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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 and potential public health impact 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 capsules, concepts, and protocols, shown in Figure 9-1 and described in greater detail in the remainder of this section.

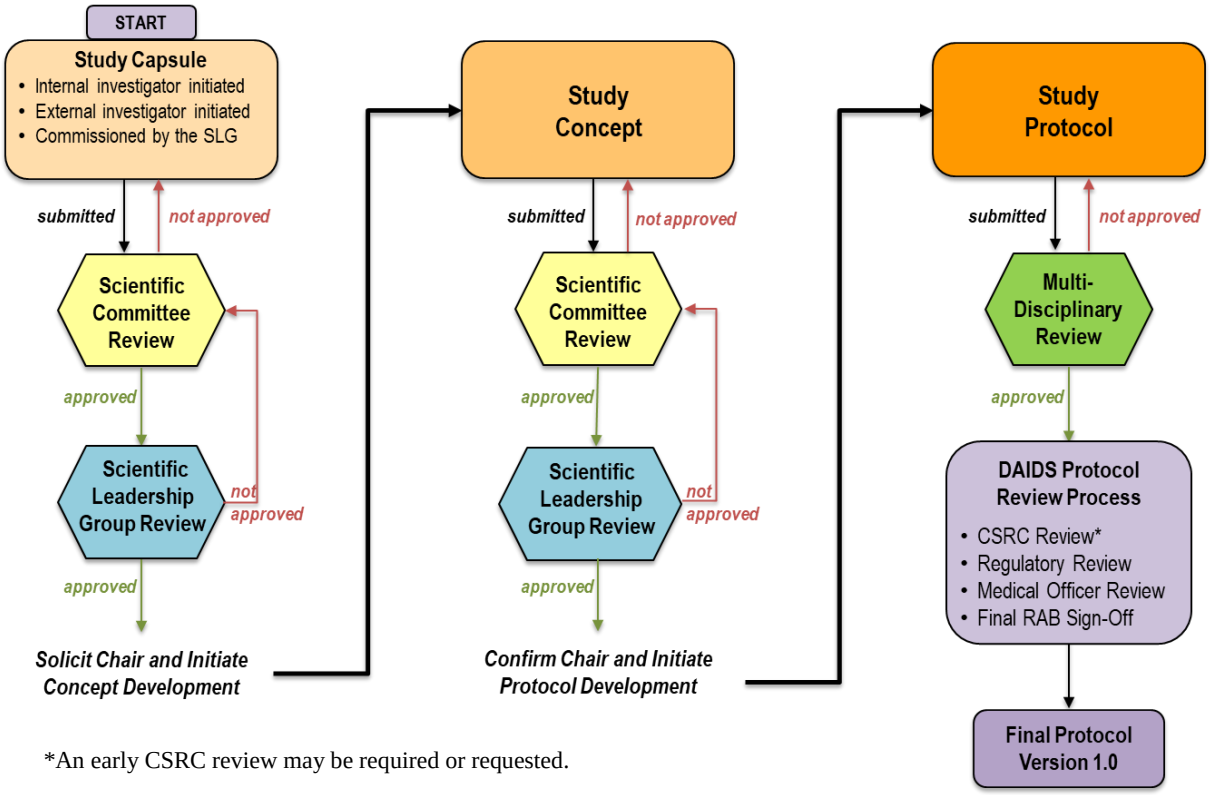
Scientific priorities for IMPAACT research are determined by the SLG in collaboration with the SCs, in alignment with the network's mission and research agenda (outlined in Section 1). New studies may be proposed by IMPAACT investigators, by external investigators or may be commissioned by the SLG. Regardless 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 a short study proposal in the form of a 'capsule' document that briefly outlines the proposed study so that an initial determination can be made about whether further development within the network is warranted (see Figure 9-2 for review criteria). If so, the capsule is further elaborated into a study concept so that a determination can be made about whether the network should commit resources to full protocol development and study conduct.

For high priority studies, the SLG may approve a capsule for full protocol development – eliminating the concept development and review step. Likewise, the SLG may commission development of a study concept – eliminating the capsule development and review step.

