13 LABORATORY COMPONENT

The following section applies to any site laboratory performing a study under the guidance of the HPTN Laboratory Center (LC). These laboratories will be referred to as Clinical Trials Unit (CTU)/Clinical Research Site (CRS) laboratories in the remainder of this document.

All CTU/CRS laboratories are required to adhere to standards of the Division of AIDS (DAIDS) Good Clinical Laboratory Practice (GCLP), the HPTN Quality Assessment and Quality Control Policies, and local Standard Operating Procedures (SOPs) for proper handling and storage of laboratory specimens. The CTU/CRS laboratories should also have in place a well-defined quality management plan that comprehensively covers specimen management issues including specimen collection/acquisition, tracking, processing, testing and storage, as well as back-up plans, assay validations, and procedures for quality assessment and quality control (QC).

The documents, HPTN Quality Assessment and Quality Control Policies, outline specific requirements for laboratory Quality Assessment procedures and QC activities. These policies cover required Quality Assessment activities for the laboratory, including handling of reagents and conducting of assays. References for applicable United States (US) federal and non-US regulations are also included.

In addition to this Network-level set of SOPs, the Study Specific Procedures (SSP) Manual developed for each protocol contains a section on laboratory procedures that includes detailed instructions for the specific study.

13.1 HPTN Laboratory Program

13.1.1 HPTN Laboratory Quality Assessment Policy

The HPTN LC has developed and implemented a generic LC Quality Assessment policy that is the basis for a range of quality assurance (QA) activities carried out by the LC and CTU/CRS laboratories. This laboratory Quality Assessment policy applies to all CTU/CRS laboratories and CTUs and is designed to monitor, evaluate, and improve the quality of laboratory data, ensure the reliability of test data, and evaluate the competency of the site laboratory and appropriate clinical staff; this includes personnel (laboratory and clinical) involved in phlebotomy, collection of other samples and performing tests in site clinics/laboratories. The Principal Investigator (PI) of each CTU/CRS is responsible for assuring the implementation of the quality assessment policy at the laboratories and clinics that support their CTU/CRS.

The objectives of HPTN laboratory Quality Assessment Policy (and related programs) are to:

- Ensure that the quality assessment activities are comprehensive and coordinated, and that appropriate information is reviewed and reported.
- Establish, maintain, support, and document an ongoing Quality Assessment program that includes effective and systematic mechanisms for monitoring, collecting, and evaluating information about important aspects of laboratory procedures, in order to identify opportunities for improving data quality and participant care.
- Assist in improving care and identifying problems through the use of ongoing monitors by focusing on identification, assessment, correction, and follow-up of problems that affect laboratory performance.
- Implement corrective action when problems are identified.
- Follow-up on identified problems to assure improvement and resolution.

See HPTN Laboratory Quality Assurance Policy Version 5.0, Quality Assessment Policy Version 3.

13.1.2 HPTN Laboratory Quality Control Policy

The HPTN policy on laboratory QC contributes to the laboratory Quality Assessment. The institution of appropriate QC practices will maximize the accuracy of reported results and will provide mechanisms for early identification of potential problems. As part of the laboratory Quality Assessment program, each site is expected to develop its own internal QC procedures. Required components of a QC program are included below in Section 13.2, and described more fully in HPTN Laboratory Quality Control Policy Version 6.0.

CTU/CRS laboratories are evaluated by the HPTN LC and other monitoring groups to ensure that they meet an established standard for data quality, participant care, and laboratory compliance. Key performance areas (listed in Section 13.2.1) are monitored through collection, recording, and investigation of data pertaining to the laboratory area; findings are evaluated to detect trends and overall compliance with the laboratory Quality Assessment program. When indicated, corrective action will be implemented and documented. Monitoring is on-going to assure appropriate action is taken and that those actions result in correction of any problems. In addition to complying with monitoring and oversight by the HPTN LC, DAIDS contractors, and the DAIDS Clinical Site Monitor, sites are required to develop and implement internal QC plans for laboratory procedures. Site-specific Quality Assessment/QC procedures are a requirement for site activation for HPTN protocols; these procedures may be adapted from the HPTN generic program with additional input from DAIDS contractor programs, or may be developed by the site. Documents related to the site's Quality Assessment/QC program must be submitted to the HPTN LC for review, comment, and approval. Key areas covered in the Quality Assessment Policy, which guide Quality Assessment/QC procedures at study sites, are described below.

