.52, or 50.53).

- If a site is required by its IRB/IEC to obtain signatures from both parents/guardians, only one is needed if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Details on the availability of the second parent/guardian, if needed, should be documented in chart notes.
- If two parents/guardians must consent, this can be done separately or together and they can sign the same or different forms. The site process for this should be detailed in the site Informed Consent (IC) SOP and in accordance with IRB/EC 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 by delegation of all study staff involved in the informed consent process, to deliver all required information to potential study participants and their parent/guardians.

It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the potential study participant
- 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

Per protocol, an illiterate mother can consent for her and her infant to enroll in MTN-043, providing the mother is otherwise willing and eligible, and if independent consent is ensured. If a participant is illiterate, an impartial witness should also be present for the informed consent process.

For participants who do not provide consent for themselves and their infant, no procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

4.2 Informed Consent SOP

As a condition of study activation, each study site must establish an SOP for obtaining informed consent from the potential participant for herself and infant. It is recommended that the SOP contain the following elements:

- 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
- If required by IRB/EC, procedures for obtaining permission from second parent, understanding and determining reasonable availability of second parent, including the procedures for determining if the second parent is reasonably available to provide permission
- Should the mother no longer be living, procedures for confirming guardianship of an infant, and reconsenting of the guardian before continued infant participation
- Storage locations for blank ICFs
- Storage locations for completed ICFs
- Procedures (e.g., color-coding) to ensure that the different study ICFs and related forms are easily distinguished and used appropriately, if applicable
- Procedures for implementing a change in the versions of the ICFs used
- Staff responsibilities for all the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

At each site, the informed consent process will be conducted per site informed consent SOPs. Additional details related to key steps in the process are provided in the remainder of this section.

4.3 Informed Consent for Screening and Enrollment

For MTN-043, the Mother and Infant Informed Consent Form (ICF) for screening, enrollment, off-site visits and long-term specimen storage is obtained at one time point at Screening. Some sites may conduct a separate consent at Enrollment, as per IRB/EC requirements and specified in their Informed Consent SOP. See section 5.4 for more guidance on conducting enrollment IC at the Enrollment Visit.

For this study, mothers are selected to participate in in-depth interviews (IDI) after enrollment and, therefore, consent for their possible participation is imbedded within the main consent. No additional signatures are needed for this component of the study unless required by the IRB/IEC.

Regardless of when written consent is obtained, informed consent is an ongoing process that continues throughout the study follow-up period through open dialog between study staff and the participant.

4.4 Informed Consent for Off-site Visits and Specimen Storage

Included in the ICF is a consent for off-site visits in which enrolled study participants are asked to provide informed consent for visits that may take place outside of the research clinic. Participants may choose not to be visited off-site or withdraw their consent for off-site visits at any time and still remain in the study. See SSP Section 5.5.4 for more information on conducting off-site visits.

Participant informed consent for future long-term storage and testing of breastmilk, blood specimens, and/or vaginal fluids for mother participants, and blood for infants, and related health information collected during the study is optional. The mother may choose to not have the specimens stored for future research testing for her an/or her infant and both may still enroll/remain in the study. For participants who do not consent to long-term specimen storage and testing, specimens collected and stored on-site per protocol will be retained until the study is completed and all protocol-specified testing has been done. Thereafter, any remaining specimens collected from these participants will be destroyed.

Some sites may choose to separate consent for off-site visits and/or specimen storage into stand-alone ICFs from the main ICF, per IRB/EC requirements or site preference. Regardless of whether the off-site visits and/or specimen storage ICF is a stand-alone form or included as part of the main ICF, these components should be conducted at the same visit as the main ICF, or together with the Enrollment ICF, if screening and enrollment consent are separated as well.

4.5 Site Specific Informed Consent Forms

Sites are responsible for adapting the Sample ICF provided in the MTN-043 study protocol as needed for local use. Local adaptation may include reformatting the ICFs in accordance with local IRB/EC requirements, as well as translating the forms into applicable participant languages. Sites are responsible for following the procedures in the MTN Manual of Operational Procedures (MOP) Section 9 and the DAIDS protocol registration requirements when adapting and translating site-specific ICFs. Unless waived by the IRB/EC, all adapted ICFs must still contain the nine required elements of informed consent as defined in 45 CFR 46.116. All ICFs (English, translated, and back-translations) must be reviewed and approved by MTN LOC (FHI 360) prior to IRB/EC submission. After ethics approval, ICFs must be submitted to the DAIDS PRO prior to their initial use.

