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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 and researchers/experts who bring complementary expertise. Key steps in the process are shown in Figure 9-1 and are further described below.

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 Scientific Committees (SCs) and Working Groups (WGs), and in alignment with the scientific agenda of the network (Integrated Strategies and Pre-Exposure Prophylaxis [PrEP]). In cases where a specific priority study is identified, then a concept team will be established to develop the concept plan. For newly identified research priorities, an SC may solicit the submission of concepts to meet predetermined scientific needs. Investigators (both within and outside of the Network) can submit ideas for consideration by an SC as well. The number of concept plans developed into protocols will be based on the Network's current and future priorities.

A concept team should be formed, and may include a proposing investigator(s), as well as representatives from the NIH and the relevant SCs. 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 during one of the four periods per year (typically January, April, July and October) (or more frequently to accommodate emerging science or other opportunities; 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. If a concept plan is longer than 10 pages it will be considered as non-responsive (the review will not be completed). 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. All documents may be submitted electronically for review.

9.1.2 Concept Plan Review

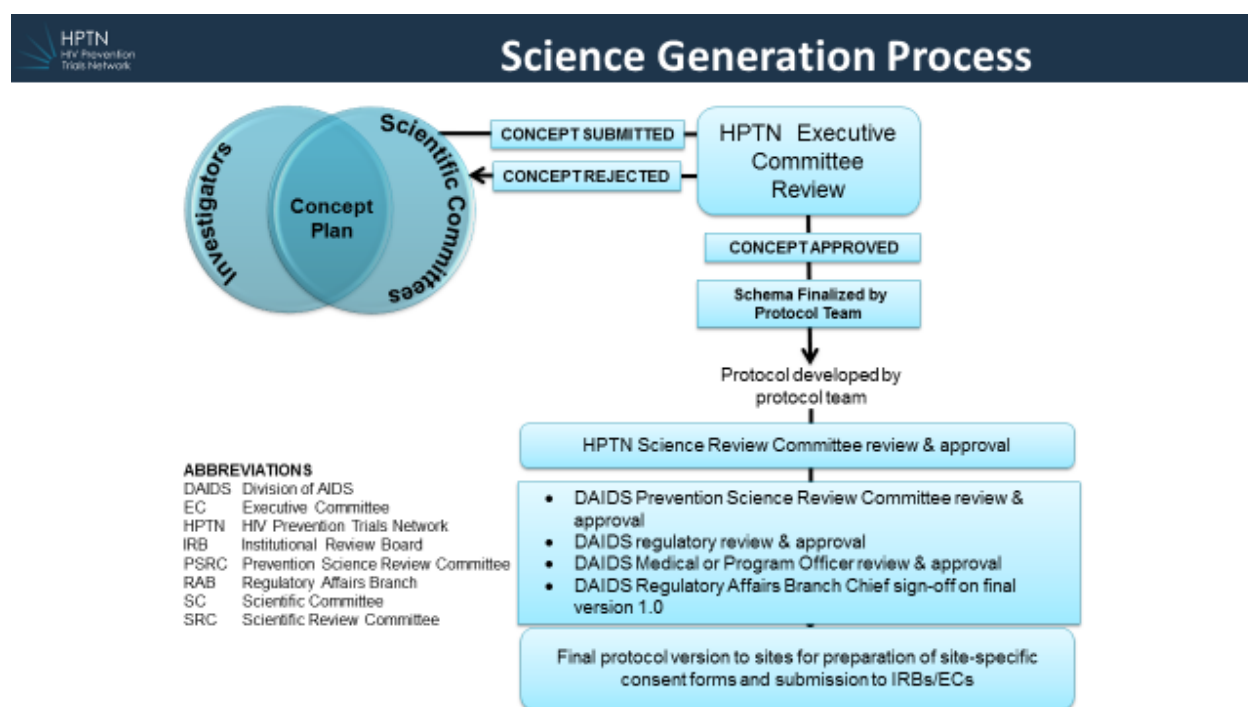
All concept plans must be reviewed and approved by the EC.

