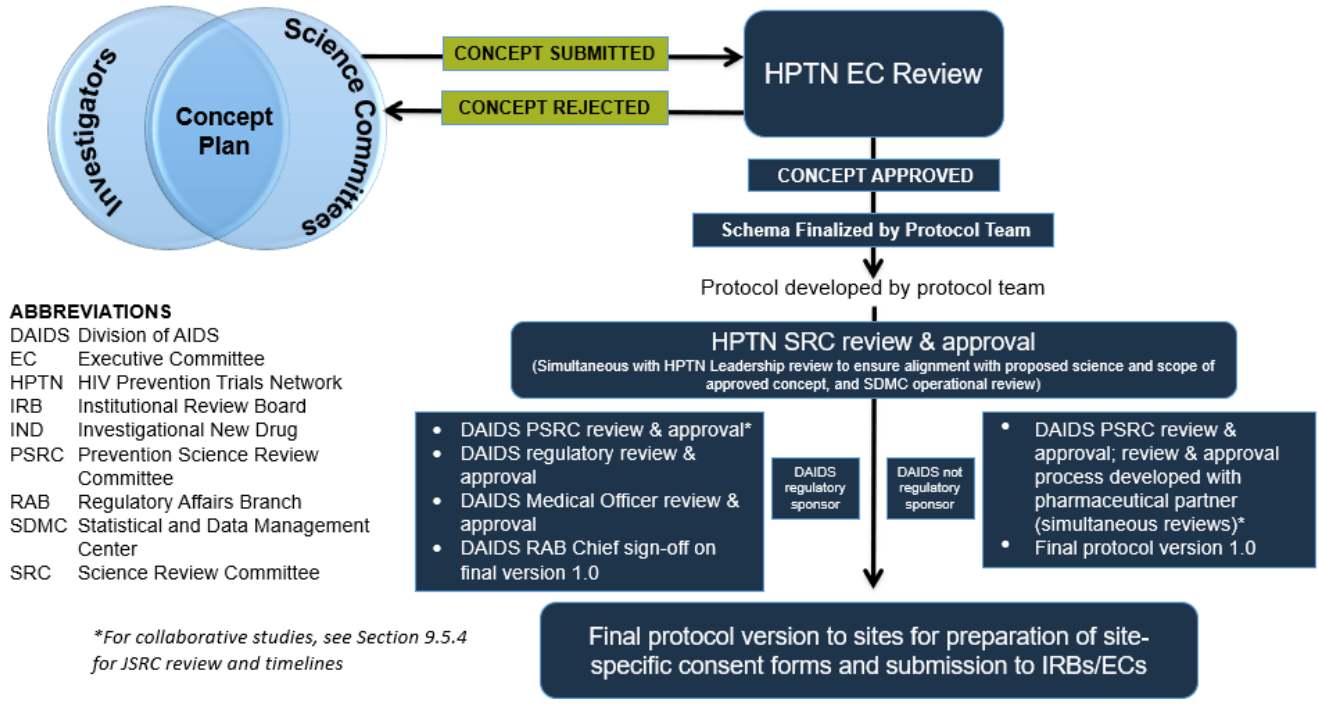
9 PROTOCOL DEVELOPMENT

HPTN studies are developed through multidisciplinary collaboration among HPTN investigators, the Statistical and Data Management Center (SDMC), the Laboratory Center (LC) and the Leadership and Operations Center (LOC), together with non-HPTN investigators, pharmaceutical partners, and researchers/experts who bring complementary expertise. Key steps in the process are shown in Figure 9-1 and are further described below. For studies where DAIDS is not the regulatory sponsor, deviations from these steps will be described and documented in central study files.

Figure 9-1 Protocol Development Process



9.1 Selection/Approval of Concepts for Protocol Development

9.1.1 Concept Plan Development

Overall scientific priorities will be determined by the Executive Committee (EC) in collaboration with the Science Committees (SCs) and Working Groups (WGs), and in alignment with the scientific agenda of the network (Integrated Strategies and Pre-Exposure Prophylaxis). See Section 9.5 for considerations related to the protocol development process for collaborative studies. In cases where a specific priority study is identified, a concept team will be established to develop the concept plan. For newly identified research priorities, Network leadership will release a call for concepts to meet specified scientific needs. Investigators (both within and outside of the Network) can submit ideas for consideration. The number of concept plans developed into protocols will be based on the Network's current and future priorities and availability of resources.

