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## 10. PROTOCOL DEVELOPMENT

Microbicide Trials Network (MTN) studies are developed through multidisciplinary collaboration among MTN investigators, the Coordinating and Operations Center (CORE-University of Pittsburgh [PITT] and FHI), Statistical and Data Management Center (SDMC), Network Laboratory (NL), Biomedical Science Working Group (BSWG), Behavioral Research Working Group (BRWG), and Community Working Group (CWG), when applicable, with non-MTN investigators and researchers/experts who bring complementary expertise.

### 10.1 Protocol Development, Review, and Approval

#### 10.1.1 Initial Protocol Development Process

The grant submission for the MTN included a portfolio of studies planned for the duration of MTN funding. The MTN Principal Investigator (PI) and Co-PI, with input from the MTN Executive Committee (EC), direct the order in which MTN protocols will be developed.

MTN protocols are developed through an iterative drafting and review process led by the Protocol Chair(s) and CORE (PITT) Protocol Specialist (PS) assigned to the protocol (see Figure 10.1). To initiate the protocol development process, the PS first works with the PI, Co-PI, or designee to specify the study objectives. The study design is then established with input from the SDMC prior to the generation of a protocol draft. Next, the PS, Protocol Chair(s), and, when possible, the Protocol Statistician create a first draft protocol (usually labeled Version 0.1) with input from the SDMC Project Manager (PM), CORE (FHI) Clinical Research Manager (CRM), NL, Protocol Physicians, Protocol Safety Physicians, BSWG, and BRWG.

After the study design and visit and procedures schedule have been reasonably well defined, the CORE (PITT) PS drafts the sample informed consent form(s) with input from a CWG representative. Next, the sample informed consent(s) is appended to the protocol. For some studies, only one sample informed consent form will be needed. For others, multiple forms will be needed (e.g., for screening, study participation, storage, and possible future testing of specimens). All sample forms will follow current U.S. Division of AIDS (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.

**Figure 10.1 Protocol Development Steps**

|    |  |
|----|--|
| A. | MTN PI triggers protocol development of planned MTN protocol.  |
| B. | PS works with the PI and/or Co-PI or designee to specify the study objectives.   |
| C. | Study design is established with input from the SDMC and concept is finalized.   |
| D. | PS, Protocol Chair(s), and Protocol Statistician create draft protocol (including sample informed consent) with input from SDMC PM, CORE (FHI) CRM, NL, Protocol Physicians, Protocol Safety Physicians, BSWG, and BRWG.   |
| E. | 4 weeks before the Protocol Development meeting, protocol is sent to Protocol Team for review.   |
| F. | 2 weeks before the meeting, Protocol Development comments due to PS.   |
| G. | 1 week before the meeting, revised protocol sent to Protocol Team.   |
| H. | At the meeting, Protocol Team members give feedback on revised draft.  |
| I. | Within 2 weeks after the meeting, revised draft (including sample informed consent forms) is sent to Protocol Team for final comments.   |
| J. | Protocol prepared for Prevention Science Review Committee (PSRC) submission based on final comments received.  |
| K. | CORE (PITT) PS submits protocol electronically to DAIDS Medical Officer (MO).  |
| L. | The MO reviews the protocol for completeness and forwards it to PSRC Administrator at DAIDS Regulatory Support Center (RSC).   |
| M. | PSRC Review Meeting  |
| N. | PSRC review discussions summarized in a consensus review memo that is provided to Protocol Team.   |
| O. | 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.  |
| P. | After notification of PSRC approval or documentation from the DAIDS MO of anticipated PSRC approval, the CORE (PITT) PS prepares a revised protocol version—labeled “Regulatory Review Version”—and submits the protocol electronically to the DAIDS RSC.  |
| Q. | DAIDS RSC reviews the protocol and sample informed consent form(s) in detail and forwards the protocol with comments to the DAIDS Regulatory Affairs Branch (RAB), DAIDS Human Subjects Protection Branch (HSPB), and DAIDS SPT. DAIDS RAB, DAIDS HSPB, and DAIDS Safety and Pharmacovigilance Team (SPT) review the protocol and DAIDS RSC review findings, and adds any further comments as necessary. DAIDS RSC incorporates all DAIDS comments into a review summary document and transmits the document electronically to the PS. |
| R. | 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 DAIDS RSC for MO review.  |
| S. | DAIDS RSC reviews the protocol to ensure that all Regulatory Review findings have been satisfactorily addressed, and then forwards the protocol for review by the DAIDS MO.  |
| T. | The MO reviews the protocol to confirm an acceptable response to Regulatory Review and completes a final quality assurance check of the protocol.  |
| U. | DAIDS RSC incorporates all comments into a review summary and transmits electronically to the CORE (PITT) PS.  |
| V. | The Protocol Team addresses MO review findings in a revised protocol version—labeled “FINAL Version 1.0”—and submits electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB.  |
| W. | Once sign-off is obtained, DAIDS RSC informs the CORE (PITT) PS electronically and files the final protocol (when applicable, DAIDS RSC also prepares the protocol for submission to the U.S. Food and Drug Administration [FDA]).   |
| X. | Upon notification of RAB Chief sign-off, CORE (PITT) posts the final protocol on the MTN website. The CORE (PITT) PS notifies the Protocol Team and all participating study sites that the protocol has been finalized and can be accessed from the MTN website.   |

