# 9 PROTOCOL DEVELOPMENT AND MODIFICATIONS

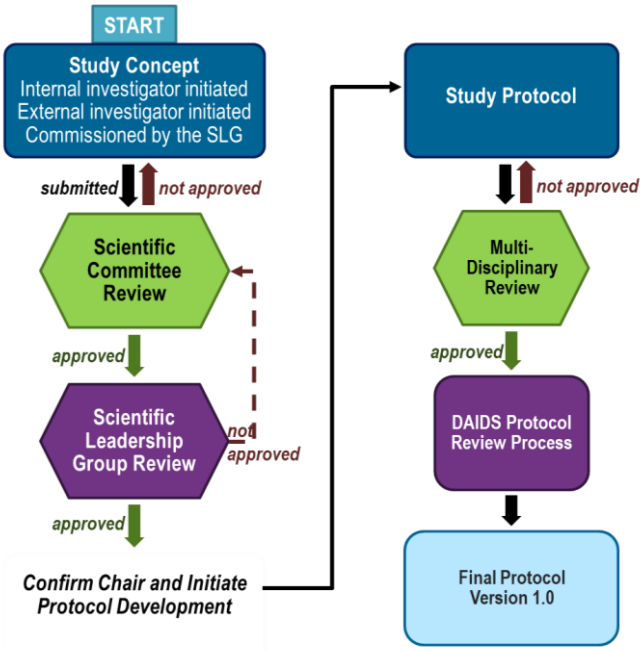
The IMPAACT Network has an open and iterative process for review of new study proposals designed to efficiently identify those of highest scientific merit, potential public health impact, and feasibility/sustainability within the Network for further development. Network studies are developed through multidisciplinary collaboration among investigators, the Scientific Committees (SC), the Scientific Leadership Group (SLG), the Management Oversight Group (MOG), the central Network resources (Operations Center, Statistical and Data Management Center [SDMC], and Laboratory Center [LC]), the IMPAACT Community Advisory Board (ICAB), site representatives, and external collaborators. The process involves sequential development and review steps for study concepts and protocols, as shown in Figure 9-1 and described in greater detail in the remainder of this section.

Scientific priorities for IMPAACT research are determined by the SLG in collaboration with the SCs, aligned with the Network's mission and research agenda (outlined in Section 1). New studies may be proposed by IMPAACT investigators, proposed by external investigators, or commissioned by the SLG. Regardless of origin, initial review and prioritization is the responsibility of the relevant SC (see Section 2 for more detail on SC roles and responsibilities). As depicted in Figure 9-1, new study development begins with development of a study concept. The study concept is reviewed to determine whether the Network should commit resources to full protocol development and study conduct (see Figure 9-2 for review criteria).

Throughout all reviews, from concept through protocol reviews, the IMPAACT SC, SLG, and the IMPAACT Multidisciplinary Protocol Review Group (MPRG) determinations are considered final.

The Network follows a strict conflict of interest policy throughout the concept and protocol review process. Any SC or SLG member involved in the development of a proposed study recuses themself from scoring and voting on that study and only participates in discussions of the study proposal when proposing investigators and/or protocol team members are expected to participate (e.g., in open sessions of review calls).

**Figure 9-1. Protocol Development, Review, and Approval Process**




*An early Scientific Review Committee (SRC) review may be required or requested.
Note: Each review step may require revisions and resubmissions.

**Figure 9-2. IMPAACT Study Review Criteria**

*The criteria outlined here are used for study proposal review of concepts. For each of the three criteria, proposals are assigned numerical scores of 1 to 5, with 1 being the most favorable.*

- Scientific merit
  - Study is aligned with IMPAACT's scientific agenda and priorities
  - Hypothesis is scientifically sound and can be appropriately tested with the proposed study design
  - Study design and methods will yield the proposed outcomes
- Potential public health impact
  - Study is relevant to one or more IMPAACT study populations (infants, children, adolescents, pregnant/postpartum people affected by human immunodeficiency virus (HIV))
  - Study will answer important public health questions or is in the critical path of research toward such answers
- Feasibility and suitability for Network implementation
  - Study population is available at IMPAACT-affiliated sites
  - Study conduct is feasible within the Network structure
  - Study will benefit from a multisite and multidisciplinary collaboration with Network support and oversight

## 9.1 Concept Development and Review

### 9.1.1 Development

Proposals for new studies are reviewed by the Network in the form of a concept. Concepts are developed using a template that is available on the IMPAACT website and includes the elements outlined in Figure 9-3. Concepts are expected to be approximately 5-10 pages in length (excluding references and budget estimate).

**Figure 9-3. Elements of IMPAACT Concepts**

- Title of proposed study
- Proposed protocol chair and vice chair
- Rationale
- Objectives and outcome measures
- Hypotheses
- Study design
- Treatment regimen(s), if applicable
- Key study population characteristics
- Approximate sample size to address the primary objective(s)
- Study duration (enrollment and follow-up)
- Laboratory assays required
- Anticipated study implementation at international sites and/or sites in the United States
- External support/collaboration/funding (if any)

Completed concepts should be submitted by the proposing investigator(s) to the Operations Center via the following email address: impaact.capsubmissions@fstrf.org. The concept is then assigned an identification number for tracking purposes and forwarded to the appropriate SC for review.

Concepts may be submitted at any time; however, they must be submitted at least two weeks in advance of the review date. These dates are shared with proposing investigators in advance of the deadline.

The Operations Center, SDAC, and LC may assign staff to provide limited support for the development of each concept. The Operations Center may provide administrative and coordination support to the concept development group. The SDAC statistician(s) may provide advice on study design and sample size calculations for the primary objective(s), and the LC may provide advice on laboratory evaluations, as needed. Proposing investigators may involve other collaborators with relevant expertise in the concept development team.

### 9.1.2 Scientific Committee Review

The Operations Center forwards each new numbered concept to the relevant SC chair and vice chair to begin the IMPAACT review process. Concepts received at least two weeks in advance of the next scheduled monthly SC call are typically reviewed on that call, unless otherwise determined by the SC chair. This lead time also allows for the ICAB representative on each SC to obtain more broad-based feedback on the concept from other ICAB members (as described in Section 5).

