15 STUDY OVERSIGHT

Study oversight within the HPTN takes place at a number of levels. The Division of AIDS (DAIDS), as the Network sponsor, has ultimate responsibility for overseeing the HPTN research. In addition to contracting with a Clinical Site Monitor (see Section 15.3.1) and organizing and convening the NIAID DAIDS Multinational Data and Safety Monitoring Board (DSMB) where applicable, DAIDS staff provide guidance and oversight to HPTN studies. For each study, the Protocol Chair is responsible for oversight of overall study performance. The HPTN also has established oversight procedures by the Executive Committee (EC) as well as the operational components of the Network including the Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC) and Study Monitoring Committee (SMC). At the Clinical Research Site (CRS), study staff and site personnel engage in continuous internal monitoring of study conduct through quality management, as outlined in the site Clinical Quality Management Plan.

15.1 Clinical Quality Management Plan

DAIDS requires that each site develop and implement a Clinical Quality Management Plan (CQMP) that addresses key aspects of a clinical research project to ensure that the rights and safety of participants are protected, and that the data collected are accurate, complete and verifiable.

Quality Management is an overall process that encompasses both quality assurance (QA) and quality control (QC). A CQMP must describe the QA and QC activities that will be performed on study records and also describe the types of "tools" and checklists that will be used in the QA and QC processes. The CQMP must also state the frequency with which QA and QC activities will be performed. A report detailing the findings of the QA/QC activities including identification of problems, identification of possible causes, and any corrective action plan must be communicated to appropriate study staff.

At DAIDS' discretion, a site CQMP may be reviewed prior to its implementation. The CRS may be required to submit revisions of the CQMP to DAIDS. On an annual basis each CRS must prepare an evaluation report of the CQMP and submit the report to DAIDS utilizing the DAIDS specified format, e.g., PHS 2590, Non-Competing Continuation (Type 5) grant progress report. The Office of Clinical Site Oversight (OCSO) Program Officer (PO) will review the CQMP annual evaluation report for trends or areas where the CQMP or related activities need revision. If significant issues are noted, the OCSO PO will provide feedback to the CRS and request modification of the CQMP.

Implementation of the CQMP may be assessed periodically by the Clinical Site Monitoring group and noted in a site monitoring report.

The requirements for CQMPs are detailed in the section on Quality Management within the DAIDS SCORE Manual.

15.2 Operations, Laboratory, Data Management and DAIDS Site Visits

Staff members from the HPTN LOC, SDMC, and LC may visit sites to:

- Assess the quality of HPTN study implementation, including data management practices
- Identify implementation strengths and weaknesses
- Troubleshoot and provide technical assistance and/or retraining related to implementation issues and problems
- Share information on successful implementation strategies identified at other sites
- Identify action items as needed to address study implementation issues and problems

While onsite, LOC, SDMC, and LC staff perform assessments and provide technical assistance, training, etc., in their respective areas of responsibility and expertise.

These visits do not replace the monitoring visits conducted by the DAIDS contracted monitors. The following types of visits may be made by the LOC, SDMC and/or LC throughout the course of the study:

- Assessment Visits: Conducted throughout course of the protocol to assess protocol implementation
- "For Cause" Visits: Conducted if needed due to problems at site such as too low or too fast enrollment, many protocol deviations, poor compliance with protocol and other procedures, unusual severe adverse events (SAE) reports, poor data management quality metrics, and/or support with close-out procedures

Site staff are required to allow LOC, SDMC, and LC staff access to inspect study facilities, specimen storage, and documentation (e.g., informed consent forms, clinic and laboratory records, regulatory documents, source documents, case report forms), and to observe the performance of study procedures. Site staff are encouraged to share with the LOC, SDMC, and LC information on study implementation successes, issues, and problems to help ensure the highest possible quality of HPTN study conduct. LOC, SDMC and LC visitors will make all possible efforts to minimize the impact that the visits have on daily study operations.

Each organization (LOC, SDMC, and LC) conducts and documents its visits according to its own organizational Standard Operating Procedures (SOPs) and/or additional directives from DAIDS. Visit reports are provided to site staff and distributed to DAIDS and key study implementation partners as appropriate. Issues and problems may be brought to the protocol team, SMC or HPTN leadership for discussion and action (see Sections 15.4, 15.5, 15.6).

The DAIDS Clinical Site Monitor also conducts periodic visits to HPTN study sites, as described in Section 15.3. DAIDS staff may visit, or accompany LOC, SDMC or LC staff on visits, on an *ad hoc* basis.