**Note:** CSIO and MTN Regulatory must be cc'd on all electronic communications between CORE (PITT) and DAIDS involving official MTN protocol submissions (i.e., PRSC, RSC, DAIDS MO, and RAB submissions, as well as all modifications).

From this point forward, protocol development proceeds according to the review and approval steps described in Section 10.1.2. The CORE (PITT) PS is responsible for all document submissions and for maintaining documentation of all review findings and protocol team responses to these findings. Additional information on DAIDS review and approval processes for protocols may be obtained at:

<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/protocolregpolicy.pdf>.

## **10.1.2 Protocol Review and Finalization Process**

### **10.1.2.1 Protocol Development Meeting Review**

The first protocol review step is the Protocol Development Meeting, which serves to ensure that MTN protocols are of high scientific quality and are accurate, consistent, complete, and standardized relative to other MTN protocols, at least to the extent possible. Meetings ideally include the following attendees or their designated representatives:

- Co-Sponsor Representative(s), if applicable
- DAIDS Medical Officer (MO)
- DAIDS Protocol Pharmacist, if applicable
- MTN Behavioral Research Working Group Chair or Member
- MTN Biomedical Science Working Group Chair or Member
- CORE (FHI) Community Program Staff Representative
- CORE (FHI) CRM
- MTN Director of Pharmacy Affairs, if applicable
- CORE (PITT) PS
- CORE (PITT) Director of Operations
- CORE (PITT) Safety Physician
- NL Director or Representative
- MTN PI or Co-PI
- SDMC PM
- SDMC Protocol Statistician
- US National Institute of Child Health and Human Development (NICHD), US National Institute on Drug Abuse (NIDA), or other MO, if applicable
- Protocol Chair(s)
- Site PI(s)

Approximately four weeks prior to the Protocol Development Meeting, the CORE (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 within two weeks after receipt of the protocol. The Protocol Chair and PS review the comments and determine which comments can be incorporated immediately into a revised draft protocol, and which require further discussion during the Protocol Development Meeting Review. Within 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 Protocol Development Meeting.

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

The Protocol Chair leads the team meeting, together with the CORE (PITT) PS. The Protocol Chair leads the team through a discussion of key issues to be resolved in the protocol. To the extent possible, protocol language is finalized during the meeting. Discussions undertaken during the meeting should ensure that:

- study research questions and objectives are clearly stated;
- 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; and
- major issues related to human subject protections and informed consent are identified and addressed.

Within two weeks after the meeting, the Protocol Chair and CORE (PITT) 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 PIs are again responsible for submitting comments based on scientific, operational, and community considerations relevant to study conduct at their site. In particular, community feedback on the draft sample informed consent forms and key study implementation issues should be obtained and provided to the PS at this time. In addition to site investigators collecting comments from community representatives, the CORE (PITT) PS convenes a call with Community Program and site community representatives to review and revise the draft sample informed consent form(s). Based on feedback received from all Protocol Team members, the Protocol Chair and PS prepare a revised draft protocol, including sample informed consent form(s) (typically labeled as Version 0.4), for submission to the DAIDS MO for review by the DAIDS Prevention Science Review Committee (PSRC) (see Section 10.1.2.3 and Appendix I).

#### **10.1.2.2 Community Participation in Concept and Protocol Development**

To ensure that the MTN is committed to community participation in all aspects of the research process, it is critical that community representatives be included and supported from the concept development stage forward.

Site investigators, including CTU PIs, CRS or Site Investigators, and study-specific Investigators of Record, are expected to involve the community and share with them the study concepts as early in the development process as possible. It is recognized that 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; however, it is critical that community input is sought as a study is being developed.

The inclusion of a community representative on a Protocol Team should not substitute for ongoing efforts to develop and foster an on-site community involvement process. One person cannot be expected to represent an entire community's views, nor is having one informed community representative sufficient. Community involvement is the responsibility of CTU and site investigators and must be actively sought on a broader basis.