It is generally expected that the SC chair assigns committee members as primary and secondary reviewers of the concept. In addition, the SDAC representative (or designee) on the SC may provide a brief

statistical review. If needed, an external expert may be invited as either a primary or secondary reviewer. These reviewers provide written comments to the Operations Center at least three days in advance of the review call for distribution to the full SC and to the proposing investigators. The proposing investigators are invited to the call to briefly introduce the concept and respond to questions or requests for clarification; however, participation is not required. Assigned reviewers lead the discussion of the concept. Other SC members provide review comments during the call (or in writing in advance if they are not able to participate). These review calls include an open portion followed by a closed portion for SC members only. After the review call, SC members with no conflicts of interest vote (typically electronically) on next steps for the concept, per the following three categories:

(1) Approve for SLG review, with SC comments to be addressed as appropriate
(2) Revise and re-submit for SC review
(3) Discontinue development with the Network

Committee members base their reviews on the extent to which the proposed study is aligned with the committee's scientific priorities, as well as the criteria listed in Figure 9-2. More information on voting member designation and when voting can be considered complete is provided in Section 2.

The Operations Center coordinates with the SC chair and vice chair to distribute each concept for review, schedule the review, organize the committee voting process, and communicate the outcome of the review in writing to the proposing investigators and SC members.

- If the SC determines that a concept should be revised and re-submitted to the SC, the proposing investigators may be asked to provide a written response to the reviewers' comments along with the revised concept.
- If the SC approves a concept for submission to the SLG, the Operations Center helps coordinate the submission. When the SC review outcome is communicated to the proposing investigators, processes related to the Network's implementation of the Representative Studies Rubric (RSR; see Section 9.2) are shared.

The RSR tool is used to guide and monitor enhanced representation in clinical research. The RSR assesses individual studies for the extent to which they are designed to include or exclude underrepresented populations. The RSR is available on the IMPAACT website on the Manual of Procedures Page under *Training Materials and Resources.*

**Note:** As research priorities evolve over time in response to emerging science and changing standards of care, and because Network resources may fluctuate, a concept that was not approved previously may be submitted for re-consideration at a later time. In such cases, the proposing investigators are encouraged to discuss their plans with the relevant SC chair and vice chair in advance.

### 9.1.3 Scientific Leadership Group Review

The SLG generally reviews new study proposals (concepts) on an ongoing basis, either via conference call or during an in-person meeting. To allow adequate time for review, proposals must be submitted at least two weeks in advance of the scheduled SLG review. This lead time also allows for the ICAB SLG representative to obtain more broad-based feedback on the concept from other ICAB members (as described in Section 5).

For proposed studies deemed of especially high priority by the SC, for which there are external or other critical timeline considerations, the relevant SC chair may submit a written request for expedited SLG

review of a concept. Decisions regarding these requests are made on a case-by-case basis by the SLG chair and vice chair.

The Operations Center coordinates submission of concepts that have been approved by the respective SCs to the SLG. A primary, secondary, and statistical reviewer are assigned to each concept. Assigned reviewers submit written comments to the Operations Center 1-2 days in advance of the SLG review for distribution to the SLG, the relevant SC chair and vice chair, and the proposing investigators prior to the review. Reviews generally include an open portion followed by a closed portion for SLG members only (which may be held on a separate day). During the open portion, the relevant SC chair, vice chair, or designee (which may be one of the proposing investigators) briefly introduces the concept and responds to questions or requests for clarification; assigned reviewers may also briefly present their comments or overall evaluation. During the closed portion of the review, assigned reviewers lead the discussion of the concept. Other SLG members provide comments during the review (or in writing in advance if they are not able to participate). In some cases, all SC chairs and vice chairs are invited to participate in the review, for example, when the review is held during the IMPAACT Annual Meeting.

After the review, SLG voting members who participated in the review assign a priority score to the concept using the criteria specified in Figure 9-2 and vote on next steps for the concept, per the following categories:

(1) Approve for protocol development, with SLG comments to be addressed as appropriate
(2) Revise and re-submit for SLG review
(3) Discontinue development with the Network

The SLG evaluates and confirms through the voting process the proposed protocol chair and vice chair based upon past leadership performance, current commitments, and relevant expertise and experience. A maximum of 10-15% full time equivalent (FTE) direct support is provided for protocol team leadership (across both/all chair and vice chair positions). One chair and no more than two vice chairs will be endorsed. Section 4 describes the full roles and responsibilities for these protocol team leadership positions. The SLG may defer scoring or voting on a concept if it is determined that additional forthcoming information is critical to decision-making (e.g., results of another relevant study that is planned or underway). Concepts are considered approved for protocol development if at least 75% of voting SLG members vote for approval. While a detailed costing of the proposed study is not expected, approval of the concept for protocol development represents a commitment of resources from the Network to develop a full study protocol and the intention to conduct the proposed study within the Network. (See Section 11 for further details on the protocol budgeting process.)

If the SLG approves a concept for protocol development, SLG review comments are to be addressed in the study protocol; a separate response is not required unless specifically requested by the SLG. However, if SLG reviewers' comments are not addressed in the protocol, a separate response with an explanation is advised.

If the SLG determines that a concept should be revised and re-submitted, the proposing investigators are requested to provide a written response to the reviewers' comments along with the revised concept. Prior to re-submission, the documents should be reviewed by the SC chair and/or vice chair and the SDAC representative on the SC, as needed, to determine if further SC review is required before the revised concept and response are submitted to the SLG.

The Operations Center documents the review outcome and communicates the final result for each concept to the SLG, proposing investigators, SC chair and vice chair, and SDAC representatives (SDAC Director, Associate Director, and cbar.qb@sdac.harvard.edu) within approximately one week of voting completion.