Conflicts of Interest

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

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



*An early CSRC 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 all stages of study proposal review - for capsules, concepts, and protocols. 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 women affected by 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 Capsule Development and Review

9.1.1 Development

The first step in proposing a new IMPAACT study is a two to three-page capsule. The capsule template is available on the IMPAACT website and includes the elements outlined in Figure 9-3:

http://impaactnetwork.org/resources/study-proposals.htm

Figure 9-3. Elements of IMPAACT Capsules

- Title of proposed study
- Rationale
- Objectives and endpoints
- Hypotheses
- Study design
- Key study population characteristics and approximate sample size (e.g., 10-100, hundreds, thousands of participants)
- Study duration (enrollment and follow-up)
- Laboratory assays required
- Anticipated study implementation at international and/or sites in the United States

Completed capsules should be submitted by the proposing investigator(s) to the Operations Center via the following email address: impaact.capsubmissions@fstrf.org. The capsule is then assigned an identification number for tracking purposes and forwarded to the appropriate SC for review. The tracking number is also communicated to the Statistical and Data Analysis Center (SDAC) at cbar.attask@sdac.harvard.edu.

Capsules may be submitted at any time, however, as described below, SLG review of new study proposals typically occurs on a quarterly basis.

9.1.2 Scientific Committee Review

The Operations Center forwards each new numbered capsule to the relevant SC chair and vice chair to begin the IMPAACT review process. Capsules 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 capsule 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 capsule. In addition, the SDAC representative (or designee) on the SC provides 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 capsule and respond to questions or requests for clarification; however, participation is not required. Assigned reviewers lead the discussion of the capsule. 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 capsule, 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. When more than one capsule is approved for submission to the SLG within a review cycle, the SC prioritizes them.

The Operations Center coordinates with the SC chair and vice chair to distribute each capsule for review, schedule the review, organize the committee voting process, and communicate the outcome of the review in writing to the proposing investigators, the SC chair, vice chair and, SDAC representatives, and the full SC. If it is determined that a capsule should be revised and re-submitted to the SC, the proposing investigators may be requested to provide a written response to the reviewers' comments along with the revised capsule.

Note: As research priorities evolve over time in response to emerging science and changing standards of care, and because network resources may fluctuate, a capsule 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 reviews new study proposals (capsules) on a quarterly basis (March, June, September, and December of each year), either via conference call or during an in-person meeting. Submission deadlines and review dates are announced to the SCs in advance so that their reviews, which must precede SLG review, can be planned accordingly. 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 capsule from other ICAB members.

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 capsule (i.e., before the next scheduled quarterly review). 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 all capsules that have been approved by the respective SCs to the SLG. A primary, secondary, and statistical reviewer are assigned to each capsule. Assigned reviewers submit written comments to the Operations Center 1-2 days in advance of the SLG review for distribution to the full SLG, the relevant SC chair/vice chair and the proposing investigators prior to the review. Quarterly reviews 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 or vice chair briefly introduces the capsule and responds to questions or requests for clarification. During the closed portion of the review, assigned reviewers lead the discussion of the capsule. Other SLG members provide review comments during the call/meeting (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, for example, when the quarterly 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 capsule using the criteria specified above in Figure 9-2 and vote on next steps for the capsule, per the following categories.

(1) Approve for concept 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 may defer scoring or voting on a capsule if it is determined that additional forthcoming information is critical to decision-making, for example, results of another relevant study that is planned or underway.

If a capsule is approved for concept development, the SLG reviewers' comments are to be addressed/reflected in the concept; a separate response is not required unless specifically requested by the SLG. However, if SLG reviewers' suggestions/comments are not addressed in the concept (e.g., through inclusion of enhanced rationale for the proposed approach), a separate response with an explanation is advised. If it is determined that a capsule should be revised and re-submitted to the SLG, the proposing investigators are requested to provide a written response to the reviewers' comments along with the revised capsule. Prior to re-submission, the documents should be reviewed by the SC chair and/or vice chair to determine if further SC review is required before the revised capsule and response are submitted to the SLG.

Only capsules voted for concept approval by at least 75% of eligible voting SLG members move forward. If the number of capsules to be approved for concept development must be limited due to budgetary or other constraints, the average score assigned to each capsule is used to rank the capsules in priority order

for approval. Approval for concept development does not guarantee approval for protocol development and study implementation.

The Operations Center documents the review outcome and communicates the final result for each capsule to the full SLG, the proposing investigators, the relevant SC chair and vice chair, and SDAC representatives within one week of voting completion; for each capsule approved for concept development, the Operations Center assigns a concept number which is included in the outcome notification for tracking purposes. The Operations Center also notifies SDAC representatives at cbar.attask@sdac.harvard.edu of capsules approved for concept development or disapproved by the Network.