The timelines for concept and protocol development must include appropriate time for community education and consultation at each site.

After a site has been identified for a particular concept, the site should pair a community representative with staff (e.g., an investigator or study coordinator) involved with protocol development at the site (e.g., site co-chair for the Protocol Team). Ideally, the community representative should have two roles: represent the study community and understand the concerns of the research communities. Someone not employed by the site is required. Clearly, the need for support and mentoring may differ, depending on community members' individual needs.

Responsibility of the MTN PI includes:

- Ensure that the Network adheres to community participation in all aspects of the research process

Responsibilities of concept and Protocol Teams include:

- Demonstrate respect for (and consider for action) the input of community representatives when developing concept plans and protocols
- Share information, questions, and concerns with local Community Advisory Board (CAB) members, CORE (FHI) Community Program staff and the Network CWG

Responsibilities of the CTU PI include:

- Set aside sufficient funds in site annual budget requests to support participation for community representatives in protocol development (e.g., attendance at face-to-face Protocol Team meetings or local transportation costs, if needed, for participation in conference calls)

Responsibilities of the MTN CWG and community representatives include:

- Develop an understanding of issues with which they may have little expertise
- Voice concerns from the communities and study participants
- Provide real-life experiences
- Provide input about community concerns, beliefs, and norms, in conjunction with the site staff
- Respect and take into consideration the input of scientists when developing concept plans and protocols
- Advise the site research team and MTN Protocol Team on the development of informed consent forms and other study-related documents
- Advise in the development and implementation of study participant recruitment and retention strategies
- Suggest strategies to address ethical and operational aspects of study conduct
- Serve as a resource to community liaison officer/community educator and research team

- Function as a conduit of information between the site and potential research communities (e.g., CABs, nongovernmental organizations, or social organizations)
- When issues of concern arise, have discussions between calls with local community representatives, community representatives from the other sites involved in the trial, the site PI, and CORE (FHI) Community Program staff, and ensure a complete feedback loop in terms of information flow
- Provide protocol development updates to fellow community representatives at the site or network level

Responsibilities of the site investigators, Community Educators/Community Liaison Officers/CAB Coordinators, PIs, and other site staff in partnering with community representatives include:

- Provide one-on-one information about the concept/protocol and general research in a manner that is accessible and appropriate
- Meet with community representatives to discuss and obtain feedback on concepts/protocols throughout the development process
- Include community representatives in concept/Protocol Team conversations and communications regarding protocol development (i.e., facilitate inclusion on the conference calls or e-mail exchanges) to the greatest extent possible

Responsibilities of the CORE (FHI) Community Program Staff include:

- Participate on Protocol Team calls and meetings to clarify the community program processes and answer any questions
- Prior to attending face-to-face Protocol Team meetings, convene calls with the community representatives and site staff following distribution of the draft concept and protocol to facilitate a discussion of questions, concerns, and suggested changes to the concept and/or protocol
- Provide technical assistance to sites and community representatives to support community participation in concept and protocol development; be available to site staff and community representatives to answer questions

### **10.1.2.3 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 a description of the behavioral aims and accompanying assessments, an outline of the behavioral study procedures by visit, and a plan for analysis of the behavioral outcomes. 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. For more information about this process, please refer to Section 11.

### **10.1.2.4 DAIDS Prevention Sciences Review Committee (PSRC) Review of Protocol**

The PSRC meets twice monthly (first and third Tuesdays) to review protocols for which DAIDS provides funding. The CORE (PITT) PS submits the protocol electronically to the DAIDS MO at least 14 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 Regulatory Support Center (DAIDS RSC) at least 10 working days prior to the PSRC meeting.

The PSRC provides a scientific overview and general evaluation of research plans specified in the protocol on the basis of:

- U.S. National Institute of Allergy and Infectious Diseases' (NIAID's) HIV/AIDS scientific priorities;
- scientific merit, especially the primary objectives and the study design;
- participant safety;
- operational feasibility;
- compliance with U.S. federal regulations and applicable DAIDS policies and procedures;
- the statistical plan and proposed analysis of this plan;
- the pharmacy plan, where appropriate; and
- study oversight and monitoring.

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 three review outcomes:

- Approved without revision (minor revisions may be suggested)
- Approved contingent on addressing major concerns; protocols approved with major concerns must address those concerns in writing and receive formal approval from the DAIDS MO, or return to PSRC for further review at the chair's discretion
- Disapproved; the Protocol Team works with members of the MTN EC to determine next steps; the protocol may be resubmitted to the PSRC after incorporation of revisions that address the PSRC's 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 may contact the PSRC Chair to discuss possible modification. If the Protocol Chair believes there is a reasonable basis for proceeding despite the PSRC disapproval, he or she should contact the MTN EC. If the EC concurs with the Protocol Chair, the EC may notify the DAIDS Director and request that the appeal process be initiated. The appeal process will involve an impartial third party.

