10 PROTOCOL DEVELOPMENT

Microbicide Trials Network (MTN) studies are developed through multidisciplinary collaboration among MTN investigators, the Leadership and Operations Center (LOC) (University of Pittsburgh [Pitt]) and FHI 360), the Statistical and Data Management Center (SDMC), the Laboratory Center (LC), the Biomedical Science Working Group (BSWG), the Behavioral Research Working Group (BRWG), and the Community Working Group (CWG); and, as applicable, with non-MTN investigators, researchers, and experts who bring complementary expertise.

10.1 Protocol Concept Submission and Approval Process

The MTN accepts concepts for new protocols from all interested parties in the belief that the best clinical research program is one that is both enabling and receptive to new ideas and capable of maintaining an efficient timeline-driven protocol development and implementation process. The MTN Executive Committee (EC) reviews all study concepts that are submitted for consideration.

Importantly, many study concepts are submitted by researchers or organizations outside of the Network; most frequently, by product developers who hold the Investigational New Drug (IND) applications and are seeking to collect specific safety, pharmacokinetic, and/or efficacy data that has been requested by the U.S. Food and Drug Administration (FDA). Protocol concepts may also be submitted by MTN investigators, including members of MTN's BSWG, BRWG or CWG, LC or LOC representatives, and MTN investigators affiliated with clinical research sites (CRS).

If the proposed study fits into the mission of the MTN, the concept is routed to the MTN Working Groups for review and comment and then to the MTN EC for review. Approval by the MTN EC is based on a tally of ballots.

10.2 Protocol Development and Approval Process

10.2.1 Initial Protocol Development Process

Once the MTN EC approves a concept for development, the protocol is drafted and reviewed through an iterative process led by the Protocol Chair(s) and the LOC (Pitt) Protocol Specialist (PS) assigned to the protocol (as described in the remainder of this section and as shown in Table 10.1). To initiate the protocol development process, the LOC (Pitt) PS first receives the concept proposal and/or works with the MTN Principal Investigators (Co-PIs) or designee to clarify the study objectives. The study design is then established with input from the SDMC prior to generating a protocol draft. Next, the LOC (Pitt) PS, Protocol Chair(s), and, when possible, the Protocol Statistician create a first draft protocol (usually labeled Version 0.1) with input from other team members, as needed. For example, the SDMC Clinical Data Manager (CDM), the MTN Protocol Pharmacist, LOC (FHI 360) Clinical Research Manager (CRM), LC, Protocol Physician, Protocol Safety Physicians, BSWG and BRWG**.**

Once the protocol is drafted, it is sent to the protocol team in preparation for the Protocol Development Meeting (PDM), and protocol development proceeds according to the review and approval steps described in Section 10.2.2. The PS is responsible for all document submissions and for maintaining documentation of all review findings and the protocol team's responses to these findings. Additional information on the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) review and approval processes for protocols may be obtained at https://www.niaid.nih.gov/sites/default/files/protocolpolicy.pdf.

Table 10.1 Protocol Development Steps

A.	The protocol concept is reviewed and approved by the MTN Working Groups and the MTN EC.
B.	The LOC (Pitt) PS works with the concept author, MTN PI/Co-PI (or designee) and SDMC to clarify the study objectives and design.
C.	The LOC (Pitt) PS emails SDMC, LC, BRWG, BSWG, CWG, FHI 360, and others as needed for information as to who will serve on the Protocol Team.
D.	The PS, Protocol Chair(s) and Protocol Statistician create a draft protocol (including sample informed consent forms [ICF], when possible) with input from the MTN Protocol Pharmacist, SDMC PM, LOC (FHI 360) CRM, LC, Protocol Physicians, Protocol Safety Physicians, BSWG and BRWG.
E.	At least four weeks before the PDM, the protocol is sent to the protocol team for review.
F.	Two weeks before the PDM, comments are due to the LOC (Pitt) PS.
G.	One week before the PDM, a revised protocol is sent to the protocol team.
H.	At the PDM, protocol team members provide feedback on the revised draft.
I.	Approximately two weeks after the PDM, the revised draft is sent to the protocol team for review and final comments.
J.	Prior to the DAIDS Prevention Science Review Committee (PSRC) review, a teleconference is held to review the Sample Informed Consent (SIC). Typically, members of the community, LOC (FHI 360), site representatives, the Protocol Chair(s) and the LOC (Pitt) PS are included in this call. The SIC is then revised based on this feedback.
K.	The protocol is prepared for submission to the DAIDS PSRC based on final comments received from the team.
L.	The PS submits the protocol electronically to the DAIDS Medical Officer (MO).
M.	The MO reviews the protocol for completeness and forwards it to the PSRC Administrator at the DAIDS Regulatory Support Center (RSC).
N.	The PSRC Review Meeting is held.
O.	The PSRC review discussion is summarized in a consensus review memo that is provided to the protocol team.