9.2 Concept Development and Review

9.2.1 Development

Concepts are developed in a template format that is available from the Operations Center. Concepts are expected to be approximately 10 pages in length (excluding references and budget estimate) and describe the proposed study in greater detail than the capsule. In addition, the leadership of the protocol is proposed in the concept, including the proposed protocol chair and vice chair, for approval by the SLG.

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

Fully developed concepts are submitted to the relevant SC for review, ideally within six weeks of the capsule's approval. To allow adequate time for review, concepts must be submitted at least two weeks in advance of the regularly scheduled monthly SC call.

9.2.2 Scientific Committee Review

The SC concept review process and criteria are the same as described above for capsules.

Following the review discussion, SC members with no conflicts of interest vote 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

The outcome of the SC concept review is communicated as described above for capsules. The Operations Center also forwards approved concepts for review by the SLG.

9.2.3 Scientific Leadership Group Review

Whereas capsules are typically solicited and reviewed by the SLG on a quarterly basis, concepts that are developed from approved capsules are reviewed during the first available scheduled SLG call or meeting following submission of the concept; i.e., concept submission/review need not await the next scheduled quarterly SLG review.

Concepts are reviewed by the SLG in the same manner and according to the same review criteria as described above for capsules.

Following the review discussion, eligible SLG voting members assign a numeric score to the concept based on the criteria specified in Figure 9-2 and vote on next steps, per the following three 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

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.)

The Operations Center documents the review outcome and communicate the final result for each concept to the full SLG, the proposing investigators, the relevant SC chair, vice chair, and SDAC representatives (cbar.attask@sdac.harvard.edu) within 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.

9.3 Protocol Development and Review

The protocol development and review processes detailed below are based on the guidance posted on the RSC website (https://rsc.tech-res.com/network-and-protocol-teams/protocol-development).

9.3.1 Development

Once a concept is approved for protocol development, protocol team formation begins. As noted above, the names of the proposed protocol chair and vice chair(s) are included in the concept sheet submission for SLG review and endorsement. SLG endorsement is based on past leadership performance, current protocol/SC commitments, and relevant expertise/experience. A maximum of 10-15% FTE direct support is provided for protocol team leadership (across both/all chair and vice chair positions). No more than two vice chairs are endorsed, and SLG members are not eligible for a chair or vice chair position but may participate as a protocol team member.

The assigned Operations Center Clinical Trials Specialist (CTS) works with the SLG-endorsed protocol chair and vice chair(s) to initiate the formation of the protocol team and contacts the SDMC, LC, Division of AIDS (DAIDS) Program and Pharmacy Affairs Branch (PAB), National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH) to determine their assigned representatives. If specific expertise is needed on the team (e.g., pharmacologist, immunologist, behavioral scientist, etc.), recommendations may be sought from the relevant members of the SLG (e.g.,

LC Principal Investigator [PI]) and/or SC chairs as needed. 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 CTS incorporates all information from the approved concept and any relevant review comments into the IMPAACT protocol template and works closely with the protocol chair to specify the timeline for completion of the various sections and review steps to ensure adherence to the relevant (standard or fast-track) timeline specified, and key writing assignments are determined. A determination is made regarding whether an early Clinical Sciences Review Committee (CSRC) review should be arranged and, if so, that step is incorporated into the timeline. The protocol team or IMPAACT leadership may request an early review and/or this may be determined by DAIDS. It is generally expected that most IMPAACT protocols will not require an early review (Prevention Sciences Review Committee, PSRC, does not conduct early reviews). When an early review is required or requested, the review should occur prior to submission of the protocol for IMPAACT Multidisciplinary Protocol Review Group (MPRG) review.

Modifications of the study objectives, design, and/or schedule of evaluations that would substantively affect the size, scope, or cost of a study — relative to the previously-approved concept sheet — 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.

The protocol chair and co-chair(s), CTS, and an assigned protocol writing team then draft the full protocol through an iterative process. The team communicates frequently via email and conference calls. An in-person protocol development meeting should also be convened to facilitate the process, with the appropriate timing agreed upon by the team. Such meetings are generally expected to include team members with key writing responsibilities rather than all members. See Section 4 of this manual 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, 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, design, and eligibility criteria. 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. Within the statistical section, the sub-section describing outcome measures should correspond with the study objectives and should take into consideration requirements for submitting study results to ClinicalTrials.gov.