Although the time required for a Protocol Team to respond to the PSRC review comments will vary with the magnitude and extent of the comments, teams are encouraged to provide a written response to the PSRC (if required) and/or a revised draft protocol within 15 working days following the receipt of comments. This provides time for team discussion, drafting, and internal team review of the response.

#### **10.1.2.5 DAIDS Regulatory Review**

After notification of PSRC approval or documentation from the DAIDS MO of anticipated PSRC approval, the CORE (PITT) 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 Procedure (SOP) within 10 working days of protocol receipt. During this review, DAIDS RSC staff review the protocol and sample informed consent form(s) in detail, and forward the 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. DAIDS RSC incorporates all comments into a review summary document and transmits the document electronically to the PS.

#### **10.1.2.6 DAIDS Medical Officer Review**

The Protocol Team addresses the Regulatory Review findings in a revised protocol version within 15 working days. This revised version—labeled “Medical Officer Review Version”—is submitted electronically to the DAIDS RSC for MO review. This review is completed, per DAIDS SOP, within 10 working days of protocol receipt.

Along with the protocol, the team also submits any supporting documentation needed to explain its response to the Regulatory Review. In particular, if any Regulatory Review comments are not adopted, the team must provide adequate justification for this. During the 10-day review period, DAIDS RSC staff review the protocol to ensure that all Regulatory Review findings have been satisfactorily addressed. Next, they forward the protocol for review by the DAIDS MO.

The MO reviews the protocol to confirm an acceptable response to the Regulatory Review—including incorporation of all responses into the protocol document—and to complete 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 CORE (PITT) PS.

#### **10.1.2.7 Regulatory Affairs Branch (RAB) Chief Sign-off**

The Protocol Team addresses the Medical Officer Review findings, generally within five working days of receipt of comments, in a revised protocol version (labeled “FINAL Version 1.0”) and submits this version electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB. Along with the protocol, the team also submits any supporting documentation needed to explain its response to the Medical Officer Review. In particular, if any Medical Officer Review comments are not adopted, the team must provide adequate justification for this.

RAB Chief sign-off is expected within approximately 10 working days of submission. Once sign-off is obtained, RSC informs the CORE (PITT) PS electronically and files the final protocol. When applicable, RSC also prepares the protocol for submission to the U.S. Food and Drug Administration (FDA).

#### **10.1.2.8 Distribution of FINAL Version 1.0**

Upon notification of RAB Chief sign-off, the CORE (PITT) posts the final protocol on the MTN website. The CORE (PITT) 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 CORE (PITT) PS notifies the FHI CRM by e-mail 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/Ethics Committee (IRB/EC) approval of the protocol, site-specific informed consent forms, and other associated documents. Conduct of the study may not be initiated before IRB/EC approval is obtained from all responsible DRAs and IRBs/ECs, the DAIDS protocol registration process is completed, all other MTN study activation requirements are met (see Figure 11.1), and a site-specific study activation notice is issued by the CRM.

## **10.2 Protocol Modifications**

DAIDS-sponsored protocols may be modified by three methods:

- Clarification Memo (CM)
- Letter of Amendment (LoA)
- Protocol Amendment

These three methods, which are described in the following sections, are used for both Investigational New Drug (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/EC review and approval, and may or may not require protocol registration through the DAIDS RSC Protocol Registration Office. The modification also may or may not require approval by site DRAs.

As with the first final version of the protocol, the CORE (PITT) PS is responsible for developing protocol modifications in conjunction with key Protocol Team members. Once finalized, copies of all protocol modification documents are posted on the MTN website by the CORE (PITT).

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 documents may only be implemented after the documents are fully approved, as described below.

### **10.2.1 Clarification Memos (CM)**

CMs typically are short documents prepared to provide further explanation or more detailed information related to current protocol specifications. CMs 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 informed consent form(s). If a proposed modification requires a change to the study informed consent form(s), a CM may not be used to incorporate the modification.

The DAIDS MO must review and approve CMs prior to finalization and distribution. Once finalized, the CORE CRM distributes CMs to all Protocol Team members and study sites; sites are strongly encouraged (but not required by DAIDS) to submit CMs to their IRBs/ECs.