P.	The protocol team provides a written response to PSRC (if required) and/or a revised draft protocol, optimally within 15 working days following receipt of comments.
Q.	After notification of the PSRC's approval or documentation from the DAIDS MO of anticipated PSRC approval, the PS prepares a revised protocol version (labeled "Regulatory Review Version") and submits the protocol electronically to the DAIDS RSC.
R.	The DAIDS RSC reviews the protocol and sample ICFs in detail and forwards the protocol with comments to the DAIDS Regulatory Affairs Branch (RAB), DAIDS Human Subjects Protection Branch (HSPB) and DAIDS Safety and Pharmacovigilance Team (SPT). The DAIDS RAB, DAIDS HSPB and DAIDS SPT review the protocol and DAIDS RSC review findings and add any further comments, as necessary. The DAIDS RSC incorporates all DAIDS comments into a review summary document and transmits it electronically to the PS.
S.	The protocol team addresses the Regulatory Review findings in a revised protocol version, optimally within 15 working days. This revised version (labeled "Medical Officer Review Version") is submitted electronically to the DAIDS RSC for MO review.
T.	The DAIDS RSC reviews the protocol to ensure that all Regulatory Review findings have been satisfactorily addressed and then forwards the protocol to the DAIDS MO for review.
U.	The MO reviews the protocol to confirm an acceptable response to the Regulatory Review and completes a final quality assurance check of the protocol.
V.	The DAIDS RSC incorporates all MO comments into a review summary and transmits it electronically to the PS.
W.	The protocol team addresses MO review findings in a revised protocol version (labeled "Version 1.0") and submits it electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB.
X	Once sign-off is obtained, the DAIDS RSC informs the PS electronically and files the final protocol (when applicable). The DAIDS RSC also prepares the protocol for submission to the FDA.
Y	Upon notification of RAB Chief sign-off, the PS posts the final protocol on the MTN website and subsequently notifies the protocol team and all participating study sites that the protocol has been finalized and can be accessed from the MTN website.

*Some protocol development steps may be modified for non-IND studies whose objectives are behavioral

Note: DAIDS Clinical Study Information Office (CSIO@tech-res.com) and MTN Regulatory Group (mtnregulatory@mtnstopshiv.org) must be cc'd on all electronic communications between LOC (Pitt) and DAIDS that involve official MTN protocol submissions (that is, PRSC, RSC, DAIDS MO and RAB submissions, as well as all modifications).

In the event that the study is being conducted under an IND held by an organization other than DAIDS, the protocol will be sent directly to the IND holder and site(s) are designated within the NIAID Clinical Research Management System (CRMS) by a member of MTN LOC (Pitt). In addition, the study may need to be added to ClinicalTrials.gov.

10.2.2 Protocol Team Review Process

10.2.2.1 Protocol Development Meeting

A major step of the protocol review process is the PDM, which serves to ensure that MTN protocols are of high scientific quality, consistent and standardized relative to other MTN protocols and contain the most accurate data and study procedures. Meetings ideally include the following attendees or their designated representatives:

- IND-holder representative(s), if applicable
- Product development collaborator(s)
- DAIDS MO
- DAIDS Protocol Pharmacist, if applicable
- MTN BRWG Chair or member
- MTN BSWG Chair or member
- LOC (FHI 360) Community Engagement Program Team representative
- LOC (FHI 360) CRM
- Community Working Group representative
- MTN Director of Pharmacy Affairs, if applicable

- LOC (Pitt) Protocol Development Manager
- LOC (Pitt) PS
- LOC (Pitt) Director of Operations
- LOC (Pitt) Regulatory representative
- LOC (Pitt) Safety Physician
- LC PI or representative, if applicable
- LC Pharmacology Core representative, if applicable
- LC Virology Core representative, if applicable
- MTN Co-PIs
- SDMC CDM
- SDMC Protocol Statistician
- U.S. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), U.S. National Institute of Mental Health (NIMH) or other MO, if applicable
- Protocol Chair(s)
- Site investigators and coordinators

Approximately four weeks prior to the PDM, the LOC (Pitt) PS distributes the draft protocol (typically draft Version 0.1) for review and comment by the protocol team. Team members submit written comments to the PS approximately two weeks following receipt of the protocol. The PS and Protocol Chair(s) review the comments and determine which comments can be incorporated immediately into the revised draft protocol and which comments require further discussion during the PDM. Approximately one week after the deadline for receipt of comments, the PS issues an updated draft protocol (typically labeled as draft Version 0.2) to be discussed at the PDM.