A concept team will include a lead investigator(s), as well as relevant contributors to support the proposed work (e.g. statistician, behavioral scientist (Socio-Behavioral and Structural Working Group (SBSWG) will be consulted to determine need), mathematical modeler, etc.). Central Resources will be assigned only after the approval of the concept by the EC.

The team will submit the developed concept to the EC where it will be reviewed as needed (see Section 9.1.2 below).

The concept plan presents, as concisely as possible, sufficient information for reviewers to evaluate the scientific merit and feasibility of a proposed study. The concept plan should be a maximum of 10 pages (unless otherwise specified). The template concept plan is posted on the HPTN website, and includes key elements, such as background/rationale, study objectives, study design, budget, timeline, etc.

9.1.2 Concept Plan Review

All HPTN-only concept plans must be reviewed and approved by the EC. Concepts submitted as part of an HVTN/HPTN network collaboration will be reviewed by the HVTN/HPTN Joint Science Review Committee (JSRC) as described in Section 9.5.4.1.

Concept plans must be submitted to the LOC at minimum two weeks prior to the planned EC review conference call or meeting. At that time, the EC Chair assigns a primary and secondary reviewer per concept, and the following groups assign their own reviewers: NIH, LOC, LC, SDMC (statistical and operational), and the Community and Ethics Working Groups. Assigned reviewers submit written comments in advance of the review. The proposing investigator presents a brief description of the concept during an EC call or at an in-person meeting, using a provided template slide deck. Reviewers ask any clarifying questions, and then the authors are asked to leave. The concept and reviewers' comments are discussed by the reviewers. The criteria for review are described below:

- Scientific merit (50%)
  - hypothesis is scientifically sound and answerable by the proposed design
  - study design and methods will yield the proposed outcomes
  - plan for analysis of data is adequate and appropriate
  - population is appropriate for the research; relevance of research to the community is considered
- Importance/public health impact (30%)
  - relevance of the planned research to the prevention of HIV infection
  - proposed study is part of a critical path in a research continuum (including would potentially lead to an efficacy trial)
- Research advantage of the HPTN (20%)
  - study is aligned with the scientific agenda and priorities of the HPTN (refer to the HPTN concept page for HPTN priorities listing)
  - proposed research will benefit from a multi-site, multidisciplinary collaboration involving different populations either in the initial phase or in a subsequent phase

Following review discussion, all voting EC members must cast a vote. The EC votes are kept confidential and anonymous. Any identifying information is known only to the EC Administrator. Concepts will be approved for protocol development if a "Yes" vote of 80% of the eligible EC voting members is received. Eligibility is defined by the Conflict of Interest policy that is reiterated prior to each review process in addition to participation in the review/discussion. If more than one concept is being considered and prioritization is required due to budgetary constraints, concepts could be scored by the reviewers using the guidance mentioned above and a scoring system of 1 to 5 with 1 being the highest.

The EC follows a strict conflict of interest policy throughout all of its discussions and votes. Any EC member (or his or her institution) directly involved in a concept, protocol, or study recuses himself or herself from the discussion and vote.

Investigators who submit concept plans are informed directly of the outcome of the review and vote through a summary of the review discussion and all reviewers' comments.