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, and the concept and reviewers' comments are discussed during an EC call or at an in-person meeting. 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 of research
- proposed study is or would potentially lead to an efficacy trial
- Research advantage of the HPTN (20%)
 - study is aligned with the scientific agenda and priorities of the Network (i.e., integrated strategies and PrEP)
 - proposed research will benefit from a multi-site, multidisciplinary collaboration involving different populations either in the initial phase or in a subsequent phase

Figure 9-1 Protocol Development Process



Following review discussion, all voting EC members must cast a vote via email (or on paper if at an in-person meeting). 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. 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), Ethics Working Group (EWG), LOC, LC, SDMC, DAIDS Medical Officer/Program Officer, Pharmaceutical Affairs Branch Representative (if applicable), and other members as applicable. Once sites are selected, the Site Investigators will be a part of the protocol team.

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 CRM documents all key decisions made during the process, generally by maintaining and updating the draft protocol document.

The protocol writing team will convene either by conference call or in person. During this meeting the CRM will review the protocol development process and expected timeline. The team will develop writing assignments, roles, responsibilities, and expectations for team members, and should have a detailed Schema by the end of the meeting.

Once the study design, objectives, measurements, safety monitoring and the schedules for visits and procedures have been well defined, the 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](#).

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. The LOC CRM is responsible for all document submissions and for maintaining documentation of all review findings and protocol team responses to these findings.

9.2.2.1 Protocol review by the Science Review Committee

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. Should the protocol involve PrEP, the PrEP Review Committee must also be given opportunity to review simultaneously. Submit the protocol to PrEPWG@hptn.org.

This review will ensure that study protocols are scientifically rigorous, accurate, consistent and complete to the extent possible relative to other HPTN protocols. 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 SRC will review the protocol and comment within five working days of receiving a draft, with a call scheduled immediately following. The SRC members submit written comments to the Chair, either prior to or immediately following the review call. Following the closed SRC discussion, the Chair(s) of the protocol being reviewed join(s) the call to answer questions and to discuss key review findings from SRC primary review group members. The LOC CRM will summarize the call and its outcome in writing and distribute the summary to the SRC, the relevant SC chair 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 revision — the protocol team may proceed to the next review step (DAIDS Prevention Science Review Committee [PSRC] review)
- Approved contingent upon revision — the protocol team prepares a written response to any “major” review findings which must be reviewed and approved by the SRC Chair
- Protocol disapproved as written — the protocol team will work with the SC Chair and/or other members of the HPTN leadership to determine next steps

If a protocol is approved contingent upon revision, protocol teams will strive to provide a written response to the comments of the primary review group 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. 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.

9.2.2.2 SDMC Operational Review

The SDMC conducts a detailed operational review of HPTN protocols at an appropriate time as determined by the LOC CRM, and the SDMC Senior Clinical Data Manager (SCDM) and Program Manager, but typically prior to submission to the DAIDS Prevention Sciences Review Committee (PSRC). Ideally, the review is scheduled ahead of time, once the target date for PSRC submission has been determined, allowing enough time for SDMC review and for returning comments to the LOC CRM with enough time to incorporate requested changes. If the protocol changes substantially due to PSRC review, the SDMC may perform an additional operational review.

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 electronically 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/Program 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/Program Officer in advance. If the DAIDS Medical/Program 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/Program Officer, at least 15 working days

prior to the scheduled PSRC meeting. The DAIDS Medical/Program Officer reviews the protocol and accompanying documents for completeness (within one week) and forwards them to the PSRC Administrator at PSRC@tech-res.com at least two weeks (10 working days) prior to a PSRC meeting, with a copy to the Clinical Study Information Office (CSIO) at CSIO@tech-res.com.

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 [Protocol Registration Checklist](#) to the DAIDS RSC for a 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 or Program 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/Program 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/Program Officer.

The Medical/Program 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/Program 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/Program Officer review.

RAB Chief sign-off is expected within approximately 10 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.

As part of the study activation process described in Section 10, study sites then seek 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 (see Section 10) for the study. 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).

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/Program 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/Program Officer prior to finalization and distribution. Once finalized, CMs are distributed to all protocol team members and study sites by the 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.

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 involve relatively minor modifications of study informed consent forms, if any. LoAs are developed by the protocol team according to the [LoA Template](#) which is available on the [HPTN website](#). 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 site 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 protocol team's recommendations, site 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 until IRB/EC approval is obtained from all responsible IRBs/ECs.

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](#)).

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.*

***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 drug added to the protocol
- Change to inclusion or exclusion criteria
- New safety information on drugs in the protocol

Protocol amendments are developed by the protocol team and, as shown in the table above, and 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/Program 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/Program 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.

9.4 Revised Informed Consent Forms

If consent forms need revision, site staff should refer to Section 10.9.1 and consult with the LOC staff to determine the process for review and translation.