All meeting participants bring comments regarding the draft protocol to the meeting. Site investigators are responsible for providing comments based on scientific, operational and community considerations relevant to study conduct at their site. To obtain this input, they discuss and review the draft protocol with relevant site staff and community representatives prior to the meeting.

Together, the Protocol Chair(s), LOC (Pitt) Protocol Development Manager and the PS lead the team meeting and discussion of key issues to be resolved in the protocol. To the extent possible, protocol language is finalized during the meeting. The purpose of the meeting is to determine the following:

- Study research questions, objectives and endpoints are clearly stated.
- The study design is appropriate to answer the research questions.
- Study procedures are feasible and appropriate to meet the study objectives.
- Study product considerations are clearly specified.
- Major safety issues are identified and addressed.
- Major issues related to the protection of human subjects are identified and addressed.
- Potential issues related to the design of the study identified by the community are discussed.

Two weeks following the meeting, the Protocol Chair(s) and PS prepare and distribute a revised draft protocol (typically labeled as Version 0.3) reflecting the meeting discussions and outcomes. Protocol team members submit written comments to the PS within two weeks after receipt of the protocol.

Site investigators are responsible for submitting comments based on scientific, operational and community considerations relevant to study conduct at their site. After the study design and visit procedures schedule have been well defined, the PS drafts the sample ICFs. Next, the SICs are appended to the protocol and thus are included in the subsequent reviews. Site investigators are responsible for obtaining community feedback on the draft sample ICFs and key study-implementation issues should be obtained and provided to the PS at this time. The site investigators collect comments from community representatives, and the LOC (Pitt) PS convenes a call with the LOC (FHI 360)

Community Engagement Program Team and the study-specific CWG representative(s) to review and revise the draft sample ICFs. Based on feedback received from all protocol team members, the Protocol Chair(s) and PS prepare a revised draft protocol (typically labeled as Version 0.4), including sample ICFs, for submission to the DAIDS MO for review by the DAIDS PSRC. (See Section 10.2.3 and Table 10.1 for further information.)

For some studies, only one sample ICF will be needed. For others, multiple forms will be needed (for example, for screening, enrollment, storage and possible future testing of specimens). All sample forms will follow current DAIDS guidelines and will include all required elements of informed consent specified in the U.S. Code of Federal Regulations (CFR) 45 CFR 46 and 21 CFR 50, as delineated in Section 9.5 of this manual.

10.2.2.2 Community Engagement in Concept and Protocol Development

Obtaining community input is critical to the development of a successful study. To ensure that the community participates in all aspects of the research process, MTN engages community from the initial stages of protocol development through implementation and results dissemination. The timelines for concept and protocol development include appropriate time for community education and consultation at each site.

Site investigators, including Clinical Trial Unit (CTU) PIs, CRS and/or study-specific Investigators of Record will involve the community and share the available study concepts with their community members as early in the development process as possible. The appropriate time for sharing a study idea with the community may vary from site to site, depending on a number of factors, including the level of site development, the level of community organization or cultural factors.

After a site has been identified for a particular concept, the site should pair a community representative with a staff member who is involved with protocol development at the site (such as an investigator or study coordinator). Ideally, the community representative must be someone who is not employed by the site and he or she should have two roles: to represent the study community and to understand the concerns of the research communities. Typically, a CRS will obtain community input through its Community Advisory Board (CAB); although a CRS may refer to this structure by any locally chosen name or establish an alternative structure. The need for support and mentoring may differ, depending on community members' individual needs and understanding of the research process.

The MTN Co-PIs are responsible for ensuring that the Network adheres to community participation in all aspects of the research process. It is the responsibility of the protocol team to:

- Demonstrate respect for input from community representatives and take them into consideration when developing concept plans and protocols
- Share information, questions and concerns with CAB members; the LOC (FHI 360) Community Engagement Program Team; and the MTN CWG

It is the responsibility of the CTU PI to set aside sufficient funds in the site's annual budget requests to support community representatives' participation in protocol development (for example, attendance at face-to-face protocol team meetings or participation in conference calls).