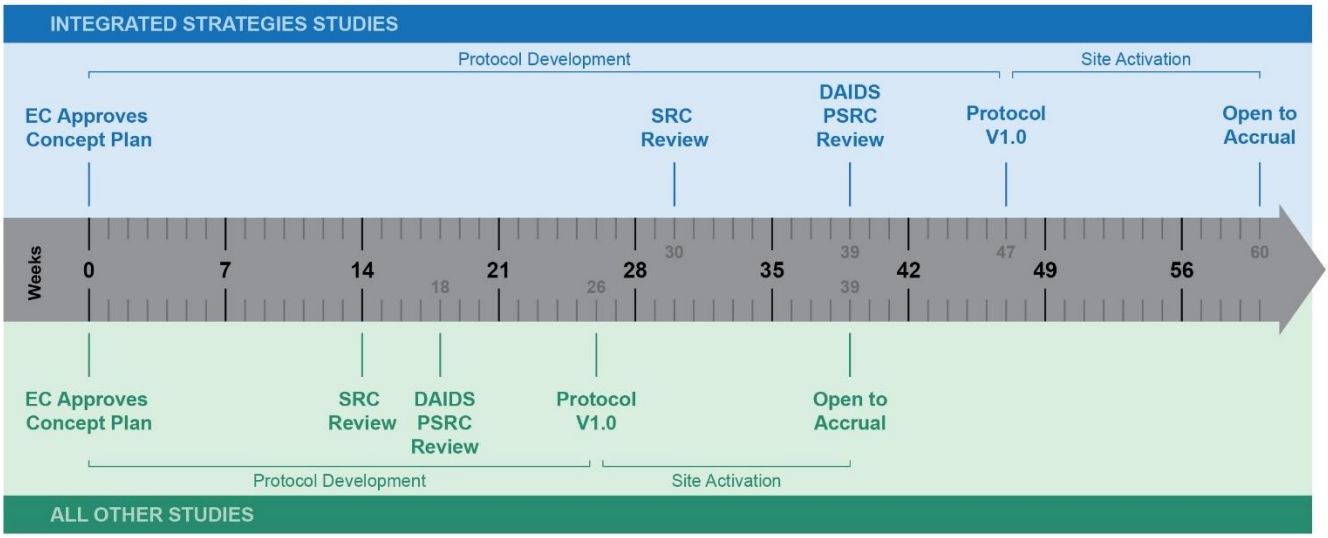
9.2 Protocol Development, Review and Approval

9.2.1 Protocol Development Process

Once a concept plan proceeds to the protocol development stage, the EC will approve a proposed Protocol Chair for the study, who will work with the Central Resources groups and others as necessary to assemble a protocol team. Section 4.5.2 has more information about protocol chair selection. The protocol team is typically an expansion of the concept plan team and will include investigators with expertise pertinent to the study, investigators (and other site staff as necessary) from the participating sites, as well as representatives from the Community Working Group (CWG), LOC, LC, SDMC, DAIDS Medical Officer, DAIDS PAB Pharmacist, and other members as applicable. HPTN Leadership will decide after concept approval whether the proposed study requires a socio-behavioral scientist or an ethicist. If required, the chairs of the SBSWG and the Ethics Working Group will identify an appropriate representative, in discussion with the protocol chair. If the study team has identified a socio-behavioral scientist external to the SBSWG, the rationale for doing so will need to be provided to Leadership for their approval.

HPTN protocols are developed through an iterative drafting and review process led by the Protocol Chair(s) and a primary protocol writing group (a subgroup of the protocol team), coordinated by the LOC Clinical Research Manager (CRM) assigned to the protocol. To initiate the protocol development process, the LOC CRM inserts all relevant information from the approved study concept plan into the HPTN protocol template. The LOC CRM documents all key decisions made during the process, by updating the draft protocol document.

The timeline for protocol development may differ based on the type of study; specifically, protocols for most studies, including biomedical interventions, are expected to be developed more expeditiously (PSRC submission within 16 weeks) than integrated strategies protocols (PSRC submission within 37 weeks). The LOC CRM develops a study-specific timeline with standard timeframes for the type of study and monitors and adjusts as needed during protocol development.



Abbreviations:

DAIDS - Division of AIDS
EC - Executive Committee
PSRC - Prevention Science Review Committee
SRC - Scientific Review Committee

The protocol writing team will convene either virtually or in person. During this meeting, the LOC CRM will review the protocol development process and expected timeline based on whether the study is an integrated strategies study. The team will develop writing assignments, roles, responsibilities, and expectations for team members. For integrated strategy protocols, a schema is expected as a meeting goal. For all other studies, the development of a schema, a schedule of evaluations (SOE), a site selection method/criteria and draft budget are expected. Integrated strategy studies will hold a second core virtual or in-person meeting to develop these items.

Once the study design, objectives, measurements, safety monitoring and the schedules for visits and procedures have been well defined, another in-person or virtual protocol development meeting with the full protocol team will take place to finalize the protocol. The LOC CRM will draft the sample informed consent form(s) that must be appended to the protocol. For some studies, only one sample informed consent form may be needed. For others, multiple forms may be needed (e.g., screening, study participation, assent). All sample forms will follow Division of AIDS (DAIDS) informed consent templates and will include all required elements of informed consent specified in 45 CFR 46 and 21 CFR 50, as delineated in Section 8. A template Informed Consent Form is located in the HPTN protocol template.