Each site is responsible for preparing bulk supplies of their approved ICFs and for only using the currently approved versions of the ICFs during the study. It is recommended that sites consider the use of color-coding or other techniques to ensure that the various study ICFs are easily distinguished and used appropriately. A strong system for tracking version control and approvals of ICFs is also recommended and should include, at a minimum, the version number and date of the ICF as well as the implementation dates (start and end) when that version was in use. If additional guidance on version control tracking is needed, sites are encouraged to ask their FHI 360 CRM for assistance.

Upon receiving final IRB/EC and any other applicable regulatory approval(s) for an amendment to the ICFs, sites should implement the ICFs immediately and submit updated versions to DAIDS PRO per the timelines outlined in the protocol registration manual.

4.6 Informed Consent Support Materials

4.6.1 Fact Sheets and Study Education Slides

Fact sheets and Study Education Slides have been developed for MTN-043 and are available on the MTN-043 web page (<http://www.mtnstopshiv.org/node/6826>) for use with participants, partners, and community members, as study staff deem appropriate. These documents include information on the B-PROTECTED study, the dapivirine vaginal ring and the oral Truvada. Materials used for participant education in the consent process should be translated into local languages as appropriate and IRB/EC approved before use. Sites are encouraged to use these resources in whatever ways they find most useful. For example, different presentations can be assembled from this 'master slide bank' to cover various topics with different audiences. Another way to use is to print the B-PROTECTED Study Overview and General Information about Participation in Research and used as a tabletop IC flipchart. The study education slides also have talking points (for staff reference) that include additional details related to each topic presented. These materials can be used during the informed consent process, or any other time throughout the study once they are approved for use.

4.6.2 Other Informed Consent Visual Aids

Use of visual aids, in addition to the fact sheets and slides, is encouraged throughout the informed consent process to facilitate participant comprehension. Each site should determine the most appropriate visual aids for its study population and ensure that a "kit" containing each of these aids is available in each room where informed consent discussions take place. Sample study products and supplemental study illustrations have been provided to each site to use as visual aids. In addition to the visual aids decided upon at each site, it may be helpful to point out such things as a locked file cabinet, a referral clinic across the way, or a calendar on the wall. It may not be necessary to use each visual aid with each participant. Study staff should use their best judgment of each participant's information needs and how best to address those needs. Sites are encouraged to have the following items available in the clinic for demonstrations with participants:

- Calendar
- Male and female condoms
- Sample vaginal ring and packaging
- Sample Truvada tablets and packaging
- Urine specimen cup
- Blood collection tubes
- Vaginal swabs
- 4 L jug (to demonstrate the total blood volume in the human body)
- Vaginal and/or pelvic model or illustrations, including anatomy of a pregnant women
- Speculum
- Manual breast pump
- Randomization explanation visual aids (e.g., sack or box containing two items of different colors)

When using vaginal and pelvic models, remember that participants may not be familiar with such models. Introduce the models in a sensitive manner and use information, rapport, and humor to help make the participant feel comfortable with the models. If using a pelvic model to demonstrate ring placement, it may be necessary to first orient the participant to the model and the anatomical parts shown. Point out that the vaginal opening starts at the outside edge of the plastic model and that the model is a smaller scale than a women's anatomy (in the case of shown the model and demo VR side-by-side).

Regardless of use of the vaginal and pelvic models, study staff who take part in informed consent discussions should be prepared to demonstrate the various insertion positions and "mime" the insertion of the ring.

This study may be the first time mothers are exposed to a manual breast pump to assist with expressing milk, needed for sample collection. Although, using the pump is optional and mothers may choose to hand-express, the IC discussion is a good opportunity to introduce them to the pump. Similar to the pelvic model, the pump should be introduced in a sensitive manner and staff will want to explain how the pump works including 'miming' the action, and explain its benefits compared to hand-expression.

4.7 Comprehension Assessment

Study staff are responsible for determining whether each potential participant understands all information provided to them to ensure they can make an informed decision about study participation. This assessment of informed consent comprehension administered to the mother and she must not be asked to agree to take part in the study, or sign either ICF, until she fully understands the study.

It is expected that study staff administering the ICFs and informed consent assessments will be sufficiently knowledgeable about MTN-043 to make good judgments about potential participants' comprehension of the required information. Study staff should ask questions that indicate if the mother understand significant points of the study. If the mother does not mention one or more of the main points, study staff should follow-up with another open-ended question to elicit a response about that point. Study staff should use an Informed Consent (IC) comprehension assessment form to assist with this assessment. A sample IC comprehension assessment form with open ended questions is available on the MTN-043 website under Study Implementation Materials. All comprehension assessment forms used should be submitted to local IRB/ECs for approval prior to use.