15.3 Monitoring

DAIDS has regulatory responsibility for oversight of all HPTN trials under the US Code of Federal Regulations (CFR) Title 45, Parts 46, 160, and 164; Title 21, Parts 11, 50, 54, 56, and 312; and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E6(R2). DAIDS uses a risk-based approach to monitoring. Monitoring plans are protocol specific and developed based on the design, size and complexity of the clinical trial.

The purposes of monitoring a research study are to verify that:

- The rights and well-being of human subjects are protected
- Data integrity; the reported trial data are attributable, legible, contemporaneous, original, accurate, and verifiable from source documents
- Quality systems compliance; the data are complete, consistent, enduring and available (CCEA)
- The conduct of the trial is in compliance with the currently approved protocol/amendment, ICH Good Clinical Practice (GCP) guidelines, and the applicable regulatory requirements

15.3.1 Clinical Site Monitor

In keeping with this regulatory oversight obligation, DAIDS has delegated the responsibility for onsite or remote monitoring to a contractor, the clinical site monitor.

Under some circumstances, DAIDS may elect to delegate a specific monitoring assignment and/or auditing duties to an alternative contractor instead of the primary contractor. In such situations, DAIDS will advise the Clinical Trials Unit (CTU) Principal Investigator (PI) and/or in-country investigator, also known as the CRS Site Leader, in advance of the specific assignment so that required arrangements can be made.

The primary goals and objectives of clinical site monitoring are:

- Performing source document verification and lab specimen verification to ensure the accuracy and completeness of trial data
- Reviewing informed consent forms, procedures, and documentation
- Identifying problems with protocol compliance relative to protocol procedures, ICH GCP guidelines, and all applicable regulatory requirements (US and in-country)
- Verifying the proper storage, dispensing, and accountability of study products under investigation, when applicable
- Documenting the implementation of appropriate internal site quality control and quality assurance procedures
- Assessing the need for additional site personnel training

All sites are expected to use the Clinical Site Monitoring (CSM) module of the NIAID Clinical Research Management System (NCRMS) to view the status of the Clinical Site Monitor's report.

15.3.2 Clinical Monitoring Visits

Clinical monitoring visits may be conducted onsite or remotely. DAIDS will determine the frequency of clinical monitoring visits based on the risk, size, and complexity of the trial. The clinical site monitor will contact site staff in advance to schedule the monitoring visits confirming the dates of the visit and listing the items to be monitored during the visit.

Site monitoring visits may be protocol-specific, site-specific (i.e., examining all studies and procedures at the site), or targeted (e.g., laboratory monitoring). The purpose of the visit will depend on the assignment, but may include:

- CTU/CRS site initiation
- Review of participant records and source document verification of trial data
- Review of informed consent forms
- Regulatory file review
- Study close-out review

In addition, the monitor may assess the adequacy of the pharmacy, clinic, laboratory, and other facilities; medical records; case report forms; and any aspect of the clinical research that may affect participant safety. Special monitoring assignment visits may be requested of the clinical site monitor at the discretion of the DAIDS, when necessary, to verify any particular aspect of trial conduct.

The site will arrange for the monitor to meet with the appropriate study staff during the visit and will ensure that all documentation to be monitored is readily accessible. The site must identify an appropriate place for the monitor to work during the visit.

The monitor holds a debriefing toward the end of the visit, typically on the last day, to review the findings of the visit. The monitor meets with the Investigator of Record (IoR) and any study staff that he or she would like to include. If available, DAIDS also strongly recommends that the CTU and/or in-country PI, if different from the IoR, the DAIDS Medical Officer, as well as the OCSO representative be present (in person or remotely) at the debriefing. The monitor will leave a list of the pertinent findings with the PI or IoR at the end of the visit so that, if necessary, corrective actions can begin at once.

15.3.3 Monitoring Reports

A detailed written report based on the monitor's observations during the site monitoring visit is completed by the monitor and entered into the NCRMS CSM module within 20 working days of the visit. The system will notify all appropriate persons that the report is available. The OCSO Program Officer (PO) and/or Pharmaceutical Affairs Branch (PAB) representative review the report and enter select monitoring findings, such as observational trends, into the CSM module within 15 days.

The system will automatically notify the site that there are issues that require their action.

15.3.4 Procedures for Site Response to Monitoring Reports

Upon receipt of the electronic notification, the site will respond through the CSM module to the Program Officer's requirements. The system will then automatically notify the Program Officer that a response has been sent.

