10. PROTOCOL DEVELOPMENT

Microbicide Trials Network (MTN) studies are developed through multidisciplinary collaboration among MTN Investigators, the MTN 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 the Network; most frequently, they are submitted by Product Developers who hold the Investigational New Drug (IND) applications and are seeking to collect specific safety, pharmacokinetic, and/or efficacy data requested by domestic and international regulatory bodies. Protocol concepts may also be submitted by MTN investigators, including members of the MTN's BSWG, BRWG or CWG, MTN LOC or LC representatives, and MTN Investigators affiliated with clinical research sites (CRSs).

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 and is documented according to the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual).

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 MTN LOC (Pitt) Protocol Writer (PW) 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 PW first receives the concept proposal and/or works with the MTN Principal Investigators (PI and Co-PI) or designee(s) to clarify the study objectives. The study design should be established (with input from the SDMC as needed) prior to generating a protocol draft. Next, the PW, 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. Other team members may include, for example, the SDMC Clinical Data Manager (CDM), the MTN Protocol Pharmacist, MTN LOC (FHI 360) Clinical Research Manager (CRM), MTN LC, Protocol Physician, Protocol Safety Physicians, BSWG, BRWG, CWG, and non-DAIDS IND-holder representatives, as applicable**.**

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 of this Manual. Representatives of non-DAIDS IND holders are on the Protocol Team and provide input throughout the protocol development process. The PW 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 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.	As needed, the PW works with the concept author(s), MTN PI/Co-PI (or designee), Protocol Chair(s) (if already selected) and/or SDMC to clarify the study objectives and design.
C.	The PW emails SDMC, LC, BRWG, BSWG, CWG, LOC (FHI 360), and others as needed for information as to who will serve on the Protocol Team.
D.	The PW and Protocol Chair(s) create a draft protocol (including sample informed consent [SIC] forms, when possible) with input from the Protocol Statistician, MTN Protocol Pharmacist, SDMC PM, LOC (FHI 360) CRM, LC, Protocol Physicians, Protocol Safety Physicians, BSWG, CWG, and BRWG.
E.	At least four weeks before the PDM, the protocol is sent to the Protocol Team for review.
F.	Two weeks prior to the PDM, comments are due to the PW.
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.	Within two weeks after the PDM, the revised draft is sent to the Protocol Team for review and comments.

J.	Prior to the DAIDS Prevention Science Review Committee (PSRC) review, a teleconference is held to review the Sample Informed Consent(s) [SIC(s)]. Typically, this call is led by the PW and includes members of the community, LOC (FHI 360), site representatives, the Protocol Chair(s), DAIDS MO, and other Protocol Team members as needed. The SIC(s) 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 PW submits the protocol electronically to the DAIDS 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, unless the DAIDS MO and RSC determine that a PSRC Review Waiver can be granted.
O.	The PSRC review discussion is summarized in a PSRC Consensus 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, if possible, within 15 business days if possible following receipt of PSRC Consensus Memo.
Q.	After notification of the PSRC's approval (or Waiver) or documentation from the DAIDS MO of anticipated PSRC approval (or Waiver), the PW prepares a revised protocol version and submits the protocol electronically to the DAIDS RSC.
R.	The DAIDS RSC reviews the protocol and SIC(s) 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 Full Regulatory Review summary document and transmits it electronically to the PW.
S.	The Protocol Team addresses the Full Regulatory Review findings in a revised protocol version, within 15 business days if possible. This revised version is submitted electronically to the DAIDS RSC for MO review. Prior to submitting the Full Regulatory Review response and/or revised protocol documents, the PW solicits signoff from key Protocol Team members.
T.	The DAIDS RSC reviews the protocol to ensure that all Full 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 Full 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 PW.
W.	The Protocol Team addresses MO review findings in a revised protocol version and submits it electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB (labeled "Version 1.0") when requested.
X	Once RAB sign-off is obtained, the DAIDS RSC informs the PW electronically and files the final protocol. If DAIDS is the IND holder for the study, DAIDS submits the protocol to FDA and sends an email notification to the MTN LOC (Pitt) that the protocol was submitted; this email serves as notification of RAB sign-off.
Y	Upon notification of RAB Chief sign-off, the PW asks the MTN webmaster to post the final protocol on the MTN website and subsequently notifies the Protocol Team (which includes all participating study sites and the IND holder) that the protocol has been finalized and can be accessed from the MTN website. If applicable, non-DAIDS IND-holder sign-off must precede protocol posting and distribution.