For each concept approved for protocol development, the Operations Center assigns a protocol number which is included in the outcome notification for tracking purposes. When the outcome is communicated to the proposing investigators, guidance related to Division of AIDS (DAIDS) and IMPAACT policies and procedures, including ensuring use of non-stigmatizing language as described in the NIAID Language Guide (see Section 9.2), is shared. Guidance is also provided on whether formation of the protocol team and development of the study protocol may begin immediately or should be deferred for a specified period of time (e.g., due to timeframes for study product availability or competing demands for Network resources). Generally, proposing investigators should defer further protocol development work until the full complement of protocol team members are assigned to the study and the study clinical research managers (CRMs) have initiated protocol development work.

## 9.2 Protocol Development and Review

The protocol development and review processes detailed below are based on DAIDS guidance: https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent.

Protocol team members should refer to the following DAIDS policies and guidance documents related to protocol development. These are generally applicable to IMPAACT studies and can be accessed with job aids and recommended language at the link above:

- Enrolling Children in Clinical Research
- Good Documentation Practices
- Requirements for Informed Consent Forms
- NIAID Language Guide
- Representative Studies Rubric tool

### 9.2.1 Development

Protocol team formation begins per the timelines specified in the outcome notification documenting SLG approval of the study concept.

The assigned Operations Center CRM works with the protocol chair and vice chair to initiate the formation of the protocol team and contacts the SDMC, LC, DAIDS Program and Pharmacy Affairs Branch (PAB), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH) to determine their assigned representatives, as applicable. If specific expertise is needed on the team (e.g., pharmacologist, immunologist, behavioral scientist, virologist, etc.), recommendations may be sought from members of the relevant SC or SLG. As described in Section 10, representatives from each selected site are added to the protocol team once the site selection process has been completed to ensure adequate input on operations, feasibility, and other aspects of the study.

To initiate the development of the protocol document, the CRM incorporates information from the approved concept and any relevant review comments into the IMPAACT protocol template and works closely with the protocol chair to specify writing assignments and timeframes for drafting each protocol section, consistent with an overall timeline for protocol development reflective of Table 9-1. The CRM also requests a study ID number from DAIDS Clinical Study Information Office (CSIO). In consultation with the DAIDS Medical Officer (MO), the protocol team determines whether an early DAIDS Clinical Science Review Committee (CSRC) review should be arranged and, if so, that step is incorporated into the protocol development timeline. IMPAACT leadership and/or DAIDS may also request or require an early review. It is generally expected that most IMPAACT protocols will not require an early review.

When an early review is required, the review should occur prior to submission of the protocol for IMPAACT MPRG review.

Modifications of the study objectives, design, and/or schedule of evaluations that are significant and/or would substantively affect the size, scope, or cost of a study — relative to the previously-approved concept — require review and approval from the IMPAACT leadership. To avoid delays in protocol development, such approval should be sought prior to submission of the protocol for MPRG review. If such changes are proposed prior to MPRG review, team sign-off of the proposed modifications is not required.

The protocol chair and vice chair, CRM, and other protocol team members with writing assignments draft the protocol through an iterative process. The team communicates frequently via email and conference calls. An in-person or virtual protocol development meeting may also be convened to facilitate the process, with the appropriate timing agreed upon by the team. Protocol team members with key writing responsibilities are generally expected to attend such meetings; participation from all other protocol team members is optional. See Section 4 for further details on the composition and responsibilities of the protocol team.

For efficiency, the protocol team should prioritize development of the study schema, which includes the study objectives, the study design, and eligibility criteria first, followed by the schedule of evaluations. Development of other sections of the protocol (e.g., background and rationale) may proceed concurrently with work on the schema, eligibility criteria, and schedule of evaluations. However, it is often counter-productive to develop other sections before these three sections are fully discussed and agreed upon by the team. Once such agreement is achieved, these sections should generally not be re-visited. All other sections should then be developed based on the agreed-upon content of these sections, with a prioritization of statistical and clinical pharmacology sections. When drafting outcome measures, protocol teams should ensure alignment with the study objectives and should take into consideration requirements for submitting study results to ClinicalTrials.gov (processes related to ClinicalTrials.gov are described in Section 7).

Critical input is sought from site representatives, community representatives, and other stakeholders throughout the protocol development process as needed to ensure both the appropriateness and the operational feasibility of the study. Also, throughout the process, the CRM, along with the chairs and National Institutes of Health (NIH) representatives, monitor adherence to the protocol template and ensure that all applicable research regulations, guidelines, NIH policies, and IMPAACT policies and procedures are reflected in the protocol document. Likewise, the CRM works with the team to ensure that required elements of informed consent are reflected in the sample informed consent forms (ICFs) appended to the protocol. Version control is maintained by the CRM throughout the process and key decisions are documented for future reference as needed (e.g., in conference call and meeting summaries and in subsequent iterations of the protocol document).

The protocol chair and CRM are responsible for maintaining the protocol development timeline, communicating deadlines to team members, following up on pending items, and ensuring deadlines are met. Internal organizational reviews may also be conducted (e.g., SDAC, Operations Center, and/or pharmaceutical company reviews) but must be coordinated in keeping within the overall protocol development timeline. Although these reviews should largely take place in the background, the CRM should be made aware of all anticipated internal reviews well in advance, ideally at the start of the protocol development process. See Table 9-1 for an outline of the protocol development process and timeframes.