4.7.1 Administration of the IC Comprehension Assessment

The comprehension assessment must be administered to each potential participant, after she have completed the informed consent discussions with site staff as described above but before she is asked to sign the ICF. The comprehension assessment should not be presented to participants as a "test," but rather as a way of assuring that study staff have fulfilled their responsibility to provide all information needed for the participant to make an informed decision about enrolling in the study. If any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

The IC comprehension assessment form is considered a source document that should be completed, handled, and retained in the participant's study chart like any other source document. After administering the assessment, study staff should carefully review the assessment form to verify that all required points have been satisfactorily addressed by the participant, and that this is adequately documented. Consideration should be given to having two study staff members complete this verification because failure to document comprehension of all required points before proceeding with study procedures will be considered an informed consent process protocol deviation.

Comments may be recorded in a designated area on the form (and on the back of the form if additional space is needed) or on an informed consent coversheet; however, this is not required. All required points must be satisfactorily addressed by the participant, before proceeding to the final informed consent decision and signing of the ICF.

After the informed consent process is completed, the outcome of the process should be recorded directly on the comprehension assessment form (or in a chart note) and the staff member who completed the form should ensure his/her signature is recorded in the space provided. Detailed information for how comprehension will be assessed must be specified in the site IC SOP.

After comprehension assessment but prior to the mother signing the ICF, sites should confirm the MTN-043/MTN-043 Study Enrollment Decision Tool has been completed, which may have been done during pre-screening or will be done at this point in the IC process, based on site's preferred practice. If the exercise was done during pre-screening, the mother's original worksheet should be reviewed updated with any significant changes since the participant first completed the exercise. Should the mother decide she does not want to join the study or needs more time to consider her decision, the IC process should be stopped with the outcome of the IC session clearly documented. Any worksheets completed during pre-screening or IC should be stored securely at the study site and incorporated into the PTID binders (or name file, depending on site preference) for all enrolled participants. See SSP Section 3.1 (Accrual and Retention) for further instruction.

4.8 Documenting the Informed Consent Process

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, sites should comply with the guidance provided in the DAIDS SOP on Source Documentation. Complete all signature and date lines on the ICF in dark ink. 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).


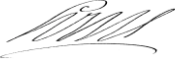

If a participant signs her name in a form that deviates from the specifications listed above (e.g. she uses initials for both her first and last names, or signs only using her first name), document in the research record that the name/initials/mark as written deviates from the DAIDS policy but represents her signature as she wrote it. Sites may choose to use a standard memo to document these deviations, provided the memo has been approved for use by the site's OCSO representative.

On the ICF, in addition to completing signature requirements as described above, the participant must indicate on the form whether they agree to the storage and future testing of biological specimens, and off-site visits, if applicable (unless the site has chosen to create stand-alone ICFs for these topics, in which case the form should be completed separately). The participant may decline this option and may herself and infant still enroll in MTN-043.

If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the ICF to attest that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the participant, in the participant's language of fluency, and that informed consent was freely given by the participant and/or parent/guardian(s). The participant's printed name, signature, and signature date lines on the ICF should be completed as described and illustrated in Figure 4-1. Following these procedures fulfills the protocol requirement for obtaining written informed consent from all study participants.

Figure 4-1: Informed Consent Form Signature Lines for Illiterate Participants and/or Parent/guardians

- *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 and date of informed consent or assent below the “participant's printed name” and “date” line, respectively, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.*
- *The participant should add her fingerprint or make her mark above the “participant's signature” line.*
- *The witness will print, sign, and date in the section designated for “Witness”*

SIGNATURES		
Participant Name	Participant Signature	Date
Mary Phiri		25 NOV 2019
<i>Participant name and date written by Martha Moore. MM 25 NOV 09</i>		
Martha Moore		25 NOV 2019
Name of Staff Person Conducting Consent Discussion	Study Staff Signature	Date
Debra Ross		25 NOV 2019
Witness Name	Witness Signature	Date

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met each time an ICF is signed. In order to also meet some of the suggestions listed in the DAIDS policy, site staff are strongly encouraged to use an Informed Consent (IC) Coversheet. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for source documentation for MTN-043 and should use the coversheet consistently to document informed consent processes with all participants. A sample IC coversheet template is available on the MTN-043 web page. The first section of the coversheet should be completed at the start of the informed consent session. The remainder should be completed at the end of the informed consent session. If a site chooses not to utilize an IC coversheet, all elements of each informed consent process must be documented in a signed and dated chart note as well as detailed in the site Informed Consent SOP.