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 CTS monitors adherence to the protocol template to ensure that all applicable research regulations, guidelines, NIH policies, and IMPAACT policies and procedures are reflected in the protocol document. Likewise, the CTS 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 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 CTS are responsible for maintaining the protocol development timeline, communicating deadlines to team members as needed, following-up on pending items, and ensuring deadlines are met. Internal organizational reviews may also be conducted (e.g., at SDAC or the

Operations Center) but must be coordinated in keeping within the overall protocol development timeline. As the final step within the timeframes specified above, the draft protocol is distributed to all protocol team members for review and sign-off prior to submission for MPRG review.

Team sign-off is accomplished with one of the following required by the protocol chair, vice chair(s), medical officers (MO), and statistician(s):

(1) Approve
(2) Approve contingent on the following changes
(3) Approved with suggested changes
(4) Revise and redistribute for sign-off

Upon Protocol Team sign-off, the draft protocol is submitted to the IMPAACT MPRG at least two weeks prior to the anticipated review date.

The CTS begins internal Operations Center coordination of the MPRG review 3-4 weeks prior to Protocol Team sign-off. See Table 9-1 for an outline of the protocol development process and timeframes.

Table 9-1. Standard and Fast Track Protocol Development Timelines

Protocol Development Timelines	Standard Process	Fast Track Process
IMPAACT Reviews		
Development of full draft protocol (including early CSRC review, if applicable, and internal SDAC review)	12 weeks	6 weeks
Protocol Team sign-off	1 week	1 week
IMPAACT MPRG Review (including advance submission, and post review revisions/response)	5 weeks	2 weeks
NIAID Division of AIDS Reviews		
Protocol Team sign-off	1 week	1 week
DAIDS Clinical or Prevention Sciences Review Committee Review (including advance submission and post review revisions/response)	6 weeks	3 weeks
DAIDS regulatory review (including advance submission and post review revisions/response)	4 weeks	2 weeks
DAIDS Medical Officer sign-off followed by protocol team response	10 working days	5 working days
DAIDS Regulatory Affairs Branch final sign-off	10 working days	3 working days
Total Time from Concept Approval to Final Protocol Version 1.0	~33 weeks	~17 weeks
Note: Revisions and resubmission may be required at each review step.		

9.3.2 Protocol Development Tracking and Oversight

Full draft protocols are expected to be submitted to the MPRG within 12 weeks (standard) or 6 weeks (fast-track) of beginning the development process, as outlined above. A high priority protocol may be designated for fast-track development by the SLG if there are urgent, time-sensitive considerations and the study must be implemented quickly in response to emerging scientific or clinical medicine priorities or due to external factors such as a pharmaceutical company's regulatory timeline. A limited number of studies may be fast-tracked at the same time, and the SLG may have to consider shifting priorities (delaying other projects) to accommodate these accelerated timelines.

The Operations Center provides monthly reports to update the MOG on protocol development status, and study implementation challenges and progress (see Section 13 Oversight). 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 is made by the SLG.

9.3.3 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, focusing on key issues such as site participation, infrastructure and capacity, relevance to the community, and any ethical, logistical, or potentially regulatory concerns. The MPRG conducts reviews on behalf of the SLG. The review is multidisciplinary to streamline and avoid multiple sequential review steps.

The MPRG is comprised of the network vice chair (who serves as MPRG chair); the chair or vice chair of the relevant SC; standing representatives of the Operations Center, SDMC, LC, and ICAB; the IMPAACT pharmacist; a study coordinator; designated NIH staff; and 1-2 external reviewers with expertise in the specific content area of the protocol.

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. There is an initial closed session for discussion of the major comments, after which the protocol chair joins the call to answer questions and offer clarifications as needed. During the final closed session, the MPRG settles on the collective major comments to be included in the review summary and agrees on one of the following 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 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 sign-off by the MPRG chair, provides the summary to the Protocol Team, typically within three working days of the review.

If required, a response to reviewers' comments and revised protocol are to be submitted to the MPRG in writing, typically within 14 working days of receiving the review summary. The protocol cannot proceed to the next review step until MPRG approval is obtained. If the protocol team has concerns about the review recommendations or outcome, and these cannot be resolved through discussion between the MPRG chair and protocol chair, the IMPAACT SLG assists with resolution.

Throughout all reviews, from capsule through protocol reviews, the IMPAACT SC, SLG, and the MPRG determinations are considered final.