**Table 9-1. Protocol Development Timelines**

| Protocol Development Steps | Timelines |
|---|---|
| ***IMPAACT Reviews*** | |
| Development of full draft protocol (including early CSRC review, if applicable, and internal SDAC reviews) | 28-32 weeks |
| Protocol team sign-off | 1 week |
| IMPAACT MPRG review (including advance submission and post-review revisions/response, including any second reviews) | 8 weeks |
| Interim revisions (as needed to address all remaining comments and any comments from additional reviews; this time may be applied during other steps, based on team agreement, but should not exceed an additional 4 weeks) | 4 weeks |
| ***DAIDS Reviews*** | |
| Protocol team sign-off | 1 week |
| DAIDS Clinical or Prevention Sciences Review Committee Review (including advance submission and post-review revisions/response) | 9 weeks |
| DAIDS regulatory review (including advance submission and post review revisions/response) | 3 weeks |
| DAIDS Medical Officer review (including time for protocol team response) | 3 weeks |
| DAIDS Regulatory Affairs Branch final review | 10 working days |
| ***Total time from first team call to Final Protocol Version 1.0*** | ~59-63 weeks |

### 9.2.2 Protocol Development Oversight

Full draft protocols are expected to be submitted to the MPRG within the timeline outlined in Table 9-1. A high priority protocol may be identified by the SLG, in consultation with DAIDS, for accelerated development if there are urgent, time-sensitive considerations and the study must be implemented quickly in response to emerging scientific or clinical considerations. A limited number of studies may be prioritized at the same time, and the SLG may have to consider shifting priorities (delaying other studies) to accommodate accelerated timelines. Development of high priority studies will generally be accelerated by shortening the time for development of the full draft protocol (prior to MPRG review), by completing reviews concurrently when possible, and/or by reducing the turn-around times for DAIDS reviews (with approval from DAIDS).

The Operations Center provides monthly reports to update the MOG on protocol development statuses, and study implementation challenges and progress (see Section 13). Should a draft protocol become significantly delayed, a change in study team leadership may be required as determined by the MOG. If a protocol in development becomes irrelevant or no longer feasible due to emerging science or changing standards of care, a decision to stop development may be made by the SLG.

### 9.2.3 Team Review and Sign-Off

The draft protocol is distributed to all protocol team members for review prior to submission for MPRG review. Team members are asked to provide review comments and whether they approve or have any requested changes. Potential response categories may include the following:

(1) Approve
(2) Approve contingent on the following changes
(3) Approve with suggested changes
(4) Revise and redistribute for review

Following the protocol team review, the CRM incorporates any additional edits into the protocol and requests sign-off from one protocol chair (chair, co-chair, or vice chair), one statistician, and one DAIDS MO. Once sign-off requirements are met, the CRM submits the draft protocol to the IMPAACT MPRG at least two weeks prior to the anticipated review date (the CRM begins internal Operations Center coordination of the MPRG review 3-4 weeks prior to sign-off).

The sign-off process described above is also completed prior to submission for DAIDS scientific review (see Section 9.2.5). No other sign-off is routinely required from the protocol team during protocol development. Additional protocol team sign-off requirements for protocol modifications are described in Section 9.3.

### 9.2.4 IMPAACT Multidisciplinary Protocol Review Group

The purpose of the MPRG review is to ensure IMPAACT protocols are scientifically rigorous, accurate, consistent, complete, and standardized to the extent possible. The MPRG critically reviews protocols for scientific and design integrity, operational feasibility, and other key issues such as site participation, infrastructure and capacity, relevance to the community, and any ethical, logistical, or potential regulatory concerns. The MPRG conducts reviews on behalf of the SLG. The review is multidisciplinary to streamline and avoid multiple sequential review steps. The draft protocol is also reviewed concurrently by ICAB representatives, as described further in Section 5, and by Operations Center representatives prior to or concurrent with MPRG in the context of the Representative Studies Rubric (RSR).

The MPRG is comprised of the Network chair or vice chair (who serves as MPRG chair); the chair, vice chair, or other designated representative member of the relevant SC; standing representatives of the Operations Center, SDMC, LC, and ICAB; an IMPAACT pharmacist; designated NIH representatives; 1-2 external reviewers with expertise in the specific content area of the protocol (as available); an IMPAACT pharmacologist (for pharmacokinetic studies); and, as needed, a representative of the Social Behavioral Science Core.

Reviewers provide written comments on the protocol in advance of the review call, divided into major and minor comments. These are collated and distributed to all reviewers prior to the review call to facilitate the discussion. The MPRG agrees on the collective major comments to be included in the review summary and agrees on one of the following outcome options:

(1) Approved as written or with specific changes stipulated; no re-review required
(2) Re-submission/re-review required by the full review group or a subset (as determined by the chair) after required changes are incorporated and a response to the reviewers' comments is submitted
(3) Disapproved

The Operations Center summarizes the review in writing, distributes the draft to the MPRG and, following approval by the MPRG chair, provides the summary to the protocol team, typically within one week of the review.

Unless otherwise specified, a response to reviewers' comments and a revised version of the protocol are submitted to the MPRG in writing, ideally within 3 weeks of receiving the review summary. Typically, the team response and revised protocol are reviewed via email (another review call is not required), and any additional comments are conveyed with the final outcome/approval within one week of submission, with no additional response required. However, in some cases, an additional response and revised protocol are required before the final outcome is conveyed. The full MPRG review timeline, from submission to final outcome, is approximately eight weeks.

Typically, the protocol cannot proceed to the next review step until MPRG approval is obtained. In some limited circumstances, with prior approval from the MRPG chair and agreed upon with DAIDS, DAIDS SRC review may be concurrent or overlapping with MPRG review.

### 9.2.5 DAIDS Scientific Review

Upon completion of the MPRG review step (or concurrently with the final MPRG step), the updated draft protocol is distributed to all protocol team members for review prior to submission for DAIDS scientific review; sign-off is required prior to submission as described in Section 9.2.3.

IMPAACT protocols are reviewed by the DAIDS CSRC or Prevention Science Review Committee (PSRC), as determined by DAIDS. The SRC evaluates the research plans specified in each protocol on the basis of:

- NIAID's and other co-sponsoring institutes' research agenda, priorities, and other NIH clinical studies
- Scientific merit and study design
- Human subjects considerations and participant safety
- Compliance with US federal regulations and ethics
- Study oversight and monitoring
- Feasibility of timely completion
- Pharmacy and regulatory considerations
- When appropriate, plans for interim monitoring and analysis

The submission process differs for CSRC and PSRC review:

- *For protocols undergoing CSRC review:* When the protocol is ready for CSRC review, the CRM submits the protocol to the CSRC coordinator CSIO, along with the MPRG's comments and the team's response (if required), and the completed RSR. Every attempt will be made to hold the review by two weeks after the complete set of documents are received by the CSRC coordinator. The DAIDS MO may help with advanced scheduling to ensure timely reviews. Reviews are generally scheduled within three weeks of submission, but this varies depending on the CSRC schedule and time of submission.

