10. PROTOCOL DEVELOPMENT

Microbicide Trials Network (MTN) studies have been 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) which existed prior to December 01, 2021, 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 is no longer accepting concepts for new protocols. However, concepts were previously accepted 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. Prior to December 01, 2021, the MTN Executive Committee (EC) reviewed all study concepts that were submitted for consideration.

Importantly, many study concepts were submitted by researchers or organizations outside the Network. Most frequently, they were submitted by Product Developers who held the Investigational New Drug (IND) applications and were seeking to collect specific safety, pharmacokinetic and/or efficacy data requested by domestic and international regulatory bodies. Protocol concepts were also submitted by MTN investigators, including members of MTN's BSWG, BRWG or CWG, MTN LOC or LC representatives and MTN Investigators affiliated with Clinical Research Sites (CRSs).

If the proposed study fit into the mission of MTN as determined by the Network Principal Investigator (PI), the concept was routed to the MTN Working Groups for review and comment and then to the MTN EC for review. Approval by the MTN EC was based on a tally of voting ballots and was 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 approved a concept for development, the protocol was 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 received the concept proposal and worked with the MTN Principal Investigators (PI and Co-PI) or designee(s) to clarify the study objectives. The study design would 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 created a first draft protocol (usually labeled Version 0.1) with input from other team members, as needed. Other team members may have included, 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 was drafted, it was sent to the Protocol Team in preparation for the Protocol Development Meeting (PDM), and protocol development proceeded according to the review and approval steps described in Section 10.2.2 of this Manual. Representatives of non-DAIDS IND holders were on the Protocol Team and provided input throughout the protocol development process. The PW was responsible for all document submissions and for maintaining documentation of all review comments and the Protocol Team's responses to these comments. Additional information on the DAIDS review and approval processes for protocols may be obtained at https://rsc.niaid.nih.gov/networks-protocol-teams/developing-protocols.

Table 10.1 Protocol Development Steps*

A.	The protocol concept was reviewed and approved by the MTN Working Groups and the MTN EC.
B.	As needed, the PW worked 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 emailed SDMC, LC, BRWG, BSWG, CWG, LOC (FHI 360), and others as needed for information as to who would serve on the Protocol Team.
D.	The PW emailed DAIDS Clinical Study Information Office (CSIO) to request a DAIDS protocol ID number be assigned to the approved protocol concept.
E.*	The PW and Protocol Chair(s) created a draft protocol (including sample informed consent [SIC] forms, when possible) with input from the Protocol Statistician, MTN Protocol Pharmacist, SDMC CDM, LOC (FHI 360) CRM, LC, Protocol Physicians, Protocol Safety Physicians, BSWG, CWG, and BRWG.
F.	At least four weeks before the PDM, the protocol was sent to the Protocol Team for review.
G.	Two weeks prior to the PDM, comments were due to the PW.
H.	One week before the PDM, a revised protocol was sent to the Protocol Team.