It is essential that all informed consent documentation (e.g., the ICFs, the coversheet, IC comprehension assessment form) record that informed consent from the participant was obtained before any study procedures were conducted.

Regulations require that participants be given a signed copy of the ICF. If a participant opts not to receive a copy, document this on the coversheet or chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

Additionally, once IC is obtained, the Informed Consent CRF must be completed for each the mother and infant participant. Completion of these CRFs serves as a check that no study procedures were conducted for before adequate IC was obtained for the respective mother or infant. The Informed Consent CRF is located in each participant's Screening Folder in Medidata Rave.

4.9 Reconsenting Requirements

There may be times when site staff have to reconsent participants, due to minor modifications, Letter of Amendments (LoAs), or protocol amendments. Reconsenting must also be done for infants if the mother is no longer the legal guardian, due to death or relinquishment as caretaker, at any point during the infant's study follow-up as required by site IRBs/ECs and per site SOPs.

When reconsenting of participants is required due to minor modifications or information contained in an LoA, the consenting procedures may be abbreviated. The staff member conducting the informed consent session should review the changes made to the ICF with the participant but does not need to read or review the entire ICF again.

Similar procedures should be conducted for participants who change their mind about participating in the optional components of the MTN-043 study, namely long-term specimen storage. Using the most current version of the appropriate ICF, review the information pertinent to the participant's decision (e.g. If a participant who previously declined long-term specimen storage later indicates that she would like to agree to storage, review the information on long-term specimen storage contained in the ICF). If the current ICF differs in any way from the version the participant originally signed, these changes should be reviewed with her as well. Note that any time reconsenting procedures are being conducted using an ICF that contains signature blocks for specimen storage, all items should be reviewed and re-signed based on the participant's current preferences. The signature lines at the end of the consent for participant, staff, and witness must also be completed in full.

Although an IC comprehension assessment form does not need to be completed in the circumstances described above, participant understanding should be assessed and all questions should be answered prior to signing the new ICF(s). Once comprehension has been evaluated and ensured, documentation of informed consent should be conducted per SSP section 4.6. The participant should be offered an updated, signed copy of the ICF to take home.

If reconsenting of participants is required due to a protocol version change, a complete review of the ICF must be conducted. When changes to the ICF have been made as a result of protocol version changes, a new IC comprehension assessment form must be completed. Documentation of informed consent should be conducted per SSP section 4.6 and participants should be offered an updated, signed copy of the ICF to take home.

For infants that require reconsenting by another parent/guardian, a complete informed consent process must be conducted and documented as outlined above. A full review of the ICF must occur and a new IC comprehension assessment completed, and the participant should be offered a signed copy of the ICF.

4.10 Informed Consent Process for Participants Who Resume Participation After Terminating Early

In the event a participant is terminated from the study early or withdraws consent and decides to rejoin the study, she/he must undergo a re-consenting process which includes a complete review of the ICF to restart participation in the study regardless of any previously documented written informed consent.

For participants resuming study participation, written informed consent from the participant, must be obtained prior to any study procedures, including clinical procedures, and prior to any procedures to determine product use eligibility (see SSP section 5). Participants rejoining the study should also undergo informed consent procedures for long-term specimen storage and testing and off-site visits, however they may decline participation in these optional components and still re-join the study.

The documentation requirements for the new written informed consent documents are the same as the requirements for participants joining the study for the first time (See SSP section 4.6).

4.11 Ongoing Assessment of Participant Comprehension

For enrolled mothers, informed consent also must be understood as an ongoing process that continues throughout the study follow-up period. Periodically, at study visits, staff should assess participants' comprehension using a discussion style similar to the screening assessment. The key elements of informed consent also should be reviewed at study follow-up visits. Sites may choose to review key elements of informed consent with individual participants, or in group sessions. Elements of informed consent can be reviewed at every visit, or periodically, as per site SOPs. Reviewing key elements of informed consent during follow-up visits may focus on the remainder of study participation. Should gaps in participant understanding about the study be identified, staff should

provide counseling or additional education as needed to clarify potential misunderstandings, especially those that impact participant safety.

Ongoing assessments will help to identify aspects of the informed consent process that are, and are not, optimally effective for study participants. The assessments also may identify rumors or misperceptions about the study that require a response by the Protocol Team, either across sites or on a site-by-site basis. This discussion should be noted in the participant's chart note for that visit date.