**Some protocol development steps may be modified for non-IND studies whose objectives are behavioral in nature, and some steps may be lengthened or shortened (or skipped altogether) depending on quality and quantity of feedback received.*

~Some protocol development steps also apply to Letters of Amendments and some to Full Protocol Amendments

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

Once RAB sign-off has been obtained by MTN LOC (Pitt), the PW emails the protocol to the Protocol Team, which includes the IND holder and all participating sites. The PW designates the participating sites within the NIAID Clinical Research Management System (CRMS), as needed. Study information may need to be added to ClinicalTrials.gov by the PW, per DAIDS policies and any relevant CTAs for the study, as described in Section 10.2.3.4.

10.2.2 Protocol Team Review Process

10.2.2.1 Protocol Development Meeting (PDM)

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), if applicable
- DAIDS MO
- DAIDS Protocol Pharmacist, if applicable
- MTN BRWG Representative - Chair or Member or designee
- MTN BSWG Representative - Chair or Member
- MTN LOC (FHI 360) Community Engagement Program Team Representative
- MTN LOC (FHI 360) CRM
- MTN CWG Representative(s)
- MTN Director of Pharmacy Affairs, if applicable
- MTN LOC (Pitt) PW
- MTN LOC (Pitt) Protocol Development and Implementation Manager (PDIM)
- MTN LOC (Pitt) Director of Clinical Trials
- MTN LOC (Pitt) Director of Operations
- MTN LOC (Pitt) Regulatory Representative
- MTN LOC (Pitt) Safety Physician
- LC PI or Representative, if applicable
- LC Pharmacology Core Representative, if applicable
- LC Virology Core Representative, if applicable
- MTN PI/Co-PI
- 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 another MO, if applicable
- Protocol Chair(s)
- Site Investigators and Coordinators

Approximately four weeks prior to the PDM, the PW distributes the draft protocol (typically Version 0.1) for review and comment by the Protocol Team. Team members submit written comments to the PW within two weeks of receipt of the protocol. The PW and Protocol Chair(s) review and adjudicate comments for immediate inclusion into the revised protocol and those requiring further discussion during the PDM. Within approximately one week prior to the PDM, the PW issues an updated draft protocol (typically Version 0.2) to be discussed at the PDM.

Meeting participants provide comments/feedback regarding the draft protocol at the PDM. 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 (e.g., site CWG Representatives and Community Advisory Board [CAB] members) prior to the meeting.

Together, the Protocol Chair(s), MTN LOC (Pitt) PDIM, and the PW lead the team discussion regarding issues pertaining to protocol content. To the extent possible, protocol language is finalized during the meeting. The purpose of the meeting is to obtain Protocol Team consensus regarding key elements of the protocol and to ensure the following:

- Study research questions, objectives and endpoints are clearly stated.
- The study design is appropriate to answer the research questions.
- The population is appropriate and inclusion/exclusion criteria are well-defined.
- 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 PW and Protocol Chair(s) prepare and distribute a revised draft protocol (typically Version 0.3) reflecting the meeting discussions and outcomes. Protocol Team members submit written comments to the PW within two weeks after receipt of the protocol.

Site Investigators are responsible for submitting any additional 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 PW drafts the sample informed consent (SIC) form(s). Site Investigators are responsible for obtaining community feedback on the draft SICs and forwarding key study-implementation issues to the PW in a timely manner. The Site Investigators collect comments from Community Representatives, and the PW convenes a call with the Protocol Team, including the study-specific CWG representative(s), to review and revise the draft SICs. Based on feedback received from all Protocol Team members, the Protocol Chair(s) and PW prepare a revised draft protocol (typically Version 0.4), including SICs (which henceforth are part of the protocol document), 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 SIC 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 9.4 of this Manual.