Early in the process of protocol development, the team may seek input from research sites where the study is likely to be conducted, from site CABs, the HPTN CWG and other community fora. Additionally, if deemed appropriate, stakeholder meetings may be conducted to foster engagement of a broad range of local stakeholders in the impacted communities.

The protocol writing team will determine when the draft protocol is ready to enter the protocol review process described below and shown in Figure 9-1.

9.2.2 Protocol Review Process

After initiating the protocol development process, the protocol goes through a series of protocol review steps, each of which is described below. When DAIDS is not the regulatory sponsor or for specialized protocols, the process may be modified on a case by case basis.

9.2.2.1 Protocol Review by the Science Review Committee and HPTN Leadership

The HPTN Science Review Committee (SRC) will conduct the first step in the protocol review process. Refer to Section 4 for composition of the SRC.

The primary charge of the SRC is to ensure the protocol is ready for the next review stages – not to rethink the scientific merit of the concept (the EC has already approved the concept to move forward). This review will ensure that study protocols are scientifically rigorous, accurate, consistent and complete. The SRC will also review the protocol for operational feasibility, focusing on key issues such as site participation, infrastructure and capacity, relevance to the community and any ethical concerns.

The LOC CRM is the primary organizer of the SRC call and review process. The SRC will review the draft protocol and comment within five working days of receiving the draft, with a call scheduled immediately following. Comments should be sent to the LOC CRM. Comments will be organized into overall summary and major and minor comments; typically, major comments should be reserved for fundamental study design, scientific, operational, or ethical issues, while minor comments should be used for stylistic input, correcting inconsistencies or errors, wordsmithing, or other editorial concerns.

On the day of the call, a closed SRC discussion takes place in which the primary SRC members summarize their major comments and review the comments of the contributing (non-voting) members; SRC voting members' attendance on this call is required. Following the closed discussion, the Chair(s) of the protocol being reviewed join(s) the call to answer questions, provide clarifications and discuss key review findings from SRC primary review group members. The LOC CRM will summarize the call and its outcome in writing and, following concordance by the SRC chair, distribute the summary to the SRC and protocol team. The approved summary is provided electronically to the protocol team typically within five working days of the review call. The summary documents one of three review outcomes:

- Approved without major revision — the protocol team may proceed to the next review step (DAIDS Prevention Science Review Committee [PSRC] review)
- Major revisions required — the protocol team prepares a written response to any "major" review findings which must be reviewed and approved by the SRC Chair and the voting SRC members.
- An additional review may be required as determined by the SRC Chair
- Protocol disapproved as written — the protocol team will work with HPTN leadership to determine next steps
- Not Approved

If revisions are needed, the protocol team will strive to provide a written response to the comments of the voting SRC members to the SRC and a revised draft within 15 working days of receiving the comments. However, consideration will be given to the magnitude and extent of the SRC's feedback. Formal responses are only required for major comments. If the protocol team has concerns about the SRC's decision, and these are not resolved through discussion between the SRC Chair and the Protocol Chair, the HPTN EC will assist in resolving the matter.

Simultaneous to the review of the protocol the HPTN Leadership ensures that the protocol is in alignment with the approved concept and the goals of the Network.

9.2.2.2 SDMC Operational Review

The SDMC conducts a detailed operational review of HPTN protocols simultaneous to the HPTN SRC and HPTN Leadership reviews.

During the review, SDMC staff from data management, statistical, clinical and programming groups review the protocol with an emphasis on data management and analysis (e.g., enrollment, randomization, visit schedule, adverse event (AE) reporting, study product discontinuation, endpoints and objectives) to ensure that the protocol is clear and thus can be efficiently and accurately implemented. The SDMC incorporates all comments and suggested edits into the draft protocol or review summary document and sends it to the LOC CRM.

9.2.2.3 DAIDS PSRC Review

After obtaining SRC approval, the protocol team submits the revised protocol, along with the SRC comments and team response, to the DAIDS Medical Officer for DAIDS PSRC review.

The PSRC meets twice monthly (typically on the first and third Tuesdays) to review protocols for which DAIDS provides funding. The readiness of the protocol and timing of submission for PSRC review should be determined in consultation with the DAIDS Medical Officer in advance. If the DAIDS Medical Officer agrees that the protocol is ready, the LOC CRM will then submit the full protocol and other required documents electronically to the DAIDS Medical Officer, at least 10 working days prior to the scheduled PSRC meeting. As part of the protocol development team, the DAIDS Medical Officer will then forward them to the PSRC Administrator at PSRC@tech-res.com with a copy to the Clinical Study Information Office (CSIO) at CSIO@tech-res.com.