- *For protocols undergoing PSRC review:* When the protocol is ready for PSRC review, the CRM submits the protocol to the DAIDS MO, along with the MPRG's comments and the team's response (if required). The DAIDS MO reviews the protocol and any accompanying documents for completeness (within one week) and forwards them to the PSRC coordinator at least two weeks (ten working days) prior to the scheduled PSRC review date.

CRMs may provide other materials to DAIDS (e.g., applicable package inserts) upon request. Protocol team representatives are generally invited to participate in an initial open session of the SRC review to provide a brief overview of the protocol and any major issues that they wish to highlight. Reviewers present their major comments to the protocol team representatives, followed by discussion of those of highest priority, as determined by the SRC chair. The SRC then proceeds in closed session.

The SRC review comments are summarized in a consensus memorandum that is provided to the protocol team typically within ten working days after the review. The memorandum identifies major and minor review findings along with one of three review outcomes:

(1) Approved for finalization and implementation: It is expected the protocol team will provide a revised letter of response addressing major comments and a revised protocol. (Note that DAIDS PSRC may request a letter of response addressing all comments).
(2) Decision deferred: It is expected the protocol team will provide a letter of response addressing major comments and submit a revised protocol for a second review.
(3) Not approved for further development or implementation.

The protocol team responds to the SRC review as specified in the consensus memorandum and submits response documents to the SRC through the SRC coordinator, ideally within 3 weeks of receipt of the SRC review memorandum; the updated draft protocol is also usually submitted. Written responses to review comments should include a description of any changes made in the protocol or justification for no change; confirmation of receipt is provided by the SRC coordinator. If the response and/or changes are deemed acceptable, the protocol team is notified in writing of SRC approval by DAIDS (generally one of the DAIDS MOs or Regulatory Support Center (RSC)) within approximately 1-2 weeks and the protocol moves forward to the next review step. If the team's response and revised protocol are not deemed acceptable, the protocol chair is notified and a plan for resolving the outstanding issues is developed in consultation with the DAIDS MO, Branch Chief, and others such as the SRC chair, Prevention Sciences Program Director, and key reviewers.

After SRC approval of the protocol is obtained, the final three steps of the DAIDS review process can begin. These steps are the DAIDS regulatory review, MO review and approval, and final DAIDS Regulatory Affairs Branch (RAB) review and approval, described below. Throughout these steps, the CRM works closely with other protocol team members to respond to review comments and make any necessary changes to the protocol.

### 9.2.6 DAIDS Regulatory Review

Once SRC approval is obtained, the CRM submits the revised protocol — labeled "Regulatory Review Version" — with the ClinicalTrials.gov checklist for regulatory review (copying CSIO). During this step, DAIDS (or its regulatory contractor) carries out a regulatory review of the protocol, completed with ten working days of protocol receipt. DAIDS (or its regulatory contractor) incorporates all comments into a review summary document and sends the document to the CRM.

For studies with more than one US site, the Operations Center will submit a draft of the protocol for an advisory review with the single institutional review board (sIRB), and address potential comments, prior

to the MO review. The intention of this review is to limit required protocol modifications that may arise from the sIRB protocol review.

### 9.2.7 DAIDS Medical Officer Review and Approval

The CRM, in consultation with the protocol chair or other protocol team members if needed, revises the protocol based on the regulatory review comments and prepares a response document, confirming that requested changes were made and providing justification if a requested change was not made.

Following the single IRB advisory review, if applicable, the CRM submits the revised protocol — labeled "Medical Officer Review Version" — with the response to the DAIDS regulatory review comments to DAIDS (or its regulatory contractor) for MO review and approval (copying CSIO). During this step, DAIDS (or its regulatory contractor) first reviews the protocol to ensure that all regulatory review findings have been satisfactorily addressed and then forwards the protocol for review by the MO, completed within ten working days of protocol receipt. The MO reviews the protocol to confirm an acceptable response to the regulatory review, including incorporation of any necessary changes into the protocol document, and to complete a final quality assurance check of the protocol on behalf of DAIDS. As a member of the protocol team, the MO has reviewed the protocol in detail multiple times prior to this step; therefore, few changes are generally expected. The possible MO review outcomes are:

(1) Approve as written
(2) Make changes as indicated and return to MO
(3) Make changes as indicated; do not return to MO

DAIDS (or its regulatory contractor) incorporates any review comments into a review summary document and sends the document to the CRM. The CRM, in consultation with the protocol chair or other protocol team members if needed, prepares a response to any MO comments and submits a revised protocol if needed, following the process described above for regulatory review. Once MO approval (option 1 or 3 above) is obtained, the CRM submits the protocol for final DAIDS RAB review and approval.

### 9.2.8 Final DAIDS Regulatory Affairs Branch Review and Approval

The CRM submits the protocol — labeled "FINAL Version 1.0" — to DAIDS (or its regulatory contractor) for final RAB review and approval (copying CSIO). RAB reviews the revised protocol and provides approval, completed within ten working days of protocol receipt. DAIDS provides a notification to the CRM when this review step has been completed; for Investigational New Drug (IND) studies, this includes notification that the final protocol has been submitted to the US Food and Drug Administration (FDA).

Once this review step is complete, the IMPAACT Operations Center sends the final protocol, along with the ClinicalTrials.gov checklist to DAIDS and their regulatory contractor as per Section 7.4.2.

### 9.2.9 Distribution of Version 1.0

Following notification from DAIDS (of approval for non-IND studies or of submission to the FDA for IND studies), the CRM distributes the final approved protocol to the protocol team and participating sites (copying CSIO). The final protocol is also posted on the IMPAACT website.