Note: See Section 7.0 of this manual for additional details regarding roles and responsibility for community involvement.

10.2.2.3 Behavioral Research Working Group Participation in Concept and Protocol Development

During the protocol development phase, the assigned BRWG member(s) will draft for inclusion in the protocol: (i) a description of the behavioral aims and accompanying assessments and method(s) of data

collection, (ii) an outline of the behavioral study procedures by visit and (iii) a plan for analyzing the behavioral outcomes to be discussed at the PDM. The behavioral assessments will be developed in parallel fashion to the protocol and will be distributed by the BRWG to the protocol team for review. Members of the protocol implementation team and SDMC are consulted, as needed. (See Section 11.12 of this manual for further information about the behavioral assessment development process.)

10.2.2.4 Biomedical Science Working Group Participation in Concept and Protocol Development

During the protocol development phase, the assigned BSWG member(s) will draft a description of the biomedical science objectives and endpoints to be presented at the PDM. This description and a sample collection with the planned assays will be included in the protocol. (See Section 4.2.1 of this manual for further information about the BSWG.)

10.2.3 Protocol Review and Approval by DAIDS

10.2.3.1 DAIDS Prevention Sciences Review Committee Review of Protocol

On the first and third Tuesday of each month, the PSRC reviews protocols for which DAIDS provides funding. More information on the PSRC can be found in Section 1 of this manual. The PS submits the protocol electronically to the DAIDS MO at least 10 working days prior to the scheduled PSRC meeting. The MO reviews the protocol for completeness (usually within one day) and forwards it to the PSRC Administrator at the DAIDS RSC at least 10 working days prior to the PSRC meeting.

PSRC review discussions are summarized in a consensus-review memo that is provided to the protocol team within 10 working days after the review. The memo identifies major and minor review findings, along with one of the following three review outcomes:

- Approved without revision (minor revisions may be suggested.)
- Approved contingent upon addressing major concerns (major concerns must be addressed in writing and receive formal approval from the DAIDS MO, or be returned to the PSRC for further review at the PSRC Chair's discretion.)
- Disapproved (the protocol team works with members of the MTN EC to determine the next steps. The protocol may be resubmitted to the PSRC after incorporation of revisions that address its concerns.)

If a protocol is disapproved, DAIDS will not permit expenditure of NIH funds for the proposed investigation. For protocols that are disapproved, the Protocol Chair(s) may contact the PSRC Chair to discuss possible modification. If the Protocol Chair(s) believes there is a reasonable basis for proceeding despite the PSRC's disapproval, he or she should contact the MTN EC. If the EC concurs with the Protocol Chair(s), the EC may notify the DAIDS Director and request initiation of the appeal process, which will involve an impartial third party.

Although the time required for the protocol team to respond to the PSRC review comments will vary with the magnitude and extent of the comments, teams aim to provide a written response to the PSRC (if required) and/or a revised draft protocol within 15 working days after receiving comments. This provides time for team discussion, drafting the response and the internal team's review of the response.

10.2.3.2 DAIDS Regulatory (RSC) Review of Protocol

After notification of PSRC approval or documentation from the DAIDS MO of anticipated PSRC approval, the PS prepares a revised protocol version (labeled "Regulatory Review Version") reflecting the protocol team's approved response to the PSRC review. The PS submits the protocol electronically to the DAIDS RSC for a Regulatory Review that is completed per DAIDS Standard Operating Procedures (SOP) within 10 working days of protocol receipt. During this review, the DAIDS RSC staff review the protocol and sample ICFs in detail and forward the review comments to the DAIDS RAB,

DAIDS HSPB and DAIDS SPT. Staff members from the respective DAIDS branches and teams review the protocol and DAIDS RSC review findings and may add further comments. The DAIDS RSC incorporates all comments into a review summary document and transmits the document electronically to the PS. After the PS has addressed and/or incorporated the DAIDS RSC comments, the protocol may be circulated for a final team review and approval. The protocol team addresses the Regulatory Review findings in a revised protocol version within 15 working days.

Note: If the protocol team and/or study leadership did not review the "RSC Review Version" then a review of the "Medical Officer Review Version" is mandatory, unless the study is an ancillary study and a PSRC waiver was obtained.