The PSRC Administrator will confirm the PSRC review date and coordinate with the DAIDS Medical Officer to communicate this date to the Protocol Chairs and LOC CRM. An invitation for the Protocol Chair(s) and LOC CRM to join an open session prior to closed PSRC review of the protocol will be sent by the PSRC Administrator.

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

- NIAID's and other cosponsoring institutes' research agenda and other NIH clinical studies
- Participant safety
- Compliance with United States (US) federal regulations
- Study oversight and monitoring
- Feasibility of timely completion
- When appropriate, plans for interim monitoring and analysis

The PSRC review comments are summarized in a consensus review 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:

- Protocol approved without revision (minor revisions may be suggested) — the protocol team proceeds to the next review step (DAIDS regulatory review).
- Protocol approved contingent upon revisions — the protocol team must respond in writing to the PSRC review within 15 working days, and the DAIDS Medical/Program Officer and/or PSRC Chair must approve the team's response within 3 working days.

- Revision of protocol and re-review by the PSRC required — the protocol team revises the protocol, develops a response to the review comments for re-submission and then the PSRC repeats the review process.
- Protocol disapproved — the protocol team will work with the DAIDS Medical/Program Officer, SC Chair and/or other members of the HPTN leadership to determine next steps. The protocol may be resubmitted to the PSRC after incorporation of revisions that address the PSRC's concerns.

If the protocol is disapproved, the Protocol Chair may contact the PSRC Chair to discuss possible modifications. If the Protocol Chair believes there is a reasonable basis for proceeding despite the PSRC denial, he or she should contact the EC. If the EC is in concurrence with the Protocol Chair, the EC Chair may notify DAIDS and request that an appeal process be initiated. The appeal process will involve an impartial third party. If a protocol is disapproved, DAIDS will not permit expenditure of NIH funds for the proposed investigation.

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

9.2.2.4 DAIDS Regulatory Review

The protocol team prepares a revised protocol version — labeled "Regulatory Review Version" — reflecting its approved response to the PSRC review. The LOC CRM submits the protocol along with the ClinicalTrials.gov Protocol Registration Checklist to the DAIDS RSC at the time of Full Regulatory Review (copying the CSIO), which is completed within 10 working days of protocol receipt. During this review, an RSC staff member reviews the protocol and sample informed consent form(s) in detail and forwards the protocol and review comments to the DAIDS Regulatory Affairs Branch (RAB). A RAB staff member reviews the protocol and the RSC review findings and may add further comments. The RSC incorporates all comments into a review summary document and transmits the document electronically to the LOC CRM.

9.2.2.5 DAIDS Medical Officer Review

The protocol team addresses the regulatory review findings in a revised protocol version within 15 working days. This revised version — labeled "Medical Officer Review Version" — is submitted to the RSC for a Medical Officer review (copying the CSIO). This review is completed within 10 working days of protocol receipt.

Along with the protocol, the team also submits any supporting documentation needed to explain its response to the regulatory review. In particular, if any regulatory review comments are not adopted, the team must provide adequate justification for this. During the 10-day review period, an RSC staff member reviews the protocol to ensure that all regulatory review findings have been satisfactorily addressed and then forwards the protocol for review by the Medical Officer.

The Medical Officer reviews the protocol to confirm an acceptable response to the regulatory review, including incorporation of all responses into the protocol document, and to complete a final quality assurance check of the protocol on behalf of DAIDS.

The RSC incorporates any review comments into a review summary document and transmits the document electronically to the LOC CRM or confirms that the Medical Officer has approved the protocol as written and that it can be submitted for final regulatory sign-off.

9.2.2.6 RAB Chief Sign-Off

The protocol team addresses any Medical Officer review findings, generally within three working days of receipt of comments, in a revised protocol version — labeled "Final Version 1.0" — and submits this version to the RSC for final review and sign-off by the RAB Chief (copying the CSIO). Along with the protocol, the team also submits any supporting documentation needed to explain its response to the Medical Officer review.

RAB Chief sign-off is expected within approximately 3 (non-IND) or 5 (IND) working days of submission. Once sign-off is obtained, the RSC informs the LOC CRM electronically and files the final protocol. When applicable, the RSC also prepares the protocol for submission to the US Food and Drug Administration (FDA).