### **10.2.2 Letters of Amendment (LoA)**

An LoA typically is 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 and involve relatively minor modifications of study informed consent forms, if any. When an LoA is prepared, any prior protocol modifications specified in CMs are incorporated into the LoA. LoAs are prepared according to a DAIDS template, which is available on the RSC website: <http://rsc.tech-res.com/>.

Site IRBs/ECs must review and approve LoAs. Most LoAs include instructions to study sites with regard to seeking IRB/EC review and approval and recommendations for how to notify participants of the changes, if applicable. In some circumstances, re-consenting of enrolled participants may be required. 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/ECs may require modification of the study informed consent forms and/or re-consenting of enrolled participants to reflect an LoA; in such cases, IRB/EC requirements must be followed.

LoAs are developed by the Protocol Team and must complete several protocol review and approval steps (see Figure 10.2). Once finalized, DAIDS submits LoAs to the FDA if applicable. The CORE (PITT) posts the LoA on the MTN website, and the PS 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/EC review and approval; modified procedures specified in the LoA may not be conducted until IRB/EC approval is obtained from all responsible IRBs/ECs. LoAs do not result in a change of the protocol version number. Each LoA must be registered through the DAIDS PRO, but sites do not need to wait for notification from DAIDS PRO prior to implementation of the LoA.

### **10.2.3 Full Protocol Amendments**

Full protocol amendments are prepared by the Protocol Team and coordinated by the CORE (PITT) PS to incorporate significant changes—involving more than minimal impact on participant safety and risk-to-benefit ratio of study participation—and 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 specified in a CM or LoA are incorporated into the amendment.

Examples of changes requiring a full protocol amendment include:

- New study product(s) added to the protocol
- Change to inclusion or exclusion criteria
- New safety information on investigational product(s) under study
- Change in the study design

Protocol amendments are developed by the Protocol Team and at the end of this section (see Figure 10.2). Any amendments must complete 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, Medical Officer Review, and RAB Chief sign-off must be completed for all amendments.

Once finalized, DAIDS submits amendments to the FDA, if applicable. The CORE (PITT) posts the amendment on the MTN website and the PS notifies the Protocol Team and participating study sites that the final amendment is online. Sites must then seek IRB/EC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (see Section 11) for the amended version of the protocol. Revised procedures specified in the amendment may not be conducted, and the revised site informed consent(s) may not be used until after protocol registration approval is obtained. Participants enrolled in a study after approval and registration of a protocol amendment must be consented to the study using the revised informed consent form(s) associated with the amended version of the protocol. For participants enrolled prior to approval and registration of an amendment, guidance on whether re-consenting is required (i.e., using the revised informed consent form(s) associated with the amendment) will be provided by the Protocol Team. Regardless of Protocol Team recommendations, site IRBs/ECs may require re-consenting of previously enrolled participants; in such cases, IRB/EC requirements must be followed.

**Figure 10.2 Requirements and Procedures for Protocol Modifications**

| <b>Modification Requirements</b>                                   | <b>Clarification Memo</b>  | <b>Letter of Amendment</b>  | <b>Protocol Amendment</b>  |
|--|--|---|--|
| Content involves change of risk-to-benefit ratio?                  | No   | Yes, but impact should be minimal.  | Yes  |
| Content must be reported to study participants?                    | No   | Possibly. Depends on content and requirements of site IRB/ECs   | Yes  |
| Content requires change of informed consent form                   | No   | Possibly. Depends on content and requirements of site IRBs/ECs.   | Yes  |
| Results in change of protocol version number?                      | No   | No  | Yes  |
| <b>Reviews/Approvals Required By:</b>                              | <b>For Clarification Memo</b>                                      | <b>For Letter of Amendment</b>  | <b>For Protocol Amendment</b>  |
| Requires approval by DAIDS Medical Officer?                        | Yes  | Yes   | Yes  |
| Requires approval by DAIDS PSRC?                                   | No   | No  | Possibly. Medical Officer determines whether PSRC review is required.  |
| Requires DAIDS Regulatory Review?                                  | No   | Yes   | Yes  |
| Requires DAIDS Medical Officer Review following Regulatory Review? | No   | Yes   | Yes  |
| Requires DAIDS RAB chief sign-off following Medical Officer Review | No   | Yes   | Yes  |
| Requires approval by site IRBs/ECs?                                | No, unless required by IRB/EC (but FYI submission is recommended). | Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.  | Yes. Amended procedures may not be undertaken until after IRB/EC approval and protocol registration approval are obtained. |
| Requires protocol registration?                                    | No   | Yes. 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 after IRB/EC approval and protocol registration approval are obtained. |

**Note:** modifications may or may not require approval by site DRAs.