I.	At the PDM, Protocol Team members provided feedback on the revised draft.
J.	Within two weeks after the PDM, the revised draft was sent to the Protocol Team for review and comments.
K.*	Prior to the DAIDS Prevention Science Review Committee (PSRC) review, a teleconference was held to review the Sample Informed Consent(s) [SIC(s)]. Typically, this call was led by the PW and included 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) was then revised based on this feedback.
L.*	The protocol was prepared for submission to the DAIDS PSRC based on final comments received from the team and after a quality control check of the document was performed by another member of the MTN LOC (Pitt).
M.*	The PW submitted the protocol electronically to the DAIDS MO.
N.*	The MO reviewed the protocol for completeness and forwarded it to the PSRC Administrator at the DAIDS Regulatory Support Center (RSC).
O.*	The PSRC Review Meeting was held, unless the DAIDS MO and RSC determined that a PSRC Review Waiver could be granted.
P.*	The PSRC review discussion was summarized in a PSRC Consensus Memo that was provided to the Protocol Team.
Q.*	The Protocol Team provided a written response to PSRC (if required) and/or a revised draft protocol, if possible, within 15 business days following receipt of PSRC Consensus Memo.
R.*	After notification of the PSRC's approval (or Waiver) or documentation from the DAIDS MO of anticipated PSRC approval (or Waiver), the PW prepared a revised protocol version and submitted the protocol electronically to the DAIDS RSC.
S.*	The DAIDS RSC reviewed the protocol and SIC(s) in detail and forwarded 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 reviewed the protocol and DAIDS RSC review findings and added any further comments, as necessary. The DAIDS RSC incorporated all DAIDS comments into a Full Regulatory Review summary document and transmitted it electronically to the PW.
T.*	The Protocol Team addressed the Full Regulatory Review findings in a revised protocol version, within 15 business days if possible. This revised version was submitted electronically to the DAIDS RSC for MO review. Prior to submitting the Full Regulatory Review response and/or revised protocol documents, the PW solicited signoff from key Protocol Team members and a final quality control check of the documents from another member of the MTN LOC (Pitt).
U.*	The DAIDS RSC reviewed the protocol to ensure that all Full Regulatory Review findings had been satisfactorily addressed and then forwarded the protocol to the DAIDS MO for review.
V.*	The MO reviewed the protocol to confirm an acceptable response to the Full Regulatory Review and completed a final quality assurance check of the protocol.
W.*	The DAIDS RSC incorporated all MO comments (if applicable) into a review summary and transmitted it electronically to the PW.
X.*	The Protocol Team addressed MO review comments (if applicable) in a revised protocol version (labeled "Version 1.0") and submitted it electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB.
Y.*	Once RAB sign-off was obtained, the DAIDS RSC informed the PW electronically and emailed the final protocol to the PW. If DAIDS was the IND holder of the study, DAIDS submitted the protocol to FDA and sent an email notification to the MTN LOC (Pitt) that the protocol was submitted; this email served as notification of RAB sign-off.
Z.*	Upon notification of RAB Chief sign-off, the PW asked the MTN webmaster to post the final protocol on the MTN website and subsequently notified the Protocol Team (which included all participating study sites and the IND holder) that the protocol had been finalized and could be accessed from the MTN website. If applicable, non-DAIDS IND-holder sign-off preceded protocol posting and distribution.

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

*--Some protocol development steps also applied and still apply to Letters of Amendments and some to Full Version Protocol Amendments (see those marked with *).*

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

Once RAB sign-off had been obtained by MTN LOC (Pitt), the PW emailed the final protocol to the Protocol Team, which included the IND holder and all participating sites. The PW designated the participating sites within the NIAID Clinical Research Management System (CRMS), as needed. Study information was added to ClinicalTrials.gov by the PW as needed, 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 was the PDM, which served to ensure that MTN protocols were of high scientific quality, consistent and standardized relative to other MTN protocols, and contained the most accurate data and study procedures. Meetings ideally included 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 or designee
- 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 & Fiscal
- MTN LOC (Pitt) Protocol or Regulatory Specialist if different from the PW
- 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) and, if applicable, Co-Chair(s)
- Site Investigators and Coordinators

Approximately four weeks prior to the PDM, the PW distributed the draft protocol (typically Version 0.1) for review and comment by the Protocol Team. Team members submitted written comments to the PW within two weeks of receipt of the protocol. The PW and Protocol Chair(s)

reviewed and adjudicated 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 issued an updated draft protocol (typically Version 0.2) to be discussed at the PDM.

Meeting participants provided comments/feedback regarding the draft protocol at the PDM. Site Investigators were responsible for providing comments based on scientific, operational, and community considerations relevant to study conduct at their site. To obtain this input, they discussed and reviewed 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 or MTN LOC (Pitt) Director of Operations and the PW led the team discussion regarding issues pertaining to protocol content. To the extent possible, protocol language was finalized during the meeting. The purpose of the meeting was to obtain Protocol Team consensus regarding key elements of the protocol and to ensure the following:

- Study research questions, objectives and endpoints were clearly stated.
- The study design was appropriate to answer the research questions.
- The population was appropriate and inclusion/exclusion criteria were well defined.
- Study procedures were feasible and appropriate to meet the study objectives.
- Study product considerations were clearly specified.
- Major safety issues were identified and addressed.
- Major issues related to the protection of human subjects were identified and addressed.
- Potential issues related to the design of the study identified by the community were discussed.

Two weeks following the meeting, the PW and Protocol Chair(s) prepared and distributed a revised draft protocol (typically Version 0.3) reflecting the meeting discussions and outcomes. Protocol Team members submitted written comments to the PW within two weeks after receipt of the protocol.