The Program Officer will review the response from the site.

- If the issues were satisfactorily resolved, the Program Officer will mark them resolved in the NCRMS and the NCRMS will automatically notify the site that the issues are resolved.
- If any issues remain unresolved, the Program Officer will return them to the site via the NCRMS with appropriate comments.
- If a major issue or multiple issues were noted, the Program Officer may recommend to:
  - Pause the study
  - Pause all National Institutes of Health (NIH)-funded studies at the site
  - Close the site

A final decision on recommended actions in the case of major or multiple issues is made by the sponsor in consultation with the Network and a letter will be sent to inform the CTU PI.

Site staff will retain copies of the correspondence between the Program Officer and the site for their regulatory files.

15.4 Protocol Team Oversight

The Protocol Chair is responsible for overall oversight of the study. Under the lead of the Protocol Chair, HPTN protocol teams are responsible for actively monitoring study conduct and progress largely through required review of study-specific reports as defined in the study reporting plan (see Section 12.5). The Protocol Chair may also visit study sites. If and when these visits occur, the Protocol Chair should notify LOC, SDMC and LC staff in advance of the visit and provide them with any relevant findings from the visit. Protocol Chair(s) are responsible for ensuring that the team discusses issues and problems in a timely manner and that a corrective action plan is implemented.

If issues cannot be resolved within the protocol team, the Protocol Chair or other protocol team members may refer issues to the EC or SMC for further deliberation and guidance.

15.5 Study Monitoring Committee (SMC) Oversight

The SMC functions to provide HPTN leadership and the Protocol Team an internal review of study data, with an emphasis on participant accrual, participant retention, protocol and intervention adherence, and other key performance indicators. In addition, for trials with no Data and Safety Monitoring Board (DSMB) oversight, the SMC will review safety data, either aggregate or by arm. For Phase IIb and III trials, the SMC, when there is no DSMB oversight, will also monitor the rate of required endpoints (in a blinded fashion) for continued feasibility of the trial.

The SMC is composed of representatives of the LOC, SDMC, DAIDS, and LC, all of whom are not associated with the protocol, and one or more *ad hoc* members with relevant technical expertise (see Section 4.3.2). Whenever possible, the composition of the SMC for each study is maintained throughout study duration.

The SDMC prepares reports based on study data received from the sites (see Section 12.5.7), provides the LOC with preferred review periods, and works with protocol teams and site staff to provide any necessary additional data from sites. The LOC queries the SMC members, Protocol Chair, and protocol statistician in order to determine the appropriate date and time and sets up the review calls. The Protocol Chair will consult with the SDMC to determine if any additional information directly relevant to study implementation status should be provided or if SMC guidance on a specific issue should be sought. If so, the Protocol Chair drafts a memorandum to the SMC for review and input by the study team or prepares other materials as needed.

The Protocol Chair (and Co-Chair if applicable) is invited to join the SMC review call during the open session of the review to respond to questions or issues raised by the SMC. Observers from the protocol team, LOC, LC, and SDMC, and NIH, as well as the HPTN PIs, are invited to join the call during the open session.

Summaries of actions and findings of the SMC are communicated to the protocol team through the review summary prepared and distributed by the LOC in conjunction with the SMC Chair. The LOC sends a summary from SMC review calls to all sites and team members for distribution to Institutional Review Boards (IRBs)/Ethics Committees (ECs) as necessary. Additionally, the HPTN PIs receive the SMC open reports and summaries.

For any study that will be conducted at more than one US site, SMC summaries are submitted by the LOC for single Institutional Review Board review on behalf of all US sites.

The HPTN PIs/leadership is informed of any significant recommendations or outcomes. Recommendations involving substantive changes to the protocol (conduct or cost) are subject to sponsor and EC approval. If the protocol team does not agree with the actions recommended by the SMC, the EC will mediate.

HPTN studies are reviewed approximately four to six months after initiation, depending on the rate of enrollment and the needs of the study. Thereafter, all studies are reviewed approximately every six months and more frequently if deemed necessary, unless review is waived by the SMC. For studies subject to DSMB monitoring, the SMC reviews the open portion of the DSMB report, and in some cases, the number of endpoints (in closed session) in preparation for the DSMB reviews (see also Section 15.8). Summaries of SMC reviews and recommendations are shared with the protocol team and the EC, and with the DSMB as appropriate.