10.2.2.2 Community Engagement in Concept and Protocol Development

To ensure that the community participates in all aspects of the research process, MTN engages community representatives from the initial stages of protocol development through implementation and dissemination of results. The timelines for concept and protocol development includes appropriate time for community education and consultation at each site.

Site Investigators, including Clinical Trial Unit (CTU) PIs, CRS Leaders and/or study-specific Investigators of Record (IoRs) will involve their community members and share the available

study concepts and draft protocol versions with them as early in the development process as possible. During the EC review and approval of the concept, MTN CWG Representatives provide input as members of the EC.

After a site has been approved by the MTN EC to participate in a study, the site partners two community representatives with a staff member who is involved with protocol development at the site (such as an Investigator or Study Coordinator). The two community representatives are a site Community Educator (paid staff) or CAB Liaison (paid staff), and a CAB Member (volunteer/non-paid staff). Additionally, he or she should understand the concerns of the research communities. Typically, a CRS will obtain community feedback through its 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 PI/Co-PI 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 their contributions into consideration when developing concept plans and protocols
- Ensure that community representatives or the MTN LOC (FHI 360) Community Engagement Program Managers attend PDMs and are provided opportunities to ask questions and share concerns and suggestions
- Ensure community representatives are included in teleconferences to review the SIC(s)
- Share information, questions and concerns with the MTN CWG members via the MTN LOC (FHI 360) Community Engagement Program Team

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 Teleconferences).

Note: See Section 7 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 with 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 (See Section 1 of this Manual for more information on the PSRC). The PW submits the protocol (typically Version 0.4) electronically to the DAIDS MO within 10 business days (or more, at the request of the MO) 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 within 10 business days prior to the PSRC meeting.

PSRC review discussions are summarized in a Consensus Memo that is provided to the Protocol Team within ten business days. 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 successfully addressing concerns as noted in the PSRC Consensus Memo. The PW develops a written PSRC Consensus Memo Response document and an updated protocol that are submitted to the MO for review to ensure that the PSRC's concerns were addressed. The revised protocol and response documents may then 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 contacts the MTN EC. If the EC members concur with the Protocol Chair(s), the EC members may notify the DAIDS Director and request initiation of the appeal process, which will involve an impartial third party.

Although the time required to respond to the PSRC review comments will vary with the magnitude and extent of the comments, Protocol Team members provide a written response to the PSRC (if required) and/or a revised protocol (typically Version 0.5), including a summary of any additional changes made to the protocol document, within three weeks after receiving comments if possible. This provides time for team discussion, drafting the response and the team's internal 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 PW prepares a revised protocol version ("Regulatory Review Version", typically Version 0.5) reflecting the Protocol Team's approved response to the PSRC review. The PW submits the protocol electronically to the DAIDS RSC for a Full Regulatory Review (FRR) that is completed per DAIDS Standard Operating Procedures (SOP) within 10 business days of protocol receipt. During this review, the DAIDS RSC staff reviews the protocol in detail and forwards their review comments to the DAIDS Regulatory Affairs Branch (RAB), DAIDS Human Subjects Protection Branch (HSPB) and DAIDS Safety and Pharmacovigilance Team (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 an FRR summary document and transmits the document electronically to the PW. The PW addresses DAIDS RSC's FRR comments with input from Protocol Team members as needed. After the Protocol Team and/or Study Leadership completes the final review of the FRR response and revised protocol, the PW solicits sign-off from key Protocol Team members prior to submitting the two documents back to RSC. Although the time required to respond to the FRR comments will vary with the magnitude and extent of the comments, Protocol Team members address the FRR findings in a revised protocol version within three weeks if possible.

10.2.3.3 DAIDS Medical Officer Review of Protocol

Along with the protocol, the team provides a written response to the DAIDS RSC FRR. In particular, the team must provide adequate justification for any FRR comments that are not addressed in the protocol. The revised protocol version ("Medical Officer Review Version", typically Version 0.6) and FRR Response document are submitted electronically to the DAIDS RSC for the MO's review. This review is completed within 10 business days of receiving the document(s). During the ten-day review period, the DAIDS RSC staff review the protocol to ensure that all FRR findings have been satisfactorily addressed.