9.3.4 DAIDS Scientific Review

Upon completion of the MPRG review step, IMPAACT protocols are reviewed by a DAIDS Scientific Review Committee (SRC), either the CSRC or the 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

Following team sign-off (process to be followed as described in Section 9.3.1, the protocol is prepared for submission for SRC review. The submission process varies between CSRC and PSRC review as below:

- *For protocols undergoing CSRC review:* When the protocol is ready for CSRC review, the CTS submits the protocol to the CSRC coordinator and Clinical Study Information Office (CSIO), along with the MPRG's comments and the team's response (if required). 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.

- *For protocols undergoing PSRC review:* When the protocol is ready for PSRC review, the CTS 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 (10 working days) prior to the scheduled PSRC review date.

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 10 working days after the review. The memorandum identifies major and minor review findings along with one of four review outcomes:

- Approved
- Approved contingent upon the protocol team adequately addressing in writing the major concerns, with the MO determining the adequacy of the response and the revised protocol
- Approved contingent upon the protocol team adequately addressing in writing the major concerns with the SRC reviewing the responses and the revised protocol
- Disapproved

When applicable, the protocol team prepares a response to all SRC comments and a revised version of the protocol (and any additional documents requested) for submission through the SRC coordinator. The response to each comment should include a description of any changes made in the protocol or justification for no change. If the response and/or changes are deemed acceptable, the protocol team is notified in writing of SRC approval 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 MO(s), 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 sign-off, and final DAIDS Regulatory Affairs Branch (RAB) review and sign-off described below. Throughout these steps, the CTS works closely with other protocol team members to respond to review comments and make any necessary changes to the protocol.

9.3.5 DAIDS Regulatory Review

Once SRC approval is obtained and the key protocol team members have reviewed the changes, the protocol — labeled "Regulatory Review Version" — is submitted with the ClinicalTrials.gov checklist by the CTS to DAIDS (or its regulatory contractor) for regulatory review (copying the CSIO). The regulatory review is to be completed within 10 working days of protocol receipt. During this step, DAIDS (or its regulatory contractor) carries out a regulatory review of the protocol. DAIDS (or its regulatory contractor) incorporates all comments into a review summary document and transmits the document electronically to the CTS.

9.3.6 DAIDS Medical Officer Review and Sign-Off

Unless otherwise instructed, the protocol team revises the protocol based on the regulatory review summary and prepares a response document, confirming that requested changes were made and providing justification if a requested change was not made. This revised version — labeled "Medical Officer Review Version" — is submitted to DAIDS (or its regulatory contractor) by the CTS for MO review (copying the CSIO). This review is completed within 10 working days of protocol receipt. During this time, DAIDS (or its regulatory contractor) reviews the protocol to ensure that all regulatory review findings have been satisfactorily addressed and then forwards the protocol for review by the MO.

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.

DAIDS (or its regulatory contractor) incorporates any review comments into a review summary document and transmits the document electronically to the CTS. The protocol team prepares a response to any MO comments and revises and re-submits the protocol as needed, following the process described above for regulatory review. Once the MO has approved the protocol, it can be submitted for final DAIDS RAB review and sign-off.

9.3.7 Final DAIDS Regulatory Affairs Branch Review and Sign-Off

Unless otherwise instructed by DAIDS (or its regulatory contractor), the CTS submits the MO-approved version of the protocol — labeled "FINAL Version 1.0" — to DAIDS (or its regulatory contractor) for final RAB sign-off (copying the CSIO). RAB sign-off is expected within approximately 10 working days of submission. DAIDS RAB reviews the revised protocol and provides sign-off. DAIDS (or its regulatory contractor) submits the finalized protocol to the FDA (for Investigational New Drug [IND] studies) and sends it to the Operations Center for distribution to sites.

9.3.8 Distribution of Version 1.0

Upon receipt of the final DAIDS approval notification, the CTS electronically distributes the final approved protocol to the protocol team and participating study sites. 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 of this manual for details regarding pre-implementation activities.

9.4 Protocol Modifications

In accordance with DAIDS policies and procedures, IMPAACT protocols may be clarified/modified by three methods:

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

These methods for protocol changes and clarifications, which are described in the following sections, are used for both IND and non-IND protocols. The protocol team determines the method to use in conjunction with the DAIDS MO, 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, below, for additional requirements and procedures.