13.2 HPTN Laboratory Quality Assessment and QC Program

13.2.1 CTU/CRS Laboratory Quality Assessment

The HPTN policy on laboratory quality assessment provides guidelines for components of a laboratory quality assessment program. Components are listed below with a fuller description of each item in HPTN Laboratory Quality Assurance Policy Version 5.0, Quality Assessment Policy Version 3.

Key components of laboratory performance termed Quality Assessment Monitors are monitored to ensure consistency and accuracy of laboratory data. These include:

- Proficiency testing. Proficiency programs are used as an external check on the QC and Quality Assessment of a test system. Any deficiencies cited by any accrediting organization and/or DAIDS-sponsored program in which the laboratory participates must be reviewed by the laboratory supervisor and/or director and/or designee. An appropriate investigative report (IR) must be completed and submitted to the DAIDS contractor, and also to the Primary Network Laboratory (PNL) assigned to the CTU/CRS. It is possible that the HPTN LC may not be the PNL
- Specimen management. Specimens sent to the laboratory are monitored to determine the effectiveness of the collection procedures outlined in the site-specific Specimen Management Plan and in the protocol-specific "chain of custody" SOP, and also to ensure the integrity of the specimens received
- Reporting of results. Results that are released to clinic or study staff are monitored to determine the effectiveness of the laboratory review, reporting system, and chain of custody

- Technical delays. Technical delays are monitored to help evaluate the overall effectiveness of the laboratory. Any time there is a delay in reporting participant test results due to a technical problem in the laboratory, the problem must be documented; clinic and HPTN LC staff must be notified
- Performance improvement monitoring. The laboratory will identify potential problems and potential areas for improvement within the laboratory. Problems and potential problems will be monitored for frequency, possible causes, corrective action, and improvement. This should also include a review of safety incidents for staff and study participants, as well as any protocol deviations
- Staff development, training, and performance are assessed through:
  - Training documentation
  - Continuing education records
  - Annual competency assessments of employees that may include: blinded specimen analysis, proficiency testing (PT) sample analysis, written exams, observation of a technique, and safety review
- Quality control (see Section 13.2.2)
- Technical procedures are monitored for:
  - Maintenance of equipment
  - Procedure review
  - Storage of laboratory records
  - Result modification/amendment
  - Result reporting change
  - Reference intervals (age/gender appropriate)
  - Instrument validation
  - Assay validation
  - Assay comparisons

13.2.2 Laboratory QC Procedures

CTU/CRS laboratory QC activities are an integral part of the laboratory Quality Assessment program. CTU/CRS QC programs are divided into the main areas of focus listed below:

- Internal QC (testing of known materials)
- Parallel testing — validation of new controls and reagent lots as well as back-up instruments
- Blinded or split-sample testing
- Proficiency (external) testing programs
- QC monitoring — corrective action logs
- Quality assessment program feedback
- Preventative maintenance program
- Result comparisons with back-up instruments/methods

Further guidance on development of a site QC program incorporating these components is contained in HPTN Laboratory Quality Control Program Version 6.0

13.3 CTU/CRS Site Laboratory Quality Assessment/QC Plan

Each site that participates in HPTN protocols is expected to expand on the generic HPTN Laboratory Quality Assessment Policy and HPTN Laboratory Quality Control Policy implemented by the HPTN LC through the development of a site-specific laboratory Quality Assessment and QC plan. The HPTN Laboratory Quality Assessment policy, generic SOPs, and the HPTN Laboratory Quality Control Policy, all of which provide guidance on development of a site laboratory Quality Assessment and QC plan, are available on the HPTN LC website. The site-specific Quality Assessment/QC plan is designed to ensure

accurate, timely, and reliable test results by providing routine monitoring of the overall laboratory operation.