Many pre-implementation activities begin during the protocol development process, while others are dependent upon the distribution of the final, approved protocol. See Section 11 for details regarding pre-implementation activities.

## 9.3 Protocol Modifications

Consistent with DAIDS Guidance for Implementing Protocol Changes and other DAIDS policies and procedures, IMPAACT protocols may be clarified or modified by the following methods:

- Clarification Memorandum (CM)
- Letter of Amendment (LoA)
- Full Version Protocol Amendment
- Urgent Safety Notification

These methods, which are described in further detail below, are used for both IND and non-IND protocols. The protocol team determines the method to use in conjunction with the DAIDS MO, based on the guidance posted by DAIDS (or its regulatory contractor) (https://rsc.niaid.nih.gov/networks-protocol-teams/developing-protocols). See Table 9-2 for additional requirements and procedures.

As with Version 1.0 of the protocol, the Operations Center CRM is responsible for working with the protocol team to develop the relevant protocol document (e.g., CM, LoA), ensuring that the applicable review steps are completed with required protocol team sign-off, as summarized below:

- Prior to submission of draft LoAs to DAIDS (either for DAIDS scientific review, if required, or for DAIDS regulatory review; see Section 9.3.2)
- Prior to submission of draft Full Version Protocol Amendments to DAIDS (either for DAIDS scientific review, if required, or for DAIDS regulatory review; see Section 9.3.3)
- Prior to distribution of final Urgent Safety Notifications (e.g., Dear Investigator or Dear Participant letters; see Section 9.3.4)

Once all applicable reviews and approvals are obtained, the CRM is responsible for issuing final versions to the team and participating sites. Copies of all final protocol documents are posted on the IMPAACT website.

While protocol modification documents are in development and under review, study implementation proceeds according to the specifications of the prior approved version of the protocol, including any previously approved LoAs and CMs. Protocol modifications specified in the modification documents may only be implemented after the documents are fully approved, as described below.

### *IMPAACT MOG/SLG Review of Amendments*

Before a protocol team develops an LoA or a full version protocol amendment with significant changes to the scientific goals, study objectives, or design, SLG review and approval must be obtained. The team should develop a memorandum detailing the rationale for the proposed amendment, summarizing the proposed scientific/study design changes, and describing study timeline implications; ideally, budgetary implications should also be described. The process of preparing, obtaining review and sign-off (see Section 9.2.3), and submitting this type of memorandum is coordinated by the CRM. SLG review may be waived at the Network chair's discretion or in the case of design changes due to regulatory requirements (e.g., FDA comments) with protocol team unanimity; in both exceptions, no memorandum is required; the

Operations Center notifies the SLG, typically by providing relevant documentation (e.g., team response to FDA comments, draft summary of changes document).

For draft amendments with significant budget increases, MOG review and approval of the updated budget must be obtained as early as possible and before draft amendment documents are submitted for DAIDS reviews (either SRC or regulatory review). The Operations Center works with the protocol chair(s) and other team members as appropriate to develop a memorandum summarizing the increased budget line items, corresponding protocol changes, and timeline implications.

**Table 9-2. Requirements and Procedures for Protocol Modifications**

| Modification Requirements | Clarification Memorandum | Letter of Amendment | Full Version Protocol Amendment |
|---|---|---|---|
| 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 IRBs/ECs | Yes |
| Content requires change of informed consent form? | No | Possibly, depends on content and requirements of site IRBs/ECs | Yes |
| Content requires changes to study enrollment or study procedures?* | No | Possibly, depends on content | Possibly, depends on content |
| Results in change of protocol version number? | No | No | Yes |
| Requires approval by Medical Officer? | Yes | Yes | Yes |
| Requires approval by DAIDS SRC? | No | Yes, unless requirement waived by MO | Yes, unless requirement waived by MO |
| Requires DAIDS regulatory review? | No | Yes | Yes |
| Requires Medical Officer approval following regulatory review? | No | Yes | Yes |
| Requires RAB approval following Medical Officer review? | No | Yes | Yes |
| Requires approval by site IRBs/ECs? | No, unless required by site IRBs/ECs | Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained | Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained |
| Requires protocol registration? | No | Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained** | Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained** |

* -An LoA or full version protocol amendment is required for collection and entry of data in the study database for any procedure or evaluation that is not currently specified in the study protocol.
-An LoA or full version protocol amendment is not typically required for entry of additional data (i.e., additional detail/information) into electronic case report forms (eCRFs) for a procedure or evaluation that is already specified in the study protocol. However, sites must be officially notified via an appropriate mechanism (e.g., protocol CM) to enter the additional data into eCRFs from available source documentation. In some cases, an LoA or full version protocol amendment may be required if entry of the additional data necessitates eCRF changes, as determined on a case-by-case basis by the protocol team in consultation with the DMC and DAIDS RAB.

** Amendments including any revised site-specific informed consent forms should be implemented upon CRS receipt of all required IRB/EC approvals, unless otherwise noted in the LoA or summary of changes. Refer to the latest DAIDS Protocol Registration Manual, section "Amendment Registration," for details.

### 9.3.1 Clarification Memoranda

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 and/or inconsistencies in a protocol. A CM cannot be used if the modifications would impact participant safety, the risk-to-benefit ratio of study participation, or the sample ICFs. IMPAACT CMs generally include:

(A) Instructions to sites regarding approvals and implementation
(B) Rationale for the modifications included
(C) A summary of how the modifications are being applied to the current protocol text

Because CMs should be implemented immediately, any study implementation materials affected by the CM (e.g., the study-specific Manual of Procedures) should be finalized prior to finalization and distribution of the CM. Although updates of these materials are generally not anticipated with changes implemented through a CM, this should be discussed and confirmed by the protocol team (including the DAIDS MO). Protocol team members who identify any such requirements are responsible for notifying the CRM and protocol chairs early in the CM development process.