As with version 1.0 of the protocol, the Operations Center CTS is responsible for working with the protocol chair and team to develop the protocol modification document (e.g., CM, LoA), ensuring that the applicable review steps are completed, and issuing final versions to the team and participating study sites. Copies of all final protocol modifications 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 SC/MOG/SLG/MPRG Review of Amendments

Before a protocol team develops a LoA or full version protocol amendment that will likely have study budget implications, as determined by the Operations Center in consultation with the protocol chair, network chair, SDMC PI, and/or LC PI, MOG approval must be obtained through submission of a brief memorandum from the protocol team summarizing and providing the rationale for the proposed changes

and describing how the study budget may be affected. Likewise, if the proposed amendment includes significant changes to the scientific goals, study objectives or design, SC and SLG approval must be obtained before amendment development is begun in earnest. The Operations Center works with the SC chair as needed and with the Network chair (who serves as the chair of the SLG and MOG) to ensure appropriate advance reviews and avoid duplicative steps. Once developed, full version protocol amendments require review and approval by the MPRG, or a subset thereof, as determined by the MPRG chair on a case by case basis depending on the nature and extent of the changes being made or if recommended by the MOG or SLG. Unless otherwise determined by the MOG or SLG during its advance (amendment proposal) review, LoAs do not require MPRG review and approval once developed.

Table 9-2. Requirements and Procedures for Protocol Modifications

Modification Requirements	Clarification Memorandum	Letter of Amendment	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
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 final Medical Officer sign-off following regulatory review?	No	Yes	Yes
Requires RAB sign-off 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

*Note: Amendments including any revised site-specific informed consent forms should be implemented upon CRS receipt of all required IRB/EC approvals. Refer to the latest DAIDS Protocol Registration Manual, section "Amendment Registration," for details.

9.4.1 Clarification Memoranda (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 and 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. A standard format for IMPAACT CMs is followed, which includes:

(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

Because CMs should be implemented immediately, any materials needed prior to implementation (e.g., participant enrollment or data collection materials) should be finalized prior to CM finalization and distribution. Note that updates to these materials are generally not anticipated with changes implemented through a CM but would need to 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 CTS 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 and sign-off. Written approval of a CM by the DAIDS MO is required prior to finalization and distribution to sites and the protocol team. Once approved, CMs are distributed to the protocol team and participating study sites by the CTS. IRB/EC approval of CMs is not required by DAIDS; however, sites may to 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.

9.4.2 Letters of Amendment (LoA)

LoAs typically are relatively short documents prepared to specify changes to a protocol that have minimal impact on participant safety and the risk-to-benefit ratio of study participation and include relatively minor modifications of study informed consent forms, if any. A 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. A LoA does not change the protocol version number and is considered part of the previously approved protocol version. A standard format for IMPAACT LoAs is followed, which includes:

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

For some LoAs, 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 SES prior to implementation of the LoA. Protocol team members who identify any such requirements are responsible for notifying the CTS and protocol chairs early in the LoA development process. The CTS 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.

Drafts are distributed to the full protocol team for review and sign-off. LoAs typically incorporate the content of prior CMs issued under the same prior version of the protocol. See Section 9.4 above for required IMPAACT network reviews and approvals. The protocol team works with the MO to make an initial assessment of whether the proposed changes may be made using a LoA (rather than a full version protocol amendment); final determination regarding the appropriate method to be used is made by DAIDS RAB once the protocol team has formally submitted a request (in the form of a LoA versus full version protocol amendment), and this determination is communicated by DAIDS (or its regulatory contractor) before the internal review of a LoA is completed. If the collective changes being requested by the protocol team are extensive and cannot be implemented easily and immediately, the DAIDS RAB may require the protocol team to develop a full version protocol amendment. LoAs follow the same DAIDS review steps outlined above for original protocols, with the exception that SRC review of LoAs is not required unless otherwise determined by the DAIDS MO in consultation other DAIDS staff.