9.2.2.7 Distribution of FINAL Version 1.0

Upon notification of RAB Chief sign-off, the LOC CRM electronically distributes the final approved protocol as a PDF file and a Word file, if needed, to the protocol team and participating study sites. Concurrent with distribution to the protocol team and participating study sites, the protocol is posted as a PDF file on the HPTN website.

Once Version 1.0 is approved, for any study that will be conducted at more than one US site, the protocol and informed consent forms are submitted by the LOC for single Institutional Review Board (sIRB) review on behalf of all US sites. After approval by the sIRB, study sites will proceed as per Section 10. For sites that are outside of the US, or for a study that is only being conducted at one US site, those study sites will seek local Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol, site-specific informed consent, and other associated documents, and complete DAIDS protocol registration procedures for the study, as part of the study activation process described in Section 10. Conduct of the study at a site may not be initiated before IRB/EC approval is obtained from all responsible IRBs/ECs, protocol registration is completed, and all other HPTN study activation requirements are met (for additional information on study activation refer to Section 10).

For DAIDS-sponsored studies, although a ClinicalTrials.gov Protocol Registration Checklist was submitted to DAIDS RSC at the time of Full Regulatory Review, the LOC CRM will also submit the checklist to the assigned DAIDS contractor after Version 1.0 is approved if the study is a DAIDS-sponsored IND study.

9.2.2.8 Expedited Development of High Priority Concepts

Emergent needs in the HIV epidemic and other health crises warrant expedited development and implementation. When these opportunities arise, the EC will discuss the potential study and will vote on whether or not to move the study directly to protocol development. In these cases, the EC or HPTN Leadership will facilitate expedited concept and protocol development, following the steps outlined in the MOP. The decision to expedite protocol development will be determined at the concept stage. The timelines outlined in the MOP may be shortened to facilitate expedited development and review.

9.3 Protocol Modifications

DAIDS-sponsored protocols may be modified by three methods:

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

These three methods, which are described in the following sections, are used for both Investigational New Drug (IND) and non-IND protocols. The protocol team determines the method to use in conjunction with the Medical Officer assigned to the protocol. Depending on the method used, the modification may or may not result in a change to the protocol version number, may or may not require IRB/EC review and approval, and may or may not require protocol registration through the RSC.

As with the first final version of the protocol, the LOC CRM is responsible for developing protocol modifications in conjunction with key protocol team members, and issuing final versions to the protocol team and participating study sites. Copies of all final protocol modifications are posted on the study specific page of the HPTN website and sent to the DAIDS RSC and CSIO.

During the time when protocol modification documents are in development and under review, study implementation proceeds per the specifications of the prior approved version of the protocol. Protocol modifications specified in the modification documents may only be implemented after the documents are fully approved, as described below.

9.3.1 Clarification Memos

CMs typically are short documents prepared to provide further explanation or more detailed information related to current protocol specifications. CMs also may be used to correct minor errors in a protocol. The content of a CM should have no impact on participant safety, the risk-to-benefit ratio of study participation, or the study informed consent form(s). If a proposed modification requires a change to the study informed consent form(s), a CM may not be used to incorporate the modification.

CMs must be reviewed and approved by the Medical Officer prior to finalization and distribution. Once finalized, CMs are distributed to all protocol team members and study sites by the LOC CRM. IRB/EC approval of CMs is not required by DAIDS. However, sites are encouraged to submit CMs to their IRBs/ECs for their information. Individual IRBs/ECs may require that CMs be approved by them before implementation. All IRB/EC requirements must be followed. CMs may be implemented by sites upon final issuance by the LOC unless the IRB/EC requires approval.

For any study that will be conducted at more than one US site, CMs are submitted by the LOC for sIRB review on behalf of all US sites.

9.3.2 Letters of Amendment

LoAs typically are 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 involves relatively minor modifications of study informed consent forms, if any. LoAs are developed by the protocol team according to the LoA Template. When a LoA is prepared, any prior protocol modifications specified in CMs are incorporated into the LoA. LoAs are prepared and follow the same DAIDS review steps outlined above for original protocols (PSRC review, unless this requirement is waived as determined by the Medical Officer, and the three-step regulatory review process through the RSC).