Site Investigators were 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 were well defined, the PW drafted the sample informed consent (SIC) form(s). Site Investigators were 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 collected comments from Community Representatives, and the PDIM and PW convened 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 PW prepared a revised draft protocol (typically Version 0.4), including SICs (which henceforth were part of the protocol document), and solicited someone from the MTN LOC (Pitt) not involved in the development of the protocol to conduct a quality control check of the document prior to 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 was needed. For others, multiple forms were needed (ex., for Screening, Enrollment, Long-term Storage and possible future testing of specimens). All sample forms followed the then current DAIDS guidelines and included 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 participated in all aspects of the research process, MTN engaged community representatives from the initial stages of protocol development through implementation and dissemination of results. The timelines for concept and protocol development included 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) involved their community members and shared 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 provided input as members of the EC.

After a site had been approved by the MTN EC to participate in a study, the site partners two community representatives with a staff member who was involved with protocol development at the site (such as an Investigator or Study Coordinator). The two community representatives were a site Community Educator (paid staff) or CAB Liaison (paid staff), and a CAB Member (volunteer/non-paid staff). Additionally, he or she should have understood the concerns of the research communities. Typically, a CRS would have obtained community feedback through its CAB; although a CRS may have referred to this structure by any locally chosen name or established an alternative structure. The need for support and mentoring may have differed, depending on community members' individual needs and understanding of the research process.

The MTN PI/Co-PI were responsible for ensuring that the Network adhered to community participation in all aspects of the research process. It was 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 attended PDMs and were provided opportunities to ask questions and share concerns and suggestions
- Ensure community representatives were 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 was 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) drafted 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 were developed in parallel with the protocol and were distributed by the BRWG to the Protocol Team for review. Members of the protocol implementation team and SDMC were 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) drafted a description of the biomedical science objectives and endpoints to be presented at the PDM. This description and a sample collection plan with the planned assays were 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 reviewed protocols for which DAIDS provides funding (See Section 1 of this Manual for more information on the PSRC). The PW submitted 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 reviewed the protocol for completeness (usually within one day) and forwarded it to the PSRC Administrator at the DAIDS RSC within 10 business days prior to the PSRC meeting.

PSRC review findings were summarized in a Consensus Memo that was provided to the Protocol Team within ten business days. The memo identified 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 developed a written PSRC Consensus Memo Response document and an updated protocol that were submitted to the MO for review to ensure that the PSRC's concerns were addressed. The revised protocol and response documents might be returned to the PSRC for further review at the PSRC Chair's discretion.
- Disapproved (the Protocol Team worked with members of the MTN EC to determine the next steps; the protocol might be resubmitted to the PSRC after incorporation of revisions that addressed its concerns).

If a protocol was disapproved, DAIDS did not permit expenditure of NIH funds for the proposed investigation. For protocols that were disapproved, the Protocol Chair(s) might contact the PSRC Chair to discuss possible modification. If the Protocol Chair(s) believed there was a reasonable basis for proceeding despite the PSRC's disapproval, he or she contacted the MTN EC. If the EC members concurred with the Protocol Chair(s), the EC members notified the DAIDS Director and requested initiation of the appeal process, which involved an impartial third party.

Although the time required to respond to the PSRC review comments varied with the magnitude and extent of the comments, Protocol Team members provided a written response to the PSRC and 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 provided time for team discussion, drafting the response and the team's internal review of both the response and the revised protocol.

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 prepared a revised protocol version ("Regulatory Review Version", typically Version 0.5) reflecting the Protocol Team's approved response to the PSRC review findings. The PW submitted the protocol electronically to the DAIDS RSC for a Full Regulatory Review (FRR) that was completed per DAIDS Standard Operating Procedures (SOP) within 10 business days of protocol receipt. During this review, the DAIDS RSC staff reviewed the protocol in detail and forwarded 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 reviewed the protocol and DAIDS RSC review findings and added further comments, if needed. The DAIDS RSC incorporated all comments into an FRR summary document and transmitted the document electronically to the PW. The PW addressed DAIDS RSC's FRR comments with input from Protocol Team members as needed. After the Protocol Team and/or Study Leadership completed the final review of the FRR response and revised protocol, the PW solicited sign-off from key Protocol Team members and solicited someone from the MTN LOC (Pitt) not involved in developing the protocol to conduct a quality control check of the two documents prior to submitting them back to RSC. Although the time required to respond to the FRR comments varied with the magnitude and extent of the comments, Protocol Team members addressed 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 provided a written response to the DAIDS RSC FRR. In particular, the team also provided adequate justification for any FRR comments that were not addressed in the protocol. The revised protocol version ("Medical Officer Review Version", typically Version 0.6) and FRR Response document were submitted electronically to the DAIDS RSC for the MO's review. This review was completed within 10 business days of receiving the document(s). During the ten-day review period, the DAIDS RSC staff reviewed the protocol to ensure that all FRR findings had been satisfactorily addressed.

