Section 1. Introduction

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This section specifies the sources of procedural information available to study staff, the responsibilities of Investigators of Record (IoR), and the process by which each site will be approved to initiate implementation of MTN-042 (DELIVER). Also included is information on required submissions to Institutional Review Boards and/or Ethics Committees (IRBs/ECs).

1.1 Current Protocol Specifications

The table below documents the history of the MTN-042 protocol, along with any Clarification Memos, Letter of Amendments, and Full Amendments, if applicable, all of which are considered Essential Documents. A copy of each document should be available to staff and a copy should be maintained in site essential files. It is not necessary for sites to file copies of the below-mentioned documents in the SSP manual itself.

Document	Date
MTN-042 Protocol, Version 1.0	16 April 2019
Letter of Amendment #01	17 December 2019
Letter of Amendment #02	09 June 2020
Clarification Memo #1	17 August 2020
Clarification Memo #2	11 December 2020

Sites are expected to operate under the protocol version and associated Clarification Memos and/or Letters of Amendment that are currently approved by the local institutional review board/ethics committee (IRB/EC). To ensure this section reflects the current specifications of the protocol, upon issuance of any future protocol Clarification Memo (CM), Letter of Amendment (LoA), or Protocol Amendment, specifications listed above will be updated accordingly. These documents are available on the MTN-042 webpage (https://mtnstopshiv.org/research/studies/mtn-042)**.** Further information on the content and required handling procedures for these documents is available in the Microbicide Trials Network (MTN) Manual of Operational Procedures (MOP), which is located on the MTN webpage (http://www.mtnstopshiv.org) under ‘resources’.

In order to respond to the ongoing COVID-19 pandemic, sites may need to rapidly implement practices and procedures that are not in line with the protocol or SSP Manual (e.g. modified visit procedures in the interest of staff/participant safety, conduct of remote visits/telemedicine, etc.). Sites should communicate about this with the study management team and document contingency plans related to COVID-19 proactively to the best of their ability (and retrospectively, as needed). For each visit where modifications due to COVID-19 considerations result in a deviation from the protocol, a single protocol deviation should be reported with “COVID-19” written in the description of the deviation, followed by what was modified during the visit. As required, sites should communicate contingency plans and protocol deviations related to COVID-19 to IRBs/ECs/regulatory bodies.

Additional guidance regarding study implementation during COVID-19 is available in LoA #1 and the COVID-19 MTN-042 Contingency Plan, dated 26 May 2020.

1.2 Sources of Procedural Information

The Study Specific Procedures (SSP) Manual serves to supplement the protocol. It does not replace or substitute the protocol or its contents. In the event this manual is inconsistent with the information and guidance provided in the protocol, the specifications in the protocol will take precedence. In the event study implementation questions are not adequately addressed by the study protocol or this manual or if any inconsistencies between the two documents are identified, please notify the MTN-042 Study Management Team at mtn042mgmt@mtnstopshiv.org.

Electronic versions of the SSP manual, the MTN-042 protocol, and all other study implementation tools are available on the DELIVER website: https://mtnstopshiv.org/research/studies/mtn-042

Note that all study documents can be searched electronically for key words and phrases using the "find" feature (CTRL+F). Sites are encouraged to become familiar with electronic searching to make specific guidance easier to locate in the study documents.

Please contact the MTN-042 Management Team using the following alias list for general questions on protocol implementation or study procedures, including clinical, lab, product, behavioral assessments, and/or CRF/data procedures: mtn042mgmt@mtnstopshiv.org

Current contact details for all MTN-042 colleagues and collaborators, as well as study alias lists, can be found in the MTN directory at: http://www.mtnstopshiv.org/people/directory

1.3 Investigator Responsibilities

MTN-042 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonisation Consolidated Guidance for Good Clinical Practice (GCP). In addition, MTN-042 must be implemented in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all such regulations, policies, and guidelines should be maintained in on-site essential document files.

The Division of AIDS (DAIDS) policy *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* and the Site Clinical Operations and Research Essentials (SCORE) Manual are useful for interpreting and operationalizing the applicable regulations and guidelines in accordance with DAIDS expectations. DAIDS policies and the SCORE Manual can be accessed at https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures.

The IoR must sign both an Investigator Signature Form (protocol signature page) and a U.S. Food and Drug Administration (FDA) Form 1572 to formally indicate his/her agreement to conduct MTN-042 in accordance with the study protocol, applicable US regulations, and MTN policies. A copy of the protocol signature page (PSP) can be found in the MTN-042 protocol. A PSP must be signed by the IoR and uploaded to DPRS for all initial protocol versions, all full protocol amendments, and all letters of amendment (LOAs). The site will keep copies of the protocol signature page(s) and 1572(s) on-site with their essential documents (See SSP Section 2).

The obligations and responsibilities assumed by the IoR when signing the FDA Form 1572 and PSP are listed on the forms themselves, also outlined in 3.4.6 of the MTN MOP. Updates to the 1572 should be submitted to the DAIDS Protocol Registration Office (PRO), as well as to MTN Regulatory Department (mtnregulatory@mtnstopshiv.org) with a short summary of any updates that were made.