10.2.3.3 DAIDS Medical Officer Review of Protocol

The revised version (labeled "Medical Officer Review Version") is submitted electronically to the DAIDS RSC for the MO's review. This review is completed, per DAIDS SOP, within 10 working days of protocol receipt. Along with the protocol, the team provides a written response to the DAIDS RSC Regulatory Review. In particular, the team must provide adequate justification for any Regulatory Review comments that are not adopted. During the 10-day review period, the DAIDS RSC staff review the protocol to ensure that all Regulatory Review findings have been satisfactorily addressed.

Next, the protocol is forwarded to the DAIDS MO, who completes a final quality assurance check of the protocol on behalf of DAIDS. The DAIDS RSC incorporates all review comments into a review summary document and transmits the document electronically to the PS.

10.2.3.4 Regulatory Affairs Branch Chief Sign-off

The protocol team addresses the MO Review findings, generally within five working days of receipt of comments, in a revised protocol version (labeled "Version 1.0"), which they submit electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB. Along with the protocol, the protocol team submits any supporting documentation needed to explain its response to the MO Review. In particular, the team must provide adequate justification for any MO Review comments that are not adopted.

The RAB Chief sign-off is expected within approximately 10 working days of submission. Once sign-off is obtained, RSC informs the PS electronically and files the final protocol. When DAIDS holds the IND, RSC also prepares the protocol for submission to the FDA. In the event that DAIDS does not hold the IND, the study sponsor submits the protocol to the FDA and MTN LOC (Pitt) and/or RAB (if DAIDS holds the IND) designates site(s) within the NIAID CRMS. In addition, the study and study details are added to www.clinicaltrials.gov.

10.2.4 Distribution of Version 1.0

Upon notification of RAB Chief sign-off, the LOC (Pitt) posts the final protocol on the MTN website. The PS notifies the protocol team and all participating study sites that the protocol has been finalized and can be accessed from the MTN website. The PS notifies the LOC (FHI 360) CRM by email that the protocol has been approved and the CRM provides instructions to study sites related to seeking Drug Regulatory Authority (DRA) and Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, site-specific ICFs and other associated documents. Conduct of the study may not be initiated before IRB/IEC approval is obtained from all responsible DRAs and IRBs/IECs, the DAIDS protocol registration process is completed, all other MTN study-activation requirements are met as described in Section 11 Table 11.1 of this manual, and a site-specific and study-activation notice is issued by the LOC (FHI 360) CRM.

10.3 Protocol Modifications

DAIDS-sponsored protocols may be modified by one of three methods: (i) Clarification Memo (CM), (ii) Letter of Amendment (LoA) or (iii) Full Protocol Amendment. These three methods, which are described in the following sections, are used for both IND and non-IND protocols. The protocol team determines the method to use in conjunction with the DAIDS MO. Depending on the method used, the modification may or may not result in a change to the protocol version number, may or may not require IRB/IEC review and approval, and may or may not require protocol registration through the DAIDS RSC Protocol Registration Office (PRO). The modification also may or may not require approval by site DRAs.

As with the first final version of the protocol, the PS is responsible for developing protocol modifications in conjunction with key protocol team members. Once modifications are finalized, the PS posts copies of all protocol modification documents on the MTN website. During the time when protocol-modification documents are in development and under review, study implementation shall proceed based on the specifications of the last-approved version of the protocol. Protocol modifications specified in the modification document may be implemented only after the document is fully approved, as described below.

10.3.1 Clarification Memos

The CM is typically a short document that is prepared to provide further explanation or more detailed information related to current protocol specifications. A CM also may be used to correct minor errors in a protocol. The content of a CM should have no impact on participant safety, the risk-to-benefit ratio of study participation or the study's ICFs. If a proposed modification requires a change to the study's ICFs, a CM may not be used to incorporate the modification.

If the DAIDS MO agrees that the issue can be addressed in a CM rather than a protocol amendment, the PS drafts the CM and circulates it to the study team to solicit any additional minor protocol clarifications that should be included, such as roster changes. The DAIDS MO must review and approve CMs prior to finalization and distribution. After finalizing a CM, the PS posts the CM on the MTN website and distributes it to all protocol team members and study sites. Sites are strongly encouraged (but not required by DAIDS) to submit CMs to their IRBs/IECs.

10.3.2 Letters of Amendment

A LoA is typically a short document prepared to specify changes to a protocol that have minimal impact on participants' safety and the risk-to-benefit ratio of study participation. The letter involves specific changes to the protocol that result in the addition of new information or the deletion of incorrect or unnecessary information, and possibly minor modifications, if any, to a study's ICFs. When a LoA is prepared, any prior protocol modifications that were specified in the CM(s) may be incorporated into the LoA. The LoA is prepared according to a DAIDS template, which is available on the RSC website: http://rsc.tech-res.com/network-and-protocol-teams/protocol-development.