Next, the protocol was forwarded to the DAIDS MO, who completed a final check of the protocol on behalf of DAIDS. The DAIDS RSC incorporated all MO review comments into a review summary document and transmitted the document electronically to the PW. The Protocol Team prepared a response to any MO comments generally within five business days of receipt of the comments, revising and resubmitting the protocol as needed. Following the resolution of all MO concerns, the RSC would circulate written confirmation of approval.

10.2.3.4 Regulatory Affairs Branch Chief Sign-off

Once MO approval was confirmed by RSC, the PW submitted 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 submitted any supporting documentation needed to explain its response to the MO Review. In particular, the

team provided and documented justification for any MO Review comments that were not adopted.

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

10.2.4 Distribution of Version 1.0

Upon notification of DAIDS RAB sign-off, the PW notified the MTN LOC (Pitt) Webmaster to post the final protocol on the MTN website. The PW also notified the Protocol Team, which included the IND holder and all participating study sites, that the protocol had been finalized and could be accessed from the MTN website. The MTN LOC (FHI 360) CRM then provided 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 could 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

Ongoing MTN protocols may occasionally need changes or clarifications. When a Protocol Team member identifies a potential issue with a protocol, the PW or PDIM will notify DAIDS and discuss how to ieffect this change. DAIDS-sponsored protocols may be modified by one of three methods: (i) Clarification Memo (CM), (ii) Letter of Amendment (LoA), or (iii) Full Version Protocol Amendment (FVPA) (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. However, any change to sample size or length of follow-up, for example, must be incorporated via an LoA or FVPA. 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 a FVPA, the PW drafts the CM and circulates it to the Protocol Team and Management Team to solicit any additional minor protocol clarifications that should be included, such as revisions to the protocol roster. The Protocol Chair(s), Co-Chair(s) and DAIDS MO must review and approve CMs prior to finalization and distribution; the DAIDS MO must also notify the PW in writing of their determination of the adequacy of using a CM to address the identified issue(s). The PW solicits someone else from the MTN LOC (Pitt) to conduct a quality control check of the final CM prior to submission to the MO for approval and to RSC for acknowledgement. After the CM is approved, 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

An 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: https://rsc.niaid.nih.gov/networks-protocol-teams/protocol-templates.

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 reconsent. 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 (analogous to Steps E and R-Z in Table 10.1). During the process, the DAIDS MO and RSC notify the PW of their determination of the adequacy of using an 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). Protocol Chair(s) and Co-Chair(s) approvals, Regulatory Review, MO Review and RAB Chief sign-off must be completed for all LoAs. 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 Version Protocol Amendments

FVPAs 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). FVPAs 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 (previously specified in a CM or an LoA) incorporated.

Examples of changes requiring an FVPA include the following:

- New study product(s) added to the protocol
- A new inclusion or exclusion criterion and/or the removal of a criterion
- Changes in risk and/or new safety information that might impact participants' willingness to take part in the trial
- A change in study design

FVPAs must go through several protocol review and approval steps (analogous to steps E and K-Z in Table 10.1). The PW contacts the DAIDS MO to ascertain whether the PSRC must review and approve the amendment. If so, the FVPA must be submitted for PSRC review. In addition, Regulatory Review, MO Review and RAB Chief sign-off must be completed for all FVPAs.

The MTN LOC (Pitt) Webmaster posts the FVPA on the MTN website; the PW notifies the Protocol Team and FHI 360 notifies the participating study sites that the final FVPA 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 FVPA. 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 the finalized FVPA to the FDA, if applicable.

Participants who were enrolled in a study after approval and registration of a protocol amendment (both LoAs and FVPAs) must be consented to the study using the revised ICF associated with the amended version of the protocol. For both LoAs and FVPAs, 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.*