Next, the protocol is forwarded to the DAIDS MO, who completes a final check of the protocol on behalf of DAIDS. The DAIDS RSC incorporates all MO review comments into a review summary document and transmits the document electronically to the PW. The Protocol Team prepares a response to any MO comments generally within five business days of receipt of the comments, revising and re-submitting the protocol as needed. Once the RSC confirms that the MO has approved the protocol through circulation of the MO Sign-Off form, it can be submitted for final RAB review/signoff.

10.2.3.4 Regulatory Affairs Branch Chief Sign-off

Once requested by RSC, the PW or PDIM submits a revised protocol version (labeled "Version 1.0"), electronically to the DAIDS RSC on behalf of the Protocol Team for final review and sign-off by 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 provides and documents justification for any MO Review comments that are not adopted.

Once RAB Chief sign-off is obtained, RSC informs the PW electronically and files the final protocol. When DAIDS is the IND holder for the study, DAIDS submits the protocol to the FDA and notifies MTN LOC (Pitt) of the submission. This notification serves as the DAIDS RAB sign-off. For studies conducted under an IND not held by DAIDS, the IND holder is responsible for initiating and maintaining content on www.clinicaltrials.gov, unless that responsibility is transferred to another party via formal agreement. For non-IND studies, MTN LOC (Pitt) is responsible for these tasks.

10.2.4 Distribution of Version 1.0

Upon notification of DAIDS RAB sign-off, the MTN LOC (Pitt) Webmaster posts the final protocol on the MTN website. The PW notifies the Protocol Team, which includes the IND holder and all participating study sites that the protocol has been finalized and can be accessed from the MTN website. The PW notifies the MTN LOC (FHI 360) CRM by email that the protocol has been approved and the CRM provides instructions to study sites related to seeking all other required regulatory entity (RE) approvals of the protocol, development of site-specific ICFs, and completion of all other study activation requirements, as outlined in the study-specific activation checklist. Conduct of the study may not be initiated at a site prior to Institutional Review Board

(IRB)/Independent Ethics Committee (IEC) approval from all responsible REs, DAIDS protocol registration; site activation approval by the DAIDS Prevention Sciences Program (PSP) Clinical Microbicide Research Branch (CMRB) Chief or PSP Deputy Director, and receipt of a site-specific study-activation notice from the MTN LOC (FHI 360) CRM.

10.3 Protocol Modifications

When a Protocol Team member identifies a potential change to the protocol, the PW or PDIM will notify DAIDS and discuss how to modify the protocol to incorporate this change, or whether a clarification can be sent to the site rather than modifying the protocol. Any change to sample size or length of follow-up, for example, must be incorporated via a protocol modification. 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 (FPA) (per DAIDS Guidance "Division of Acquired Immunodeficiency Syndrome Regulatory Affairs Branch Guidance for Determining the Appropriate Use of Full Version Protocol Amendments, Letters of Amendment, and Clarification Memos during the Lifecycle of a DAIDS-Approved Protocol"). These three methods, described in the following sections, are used for both IND and non-IND protocols. The DAIDS MO determines the method to use in conjunction with DAIDS RAB. 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). Depending on local and/or country regulations, the modification also may or may not require approval by site drug regulatory agencies (DRAs). When the IND-holder for a given protocol is not DAIDS, extra steps may need to be taken to document the IND-holder's approval of protocol modifications.