All IoRs are required to complete IoR training every 3 years, offered by MTN Leadership and Operations Center (LOC) (http://www.mtnstopshiv.org/node/4536), prior to study initiation or prior to assuming responsibility for an ongoing study; documentation of this training should be filed in site essential documents. The IoR may delegate his/her obligations and responsibilities for conducting MTN-042 to other study staff members; however, delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of

IoR responsibilities must be formally documented on the site's Delegation of Duties (DoD) Log throughout study implementation. The DAIDS SCORE Manual outlines guidance on completion of DoD logs, as well as the DAIDS DoD Log Template (https://www.niaid.nih.gov/research/daids-score-manual)

A staff member may not fulfill the IoR role in the IoR's absence. Full responsibility and authority over the protocol by anyone other than the IoR may only take place if an additional 1572 is completed and submitted to DAIDS. If there is a change in IoR, a revised Form FDA 1572 and a new PSP should be submitted to the DAIDS PRO. Sites should follow guidance in the current Protocol Registration Manual regarding procedures for a change in IoR with the DAIDS PRO. Incoming investigators should also complete IoR Training if needed, as well as update the DoD per DAIDS Delegation of Duties Log Instructions. In addition, they may need to complete an electronic financial disclosure via the HANC system; investigators who need to complete a HANC financial disclosure will be contacted by MTN Regulatory with additional guidance. Outgoing investigators should complete the end of study financial disclosure paper form and enter an 'end date' on the DoD log. Additionally, sites should notify FHI 360, MTN Regulatory, and their OCSO Program Officer (PO) of the change and complete any other documentation requested.

It is critical that staff members have documentation of training and relevant qualifications prior to being delegated trial responsibilities. Training records should be well organized and consistent, and include versions, date of training, and full titles of documents being trained on. Staff names on training logs should match those on the DoD Log and other study records. The DAIDS Score Manual has sample training logs with all required elements for reference, one that is trainee specific and one that is training topic specific.

1.4 Sub-Investigators Listed on the FDA Form 1572

Generally, staff who are regularly involved in the source documentation of safety data or are delegated to perform critical trial related procedures should also be included on the FDA Form 1572. Such components may include, but are not limited to, adverse event (AE) assessment, collecting participant safety information, confirming participant eligibility, conducting informed consent procedures, or dispensing study product. See also the FDA guidance document "Frequently Asked Questions – Statement of Investigator (Form FDA 1572)" for information about sub-investigators. Ultimately, inclusion as a sub-investigator on the 1572 is dependent on the responsibilities that have been delegated to staff and is at the discretion of the IoR. Note that full responsibility and authority over the protocol by anyone other than the IoR may only take place if an additional 1572 is completed and submitted to DAIDS.

1.5 Study Activation Process

Prior to undertaking any study procedures, the study site must obtain approval to conduct MTN-042 from all required regulatory authorities and IRBs/ECs. The site must also complete protocol registration procedures with the DAIDS Regulatory Support Center (RSC) and study activation procedures with DAIDS and the MTN LOC, MTN Statistical Data Management Center (SDMC), and MTN Laboratory Center (LC). Detailed information on the requirements of these pre-implementation steps can be found in the MTN MOP, Section 11. The MTN LOC will issue a Site-Specific Study Activation Notice when all study activation requirements have been met. No protocol-specified study procedures may be undertaken prior to issuance of the Site-Specific Study Activation Notice. Note that a separate activation is not required for each cohort of the study, but sites will be asked to complete cohort-specific readiness checklists for each cohort after Cohort 1.

1.6 IRB/EC Submissions

Figures 1-1 and 1-2 list IRB/EC submission and approval requirements pertinent to MTN-042. Figure 1-1 lists requirements that must be met prior to study initiation. Figure 1-2 lists requirements that must be met during and following study implementation.

The study site is encouraged to request that their IRB/ECs acknowledge receipt for all documents submitted to them, and to request that the IRBs/ECs note both the effective date and the expiry dates of all approvals. Procedures for IRB/EC communication must be documented in site-specific SOPs. Documentation of all correspondence to and from all responsible IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. Documentation of all IRB/EC approvals may also be requested by the MTN LOC.

Figure 1-1: IRB/EC Submissions Required Prior to Initiation of MTN-042

Documents to be submitted to IRB/EC	Written Approval Required*
MTN-042 Protocol, Version 1.0	Yes
Informed consent forms: • Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 1 • Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 2 • Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 3 • Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 4 • Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography) – INFANT	Yes
Investigator of Record current CV	No
Dapivirine Vaginal Ring Investigator's Brochure, Current Version	No
Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) Package Insert, Current Version	No
Participant pre-screening, recruitment plans and materials (prior to use)	Yes
Other written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC such as SOPs, CRFs, and interview questionnaires.	If required by IRB/EC

*Denotes approvals required by US regulations and GCP guidelines.

Figure 1-2: IRB/EC Submissions Required During and Following Conduct of MTN-042

Document to be submitted to IRB/EC	Written Approval Required*
Study status reports/updates (at least annually)	Yes
Protocol clarification memos (submission encouraged but not required by DAIDS)	No
Protocol amendments (including full amendments (to a new protocol version) and letters of amendment)	Yes
Amended informed consent forms (including forms that are amended due to protocol amendments as well as forms that are amended for site-specific reasons, e.g., to update participant incentive information or to update site contact information)	Yes
Dapivirine Vaginal Ring Investigator's Brochure updates	No
Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) Package Insert updates	No
New information that may affect adversely the safety of study participants or the conduct of the study (e.g., IND Safety Reports)§	No
Reports of adverse events, serious adverse events, and/or events meeting criteria for expedited reporting to DAIDS (per IRB/EC requirements)	No
Protocol deviations (per IRB/EC requirements and/or as directed by DAIDS)	No
Investigator of Record current CV (if Investigator of Record changes during study)	No

Updated/additional participant recruitment plans and materials (prior to use)	Yes
Updated/additional written information for study participants (prior to use)	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC
Final study report/closure report	No

*Denotes approvals required by US regulations and GCP guidelines.
§Safety information will be distributed by the DAIDS RSC or the MTN LOC. All distributions will include instructions related to IRB/EC submission of the safety information.