Site IRBs/IECs must review and approve LoAs. Most LoAs include instructions to study sites with regard to seeking IRB/IEC review and approval and recommendations for how to notify participants of the applicable changes. In some circumstances, enrolled participants may be required to re-consent. In other circumstances, protocol teams may recommend providing a letter to participants informing them of the modifications, or ask that the information be provided to the participant and noted in the case-history record. Regardless of protocol team recommendations, site IRBs/IECs may require modification of the study's ICFs and/or re-consenting of enrolled participants to reflect a LoA; in such cases, IRB/IEC requirements must be followed.

A LoA is developed by the protocol team and must go through several protocol review and approval steps (see Table 10.2). DAIDS or the study sponsor submits the finalized LoA to the FDA, if applicable. The LOC (Pitt) PS posts the LoA on the MTN website and notifies the protocol team and participating study sites that the final LoA is available online. Sites then follow instructions in the LoA with regard to seeking IRB/IEC review and approval. Modified procedures that are specified in the LoA may not be conducted at a CRS until the letter has obtained approval from all responsible IRBs/IECs. The protocol version number does not change as a result of a LoA. Each LoA must be registered through the DAIDS PRO, but sites do not need to wait for registration notification from the DAIDS PRO prior to implementing the amendment.

10.3.3 Full Protocol Amendments

Full protocol amendments are prepared by the protocol team and coordinated by the PS to incorporate significant changes (changes that are anticipated to have more than a minimal impact on participant safety and the risk-to-benefit ratio of study participation and that result in the generation of a new protocol version with a new version number). Typically, amendments also are required to incorporate a significant increase in the number of participants to be enrolled in an IND study. When amendments are prepared, any prior protocol modifications that are specified in a CM or a LoA are incorporated into the amendment.

Examples of changes requiring a full protocol amendment include the following:

- New study product(s) added to the protocol
- A new inclusion or exclusion criteria and/or the removal of a criteria (for purposes other than expediting accrual)
- Changes in risk and/or new safety information that might impact participant's willingness to take part in the trial
- A change in the study design

Protocol amendments are described in Table 10.2. Any amendment must go through several protocol review and approval steps. The DAIDS MO must determine whether the PSRC must review and approve the amendment. If so, PSRC review steps must be followed. In addition, the Regulatory Review, MO Review and RAB Chief sign-off must be completed for all amendments.

The PS posts the amendment on the MTN website and notifies the protocol team and participating study sites that the final amendment is online. Sites must then seek IRB/IEC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (as described in Section 11 of this manual) for the amended version of the protocol. Revised procedures specified in the amendment may not be conducted, and the revised site ICFs may not be used until after protocol registration approval is obtained. The IND holder (who may be DAIDS) submits amendments to the FDA, if applicable.

Participants who were enrolled in a study after approval and registration of a protocol amendment must be consented to the study using the revised ICF associated with the amended version of the protocol. The protocol team will provide guidance on whether re-consenting is required (that is, using the revised ICF associated with the amendment) for participants who were enrolled prior to approval and registration of an amendment. Regardless of protocol team recommendations, site IRBs/IECs may require re-consenting of previously enrolled participants; in such cases, IRB/IEC requirements must be followed.

Table 10.2 Requirements and Procedures for Protocol Modifications

Reviews/Approvals Required	Clarification Memo	Letter of Amendment	Protocol Amendment
DAIDS MO	Yes	Yes	Yes
DAIDS PSRC	No	No	Possibly, MO determines whether PSRC review is required
DAIDS Regulatory	MTN LOC submits as an FYI	Yes	Yes
DAIDS MO Review following Regulatory Review	No	Yes	Yes
DAIDS RAB chief sign-off following MO Review	No	Yes	Yes
Site IRBs/IECs	No, unless required by IRB/IEC (but FYI submission is recommended)	Yes. Amended procedures may not be undertaken until after IRB/IEC approval is obtained.	Yes. Amended procedures may not be undertaken until IRB/IEC approval and protocol registration.
Protocol registration	No	Yes. Protocol must be registered for informational purposes, but sites do not need to wait for notification from PRO to implement the LoA.	Yes. Amended procedures may not be undertaken until IRB/IEC approval and protocol registration approval are obtained.

Note: Modifications may or may not require approval by site Drug Regulatory Authorities (DRAs).