As with the final version of the protocol (Version 1.0), the PW is responsible for developing protocol modifications in conjunction with key Protocol Team members as needed. Once modifications are finalized, the MTN LOC (Pitt) Webmaster 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

A CM is typically a short document 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 SICs. If a proposed modification requires a change to the study SICs, 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 an LoA or an FPA, the PW drafts the CM and circulates it to the Protocol Team to solicit any additional minor protocol clarifications that should be included, such as revisions to the protocol roster. The DAIDS MO must review and approve CMs prior to finalization and distribution; the DAIDS MO must also notify the PW of their determination of the adequacy of using a CM to address the identified issue(s). After finalizing a CM, the MTN LOC (Pitt) Webmaster posts the CM on the MTN website and the PW distributes it to the Protocol Team members and study sites. Site personnel 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 participant 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 SICs. When an LoA is prepared, a new Protocol Signature page must be included. 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 to consult with their IRBs/IECs regarding notifying participants of the applicable changes. In some circumstances, enrolled participants may need 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 the Protocol Team recommendations, site IRBs/IECs may require modification of the study's ICFs and/or re-consenting of enrolled participants to reflect an LoA; in such cases, IRB/IEC requirements must be followed.

An LoA is developed by the Protocol Team and must go through several review and approval steps (see Steps D and Q-Y in Table 10.1). During the process, the DAIDS MO and RSC notify the PW of their determination of the adequacy of using a LoA to address the identified issue(s), and documentation is maintained by the MTN LOC (Pitt) per the *MTN Good Documentation Policy* (see Section 9 of this Manual). DAIDS or the study Sponsor (for non-DAIDS-held INDs) submits the finalized LoA to the FDA, if applicable. The MTN LOC (Pitt) Webmaster posts the LoA on the MTN website; the PW notifies the Protocol Team and FHI 360 notifies the 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 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 because of an LoA. Each LoA must be registered by the sites through the DAIDS PRO, but site personnel do not need to wait for registration notification from the DAIDS PRO prior to implementing the LoA.

10.3.3 Full Protocol Amendments

FPAs are prepared by Protocol Team members and coordinated by the PW to incorporate significant changes (i.e., changes anticipated to have more than a minimal impact on participant safety and the risk-to-benefit ratio of study participation, and changes that incorporate a significant [as determined by DAIDS] increase or decrease in the number of participants to be enrolled). FPAs result in the generation of a new protocol version with a new version number. When amendments are prepared, a new Protocol Signature page must be included and any prior protocol modifications that are specified in a CM or an LoA are incorporated into the amendment.

Examples of changes requiring an FPA include the following:

- New study product(s) added to the protocol
- A new inclusion or exclusion criterion and/or the removal of a criterion (for purposes other than expediting accrual)

- Changes in risk and/or new safety information that might impact participants' willingness to take part in the trial
- A change in study design

FPAs must go through several protocol review and approval steps (see steps D and J-Y in Table 10.1). The PW contacts the DAIDS MO to ascertain 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 MTN LOC (Pitt) Webmaster posts the FPA on the MTN website; the PW notifies the Protocol Team and FHI 360 notifies the participating study sites that the final FPA is online. Site personnel must then seek IRB/IEC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (See Section 11 of this Manual) for the FPA. Revised procedures specified in the amendment may not be conducted, and the revised site ICFs may not be used, until after all applicable regulatory approvals are obtained, and if specified in the amendment, until after protocol registration notification. The IND holder (who may be DAIDS) submits amendments (both LoAs and FPAs) to the FDA, if applicable.

Participants who were enrolled in a study after approval and registration of a protocol amendment (both LoAs and FPAs) must be consented to the study using the revised ICF associated with the amended version of the protocol. For both LoAs and FPAs, the Protocol Team will provide guidance on whether re-consenting is required (that is, using the revised ICF associated with the amendment) for participants 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 Summary of Operational Requirements for Protocol Modifications

	Full Version Protocol Amendment	Letter of Amendment	Clarification Memo
IRB/IEC Approval Required	Yes	Yes	No*
Submitted to FDA (IND studies)	Yes	Yes	No
Protocol Registration Required	Yes	Yes	No
Copy Sent to Drug Company Collaborator	Yes	Yes	No
RAB Makes Final Determination	Yes	Yes	No
Change in Protocol Version Number	Yes	No	No

** DAIDS does not require IRB/IEC or other RE approval of CMs. Each site must follow the requirements of their IRB/IEC and other REs as required prior to implementation.*