15.6 HPTN Leadership

The EC monitors HPTN studies with regard to protocol development, implementation, analysis, and reporting.

Routine EC oversight includes evaluation of study progress with respect to key implementation milestones. It is aided in this endeavor by information provided by the Performance Evaluation Committee (PEC), protocol teams, LOC and SDMC (e.g., timeliness of enrollment and follow-up targets, routine reports to the DSMB, or progress in data analysis and reporting). All monitoring and evaluation findings are reported to the EC. If significant laboratory-related issues or problems arise, the LC brings these to the attention of the EC for discussion.

The EC also monitors resource allocation and use by protocols. Based on this, the EC assists the NIH in determining the need for additional resources, for example, because of unexpected costs associated with planned study procedures or in order to support additional sites requested or ancillary studies endorsed by the protocol teams.

In addition, all protocols are routinely reviewed at least annually by the EC during an in-person meeting.

15.7 Study Oversight by the Sponsor

NIH staff members are active in overseeing and supporting study implementation in the HPTN. NIH staff members are part of the HPTN leadership through membership in the EC and also participate in all HPTN working groups and committees.

DAIDS assigns a Medical Officer to each protocol. This staff member is assigned to monitor the safety and efficacy of the intervention(s) for both in-development and ongoing studies and is provided with interim and final reports produced by the HPTN SDMC. Protocols sponsored by a collaborating institution or research group (i.e., National Institute on Drug Abuse (NIDA) or National Institute of Mental Health (NIMH)) may be monitored by that Institute's research groups medical representative(s).

Designated sponsor staff communicates with HPTN site staff as needed. They interact directly with the CRS regarding follow-up to monitoring reports and also work with the clinical site monitor to develop monitoring assignments and provide feedback for site development and evaluation.

DAIDS also monitors the progress of studies through review of DSMB reports.

The OCSO Program Officer will take corrective action when serious and/or persistent non-compliance with protocol, regulatory, or grant requirements is identified at a CRS. If necessary, a site may be temporarily suspended from enrolling new participants until problems are resolved.

15.8 Data and Safety Monitoring Board Oversight

The National Institute of Allergy and Infectious Diseases (NIAID) Prevention Data Safety and Monitoring Boards (DSMBs) are responsible for reviewing study conduct and safety and efficacy data for all Phase IIb/III trials, as well as select other trials. The members of the DSMB are independent investigators with no financial interest in the outcomes of the studies reviewed. Members include experts in the fields of biostatistics and medical ethics, clinicians, and other scientists who are experts in HIV transmission, plus *ad hoc* members. Appointments to the DSMB are made by NIAID.

The SDMC prepares reports for DSMB review (see Section 12.5.6). The DSMB meets at least annually or according to the monitoring plan put in place prior to initiation of the study. All Phase IIb/III trials are reviewed at least annually. Representatives of the protocol team (e.g., Protocol Chair/Co-Chair and protocol statistician) attend the open session of the DSMB review in person or remotely to discuss study progress, respond to questions, and receive the DSMB recommendations.

15.8.1 Data and Safety Monitoring Board Summary

The DSMB provides a written summary of all reviews to DAIDS and NIAID, which is also distributed to the protocol team and the HPTN Principal Investigators. Recommendations involving substantive changes to the protocol (conduct or cost) are subject to sponsor and EC approval. If the protocol team does not agree with the actions recommended by the DSMB, the protocol team may refer the issue to the EC.

15.8.2 DSMB Recommendations for Study Modification

Based on DSMB recommendations, NIAID may find it necessary to close or modify an ongoing study for one of the following reasons:

- Risk to subject safety
- The scientific question is no longer relevant
- The objectives will not be answered
- Slow accrual
- The objectives of the study have been met
- New information from other research is now available
- Ethical concerns

In the case of DSMB recommendations that require public dissemination, a press release or public statement will be developed following Network procedures (Section 6). It is imperative that the DSMB findings remain confidential until public release. In an effort to ensure study confidentiality, all study team members must sign a confidentiality agreement.

Recognizing that in some cases DSMB findings may require immediate action, communication of DSMB results with network constituents and study participants will be coordinated with the Protocol Chair, HPTN leadership and NIAID in a timely fashion. Advance communication planning and development of possible DSMB outcomes will expedite this process.

15.8.3 Non-DAIDS Sponsored Studies

For all non-DAIDS sponsored studies, study oversight responsibilities will be determined by the relevant protocol team and regulatory sponsor.