The decision to use a CM is the responsibility of the DAIDS MO and does not require DAIDS RAB approval or sign-off; however, the MO may consult with RAB if there are questions related to the content proposed in a CM prior to making a final determination. Drafts are distributed to the protocol team for review by the CRM. Sign-off on a CM by one DAIDS MO is required prior to finalization. Once approved, the CRM distributes the final approved CM to the protocol team and participating sites (copying CSIO). The final CM is also posted on the IMPAACT website.

IRB/EC approval of CMs is not required by DAIDS; however, sites may submit CMs to their IRBs/Ecs for their information or, if required by the IRB/EC, for approval prior to implementation. All applicable IRB/EC requirements must be followed. CMs may be implemented by sites upon issuance unless their IRB/EC requires prior approval.

### 9.3.2 Letters of Amendment

LoAs typically are relatively short documents prepared to specify protocol changes that have minimal impact on participant safety and the risk-to-benefit ratio of study participation and include relatively minor (if any) modifications of ICFs. An LoA can be used when there are specific changes to the protocol that result in the addition of new information or the deletion of incorrect or unnecessary information. An LoA does not change the protocol version number and is considered part of the previously approved protocol version. LoAs typically incorporate the content of CMs previously issued under the same protocol version. IMPAACT LoAs generally include:

A) Instructions to sites regarding approvals and implementation
B) A summary of and rationale for the modifications included
C) A detailed account of where and how the modifications are being applied to the current protocol text

In the instructions to sites regarding approvals and implementation, specific guidance is provided regarding protocol registration and informed consent requirements associated with the LoA. Instructions for protocol registration requirements indicate whether 1) the LoA should be implemented immediately upon obtaining all required approvals, or 2) implementation should be deferred until after obtaining a notice of LoA registration from the DAIDS Protocol Registration Office (PRO), or 3) implementation should be deferred until after obtaining notification from the Operations Center (as described further below). The first (immediate implementation) is the standard approach. The CRM coordinates with the

protocol team, the DAIDS MO, and DAIDS RAB as needed to confirm the approach to be taken for each LoA.

Members of the protocol team may determine that modifications contained in the LoA require additional time for preparation of materials prior to implementation of the LoA. For example, additional time may be needed to make investigational study products available or to update the Study Enrollment System (SES or Stars) or eCRFs prior to implementation of the LoA. Protocol team members are responsible for identifying any such requirements and notifying the CRM and protocol chairs early in the LoA development process. The CRM then incorporates wording into the instructions to sites stating that implementation of the LoA occurs upon obtaining all relevant approvals AND issuance of notification that all operational requirements for implementation of the LoA have been completed.

Review and approval steps for LoAs are similar to the steps described for original protocols in Section 9.2. As noted above, LoAs do not generally require IMPAACT reviews (e.g., SC or MPRG review). Prior to submission to DAIDS for review, draft LoAs are distributed to the protocol team for review; sign-off is obtained from key protocol team members. The process for sign-off is identical to the process followed for protocols in development, as described in Section 9.2.3. The protocol team works with the DAIDS MO(s) to make an initial assessment of whether the proposed changes may be made using an LoA (rather than a full version protocol amendment); final determination regarding the appropriate method to be used is typically made by DAIDS RAB when the LoA is submitted for DAIDS regulatory review, and this determination is communicated by DAIDS (or its regulatory contractor) before the regulatory review is completed. If the collective changes being requested by the protocol team are extensive and cannot be implemented easily and immediately, DAIDS RAB may require a full version protocol amendment. DAIDS SRC review is not required for LoAs unless otherwise determined by the DAIDS MO in consultation other DAIDS staff. The DAIDS regulatory review, MO review and approval, and final RAB review and approval steps described in Sections 9.2.6-9.2.8 must be completed for all LoAs.

Following notification from DAIDS (of approval for non-IND studies or of submission to the FDA for IND studies), the CRM distributes the final approved LoA to the protocol team and participating sites (copying CSIO). The final LoA is also posted on the IMPAACT website.

LoAs must be reviewed and approved by site IRBs/ECs prior to implementation. LoAs include instructions to sites regarding IRB/EC review and approval and recommendations on how to notify participants of the changes made in the LoA, if applicable. However, it is responsibility of the responsible IRB/EC to determine whether and how participants are to be notified of changes and all IRB/EC requirements must be followed. In all cases, the LoA may not be implemented at a site until approval is obtained from all IRBs/ECs and other applicable regulatory entities responsible for oversight of research at that site. Sites are also required to register the LoA through DAIDS PRO (see DAIDS Protocol Registration Manual). Depending on the instructions to sites contained in the LoA, sites may be required to defer implementation until protocol registration is confirmed and/or until an implementation notice is issued for the LoA by the Operations Center.

### 9.3.3 Full Version Protocol Amendments

Full version protocol amendments are prepared when required changes to a protocol are substantive in number and/or nature. Modifications made via a full version protocol amendment are incorporated directly into the protocol document and result in a new protocol version number. A full version protocol amendment must also incorporate the contents of CMs and LoAs issued for the prior protocol version.

Examples of changes requiring a full version protocol amendment may include:

- Increase or decrease of more than 10% of the total number of participants to be enrolled
- Study design changes such as addition of a new study arm, a new study drug or formulation, an increase in dosage or dosing frequency of a study drug
- Substantive changes to the sample ICF(s)

Full version protocol amendments are developed by the protocol team as described above for original protocols and are accompanied by a summary of changes document. Summary of changes documents generally include:

A) Instructions to sites regarding approval and implementation
B) A summary of and rationale for the modifications included
C) A detailed account of where and how the modifications are being applied in the protocol text

In the instructions to sites regarding approvals and implementation, specific guidance is provided regarding protocol registration and informed consent requirements associated with the amendment. Instructions for protocol registration requirements indicate whether 1) the amendment should be implemented immediately upon obtaining all required approvals, or 2) implementation should be deferred until after obtaining a notice of amendment registration from the DAIDS PRO, or 3) implementation should be deferred until after obtaining notification from the Operations Center (as described further below). The first (immediate implementation) is the standard approach. The CRM coordinates with the protocol team, the DAIDS MO, and DAIDS RAB as needed to confirm the approach to be taken for each amendment.