Once finalized, DAIDS submits LoAs to the US FDA if applicable, and the LOC CRM distributes LoAs to all protocol team members and participating study sites. LoAs must be reviewed and approved by the responsible IRBs/ECs prior to implementation. They typically include instructions to study sites with regard to seeking IRB/EC review and approval and recommendations on how to notify participants of the changes, if applicable. In some circumstances, re-consenting of enrolled participants may be required. In other circumstances, protocol teams may recommend providing a letter to participants informing them of the modifications or ask that the information be provided to the participant and noted in the case history record. Regardless of the protocol team's recommendations, responsible IRBs/ECs may require modification of the study informed consent

forms and/or re-consenting of enrolled participants to reflect a LoA; in such cases, IRB/EC requirements must be followed. Modified procedures specified in the LoA may not be conducted at a site until IRB/EC approval is obtained from all responsible IRBs/ECs for that site.

For any study that will be conducted at more than one US site, LoAs are submitted by the LOC for sIRB review on behalf of all US sites.

LoAs do not result in a change of the protocol version number but do require protocol registration through the RSC (refer to the DAIDS Protocol Registration Manual).

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

9.3.3 Full Protocol Amendments

Full protocol amendments are prepared to incorporate significant changes — involving more than minimal impact on participant safety and risk-to-benefit ratio of study participation — and result in the generation of a new protocol version with a new version number. Amendments also are typically required to incorporate a significant increase in the number of participants to be enrolled in an IND study. When amendments are prepared, any prior protocol modifications specified in a CM or LoA are incorporated into the amendment.

Examples of changes requiring a full protocol amendment may include:

- New study product added to the protocol
- Change to inclusion or exclusion criteria
- New safety information on study product in the protocol

Protocol amendments are developed by the protocol team and, as shown in the table above, must complete many of the protocol review and approval steps described in Section 9.2. Protocol amendments must be reviewed by the PSRC unless a waiver is granted. The Medical Officer for the protocol will confirm whether PSRC review is required. If so, the PSRC review steps described in Section 9.2.2.4 must be followed. In addition, the regulatory review, Medical Officer review, and RAB Chief sign-off steps specified in Sections 9.2.2.5 through 9.2.2.7 must be completed for all amendments.

Once finalized, DAIDS submits amendments to the US FDA if applicable, and the LOC CRM distributes amendments to all protocol team members and participating study sites. Sites must then seek IRB/EC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (see Section 10) for the amended version of the protocol. Revised procedures specified in the amendment may not be conducted until after IRB approval is obtained. Participants enrolled in a study after approval of a protocol amendment must be consented to the study using the revised informed consent form(s) associated with the amended version of the protocol. For participants enrolled prior to approval and registration of an amendment, guidance on whether re-consenting is required (using the revised informed consent form(s) associated with the amendment) will be provided by the protocol team, typically in the summary of changes that accompanies the amended protocol. Regardless of protocol team's recommendations, site IRBs/ECs may require re-consenting of previously enrolled participants; in such cases, IRB/EC requirements must be followed.

For any study that will be conducted at more than one US site, full protocol amendments are submitted by the LOC for sIRB review on behalf of all US sites.

HPTN Requirements and Procedures for Protocol Modifications

Modification Requirements	Clarification Memo	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	Yes	Yes
Content requires change of informed consent form	No	Yes	Yes
Results in change of protocol version number?	No	No	Yes
Requires approval by Medical/Program Officer?	Yes	Yes	Yes
Requires approval by PSRC?	No	Yes, unless requirement waived. Medical/Program Officer determines whether PSRC review is required.	Yes, unless requirement waived. Medical/Program Officer determines whether PSRC review is required.
Requires DAIDS regulatory review?	No	Yes	Yes
Requires final Medical Officer review following regulatory review?	No	Yes	Yes
Requires RAB chief sign-off following Medical Officer review	No	Yes	Yes
Requires approval by site IRBs/ECs?	No, unless required by IRB/EC (but FYI submission is recommended).	Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.	Yes. Amended procedures may not be undertaken until after IRB/EC approval.*
Requires protocol registration?	No	Yes. Amended procedures may not be undertaken until IRB/EC approval is obtained. *	Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.*

9.4 Revised Informed Consent Forms

If consent forms need revision, site staff should refer to Section 10.2.1 and consult with the LOC staff to determine the process for review and translation.

9.5 Collaborative Network Studies

9.5.1 Concept Development and Review for Collaborative Studies

Proposing investigators from collaborating networks will work with their ECs (or respective relevant body) to determine responsibilities for concept development and review process.