Once final DAIDS RAB sign-off on the LoA is obtained, DAIDS (or its regulatory contractor) notifies the CTS; if the study is being conducted under an IND, this notification includes acknowledgement that the LoA has been submitted to the FDA. The Operations Center then distributes the approved LoA to the protocol team and participating study sites. LoAs must be reviewed and approved by site IRBs/ECs prior to implementation. They typically include instructions to study sites regarding IRB/EC review and approval and recommendations on how to notify participants of the changes, if applicable. However, it is responsibility of the responsible IRB/EC to determine whether and how participants are to be notified of the changes made in the LoA, and all IRB/EC requirements must be followed. The LoA may not be implemented at a site until approval is obtained from all IRBs/ECs responsible for oversight of research at that site and any other applicable regulatory entities. Sites are required to submit a registration packet for the LoA to the DAIDS Protocol Registration Office; however, implementation of the LoA need not await this step and, instead, should proceed as soon as all relevant IRB/EC and other required approvals are obtained (see DAIDS Protocol Registration Manual).

9.4.3 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 all CMs and LoAs previously implemented since the last DAIDS approved version of the protocol.

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 informed consent form(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 that includes instructions to the participating sites regarding approval and implementation of the amendment, an overview of the changes and rationale for each, and a detailed description of where the changes (additions and deletions) were made in the protocol text.

IMPAACT review and approval steps for amendments are described in Section 9.4. 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 9.3.4 are followed. DAIDS (or its regulatory contractor) regulatory review, MO review and sign-off, and final RAB review and sign-off steps described in Section 9.3.5 must be completed for all full amendments. As described above, the protocol team works together to respond to and complete the various review steps.

Upon receipt of the final DAIDS approval notification (which includes acknowledgement that the new version has been submitted to the FDA, if applicable), the CTS electronically distributes the final approved protocol to the protocol team and participating study sites. Full amendments (new protocol versions and the accompanying summary of changes) must be reviewed and approved by site IRBs/ECs prior to implementation. The summary of changes document includes instructions to study sites regarding IRB/EC review and approval and recommendations on how to notify participants of the changes and whether re-consenting is required. However, it is the responsibility of the responsible IRB/EC to determine whether and how participants are to be notified of the changes made in the full version protocol amendment, and all IRB/EC requirements must be followed. The full version protocol amendment may not be implemented at a site until approval is obtained from all IRBs/ECs responsible for oversight of research at that site and any other applicable regulatory entities. Sites are required to register the full version protocol amendment through the DAIDS Protocol Registration Office; however, implementation of the full version protocol amendment should proceed as soon as all relevant IRB/EC and other required approvals are obtained (see DAIDS Protocol Registration Manual).

9.4.4 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 and with the approval of the DAIDS RAB. They include an explanation of and rationale for the changes and are distributed to sites for submission to their IRBs/ECs and other regulatory entities, with instructions regarding implementation. Recommendations for informing participants and re-consenting participants if needed is provided to sites by the protocol team; however, the relevant IRBs/ECs are responsible for determining the appropriate method for informing participants of the information and the appropriate methods for consenting participants.

9.5 Co-Endorsed and Co-Development of Protocols and Other Networks' 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 significantly change HIV disease and associated infections among infants, children, adolescents, and pregnant/postpartum women. To facilitate this collaborative environment, the IMPAACT Network welcomes the opportunity to cooperate with other networks, researchers, and organizations in co-sponsorship or endorsements. Such cooperation enables IMPAACT to expand its scope, avoid duplication, and enhance the interdisciplinary environment. The mutual benefits include increased awareness of relevant activities and publications; and identification of researchers with specific interests.

IMPAACT protocols co-endorsed by another network may require review by a scientific and/or leadership group of the other network; however, such reviews are typically considered advisory, with IMPAACT procedures and approvals to take precedence.

Generally, the IMPAACT Network will consider co-endorsement of a capsule or protocol if the topic is of high interest, does not conflict with other IMPAACT studies, and is thought to be feasible for IMPAACT-affiliated sites' participation. If IMPAACT is considering co-endorsement of another network's study, the relevant SC and the SLG reviews the other network's draft (or final) protocol for scientific merit and may provide comments; however, it is generally not expected that recommended changes must be made; instead – unless otherwise stipulated/agreed upon in advance – the IMPAACT SC and SLG makes a determination about co-endorsement with the assumption that their recommended changes to a protocol will not be accepted. The MOG may review the need for and availability of IMPAACT resources; depending on the collaborative group, additional Memoranda of Understanding may need to be developed and approved.

In cases in which IMPAACT and another network agree to co-develop a protocol, the roles and responsibilities of each are agreed upon in advance by the respective leadership groups on a case by case basis. Typically, protocol team leadership include representatives from both networks (e.g., as co-chairs), with other representatives from each network 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 typically provide scientific and operational review of the protocol, jointly or in parallel.