Members of the protocol team may determine that modifications contained in the amendment require additional time for preparation of materials prior to implementation of the amendment. For example, additional time may be needed to make investigational study products available or to update the SES or Stars prior to implementation of the amendment. Protocol team members are responsible for identifying any such requirements and notifying the CRM and protocol chairs early in the amendment development process. The CRM then incorporates wording into the instructions to sites stating that implementation of the amendment occurs upon obtaining all relevant approvals AND issuance of notification that all operational requirements for implementation of the amendment have been completed.

Review and approval steps for full version protocol amendments are similar to the steps described for original protocols in Section 9.2. As noted above, amendments may require IMPAACT reviews (e.g., SC or MPRG review). Prior to submission to DAIDS for review, draft protocol amendments and summary of changes documents are distributed to the protocol team for review; sign-off is obtained from key protocol team members. The process for review and sign-off is identical to the process followed for protocols in development, as described in Section 9.2.3. Depending on the nature and extent of the modifications, DAIDS SRC review may be required as determined by the MO in consultation with the SRC chair and other DAIDS staff; if so, the procedures described in Section 9.2.5 are followed. The DAIDS regulatory review, MO review and approval, and final RAB review and approval steps described in Sections 9.2.6–9.2.8 must be completed for all amendments.

Following notification from DAIDS (of approval for non-IND studies or of submission to the FDA for IND studies), the CRM distributes the final approved full version protocol amendment and final summary of changes document to the protocol team and participating sites (copying CSIO). The final documents are also posted on the IMPAACT website.

Full version protocol amendments (new protocol versions and the accompanying summary of changes) must be reviewed and approved by site IRBs/ECs prior to implementation. Summary of changes documents include instructions to sites regarding IRB/EC review and approval and recommendations on how to notify participants of changes made in the amendment, if applicable. However, it is the responsibility of the responsible IRB/EC to determine whether and how participants are to be notified of the changes and all IRB/EC requirements must be followed. In all cases, the full version protocol amendment may not be implemented at a site until approval is obtained from all IRBs/ECs and other applicable regulatory entities responsible for oversight of research at that site. Sites are also required to register the full version protocol amendment through DAIDS PRO (see DAIDS Protocol Registration Manual). Depending on the instructions to sites contained in the summary of changes, sites may be required to defer implementation until protocol registration is confirmed and/or until an implementation notice is issued for the amendment by the Operations Center.

### 9.3.4 Urgent Safety Notifications

When there is a significant and immediate participant safety concern requiring notification of sites, investigators, IRBs/ECs and participants in an expedited manner, an urgent safety notification may be required. These notifications are typically written as "Dear Investigator" and "Dear Participant" letters developed by the protocol team, in consultation with DAIDS RAB; the DAIDS MO works with DAIDS RAB to determine if additional reviews and/or approvals are required prior to finalizing these types of notifications.

Urgent safety notifications include an explanation of and rationale for protocol changes and are distributed to sites for submission to IRBs/ECs and other applicable regulatory entities, with instructions regarding implementation. Recommendations for informing and re-consenting participants if needed is provided to sites by the protocol team; however, IRBs/ECs and applicable regulatory entities are responsible for determining the appropriate methods for this at each site.

Draft notifications are distributed to the protocol team for review; sign-off is obtained from key protocol team members, consistent with the requirements indicated in Section 9.2.3 (timelines may be truncated to allow for expediency). Once sign-off is obtained, the CRM distributes the final approved notifications to the protocol team and participating sites by the CRM (copying CSIO and DAIDS RSC).

## 9.4 Collaborative Studies

The IMPAACT Network recognizes that a thriving international network of researchers and collaborators is essential to ensuring rapid and continuing advancement of the Network's mission to improve health outcomes for infants, children, adolescents, and pregnant and postpartum people who are impacted by or living with HIV, tuberculosis, and other HIV-related conditions. The Network welcomes the opportunity to collaborate with other networks, researchers, and organizations on the development and implementation of studies consistent with its research agenda. Such cooperation enables IMPAACT to expand its scope, avoid duplication, enhance the interdisciplinary environment, and create opportunities for site participation/contribution. The mutual benefits include increased awareness of relevant activities and publications and identification of researchers with specific interests.

If an IMPAACT study is to be developed and/or implemented in collaboration with another research network or organization may require review by a scientific leadership group of the other network/organization, the review process must be agreed upon in advance by the respective leadership groups on a case-by-case basis. Typically, protocol team leadership includes representatives from each network/organization (e.g., as co-chairs), with other representatives from networks/organizations included as needed, and one of the networks' Operations Center, SDMC, and LC designated to take the lead to

avoid duplication of effort. In addition, both networks/organizations typically provide scientific and operational review of the protocol and oversight of the study, jointly or in parallel; however, the scope of the collaboration may vary and could be limited to support for IMPAACT site participation.

Collaborative studies may include those with co-funding through a non-network mechanism (e.g., a U01 grant, a pharmaceutical company), with the scope of the network's contributions determined on a case-by-case basis. Generally, the IMPAACT Network will consider collaboration with another entity if the study is of high interest, does not conflict with other IMPAACT studies, and is thought to be feasible for IMPAACT-affiliated site participation. The MOG may consider the need for and availability of IMPAACT resources; depending on the collaborative group, additional Memoranda of Understanding may need to be developed and approved.

When IMPAACT and another network, researcher, or organization plan to co-develop a protocol and implement a study, the roles and responsibilities of each entity are agreed upon in advance by the respective leadership groups on a case-by-case basis. A Responsible, Accountable, Consulted, Informed (RACI) matrix or alternative project management tool, may be used to set expectations for these studies.

When IMPAACT collaborates with a pharmaceutical company on development and/or conduct of a clinical trial, the roles and responsibilities are typically outlined in a Clinical Trials Agreement (CTA) with NIAID/DAIDS, a contract with the IMPAACT Finance Office and/or other types of agreements.