9.5.2 Protocol Development for Collaborative Studies

The HPTN will work with collaborating network LOCs to determine an agreed-upon approach for protocol development and implementation. Network leadership negotiations and agreements will drive protocol team representation of each network. Typically, both networks will have balanced representation on the protocol team. For monoclonal antibody (mAb) studies conducted jointly by the HPTN and HVTN, a cross-network protocol template will be used to expedite development.

A "Responsible/Accountable/Consulted/Informed (RACI)" approach, which is a collaborative responsibility assignment matrix, will be used to set expectations for all joint studies. Study leadership will first itemize all anticipated activities during the lifecycle of the trial, and for each activity, assign who (e.g., HPTN and/or other networks' LOC/SDMC/LC, DAIDS or other party) is responsible, accountable, consulted and/or informed. Responsibilities and accountabilities may either be shared across networks or fall with one network.

9.5.3 Protocol Review Process for Collaborative Studies

All collaborative protocols will be reviewed by each collaborating network per their network procedures. Where possible, and per agreement by the participating networks, joint review processes may be instituted to increase efficiencies such as for the HPTN-HVTN collaborative studies (see below). It is generally expected that DAIDS review processes as described above will be applicable to collaborative studies. The collaborating LOCs will work together to develop a combined study timeline that incorporates and integrates milestones for each network, which will be coordinated to maximize efficiencies in the review process and monitored by LOC staff. HPTN LOC staff will be responsible for keeping the HPTN EC apprised of study timelines, key points of engagement with other networks and any obstacles that must be addressed.

9.5.4 Concept and Protocol Review Process for HVTN/HPTN Collaborative Studies

For protocols jointly led between the HPTN and HVTN, the HVTN/HPTN Joint Science Review Committee (JSRC) will review concepts in place of the EC and conduct the first step in the protocol review process. Refer to Section 4 for composition of the JSRC. Refer to the HVTN/HPTN Cross-Network MOP for additional details on concept and protocol development and review processes for HVTN/HPTN collaborative studies.

9.5.4.1 JSRC Concept Review

Concepts should include a target date for PSRC review. The JSRC will review concepts based on the following criteria: scientific merit, impact on the product development pipeline, and alignment with the scientific agenda and priorities of the networks. A JSRC call will be scheduled and the concept circulated for JSRC review a minimum of five business days in advance of the call.

Following review discussion, JSRC voting members will cast their vote. The JSRC votes are kept confidential and anonymous. Concepts will be approved for protocol development if a "Yes, approved for protocol development" vote of 80% of the JSRC voting members in attendance are received. Investigators who submit concept plans are informed directly of the outcome of the review and vote through a summary of the review discussion and all reviewers' comments.

9.5.4.2 JSRC Protocol Review

The protocol review will ensure that study protocols are scientifically rigorous, accurate, consistent and complete to the extent possible relative to other network protocols. Generally, the JSRC should review the protocol to assure that it is ready for submission to the Division of AIDS Prevention Sciences Review Committee (PSRC), taking into consideration the PSRC's review criteria. The PSRC considers the following: Whether there are major safety issues; whether the objectives are clearly stated; and can the design answer the question.

The JSRC will review the protocol and provide written comments within five working days of receiving a draft, with a call scheduled immediately following. The protocol operations team members (Protocol Team Lead/Clinical Research Manager/Clinical Trials Assistant) will provide a summary of consensus comments and distribute these to the JSRC prior to the call for discussion. After the call, these will be edited as needed and finalized by the JSRC chairs. The protocol operations team will distribute the final consensus comments to the JSRC as well as the protocol team.

Following the discussion, the chairs of the protocol being reviewed may answer questions and discuss key review findings from JSRC primary group members. The approved review comments and review outcome are provided electronically to the protocol team typically within two working days of the review call. The summary documents one of four review outcomes:

- Approved for DAIDS PSRC submission without revision – the protocol team may proceed to the next review step with no or only minor revisions
- Approved for PSRC submission contingent upon response and revision, full re-review by JSRC not required – the protocol team prepares a written response to major consensus review comments, submits a revised protocol for JSRC chairs to review and grant final approval
- Protocol disapproved as written – the protocol team prepares a written response to any major consensus review comments, revises the protocol, and submits both for JSRC re-review
- Not approved

JSRC approval is required prior to PSRC submission for all HVTN/HPTN collaborative studies.