13.4 CTU/CRS Laboratory Performance Assessment

13.4.1 Non-US CTU/CRS Laboratories

DAIDS has arranged for existing laboratories outside of the US that participate in DAIDS-funded research to receive proficiency panels from the College of American Pathologists (CAP), OneWorld (Digital PT), the United Kingdom National External Quality Assessment Service (UK NEQAS) and other approved proficiency providers - through DAIDS-funded contractors/partners for protocol-related analytes. When a new CTU/CRS is included in a new HPTN protocol, the HPTN LC will work with the site and DAIDS contractors to ensure coverage of protocol analytes; costs related to participation in these PT programs may need to be paid for by the site, unless another arrangement can be made. Each year, the appropriate DAIDS contractor will re-enroll sites based on the assays that are or will be done at that specific site for DAIDS-sponsored protocols; the assay list will be prepared with input from the LC, the CTU/CRS, and other networks affiliated with the CTU/CRS. To facilitate communication between the LCs of different networks and CTUs/CRSs outside of the US, the leadership of five of the clinical trials networks has assigned a PNL to each non-US site. A list of the PNL assignments can be found on the HIV/AIDS Network Coordination HANC website (see Section 13.15 for URL). The appropriate DAIDS contractor and the LC personnel monitor the results of PT and communicate directly with the sites and the HPTN LC, as well as the PNL (if HPTN is not the PNL), regarding any issues or problems with the results, and work with the sites and the PNL to identify appropriate investigational responses and/or corrective actions.

DAIDS staff and/or DAIDS contractors may conduct laboratory-specific audit visits to determine laboratory readiness to participate in clinical trials. These audits are conducted annually at sites outside of the US, unless the laboratory has been certified by CAP and/or has been deemed in good standing by the DAIDS Clinical Laboratory Oversight Team (DCLOT). GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results will be produced. DAIDS reserves the rights to conduct for cause or ad-hoc audits at any laboratory in the US that is participating in DAIDS-sponsored clinical trials. After an audit, an audit report will be distributed to the laboratory. The laboratory is responsible for working with DAIDS, their contractors, and the HPTN LC to resolve the audit report findings. Audit report findings must be adequately addressed by the CTU/CRS laboratory to maintain a satisfactory performance standard. The types of audits performed and process for resolution of audit findings are described GCLP Lab Audit Information document. Information regarding this process can be found on the HANC website.

In addition to the annual assessments described above, the CTU/CRS may undergo an annual visit (protocol training or protocol-related assessment visit) by HPTN LC staff. At these visits, the HPTN LC staff will provide the CTU/CRS with any recommendations or corrective actions deemed necessary, and will send this information to the appropriate site representatives, LOC, SDMC and the DAIDS HPTN LC program officer. If deemed necessary, trip reports will be written to document these actions. The HPTN LC routinely reports on site performance related to protocol testing to the HPTN Executive Committee (EC).

13.4.2 Non-affiliated External Laboratories Outside the U.S.

In certain circumstances (e.g., analyzer repair or breakdown, lack of available consumables, lack of required reagents or control material, continued failure in an External Quality Assurance (EQA) program), a laboratory may need to use back-up equipment or a back-up laboratory for testing and reporting study specimen results. To ensure the safety of study

participants and the quality of data produced using back-up equipment and/or laboratories, the primary testing laboratory must be able to demonstrate acceptable equivalency between the primary and back-up instruments and/or laboratories for the relevant analyte(s) using tools such as laboratory audit reports, EQA history, instrument validations, regular specimen comparisons, and reference intervals.

The development and approval of a back-up plan that demonstrates equivalency between back-up instruments and/or laboratories is the responsibility of the director of the primary testing laboratory.

The guidelines for the use of back-up equipment and/or laboratories for DAIDS-sponsored clinical trials is available on the HANC website.

13.4.2.1 Specific Responsibilities of CTUs for Quality Assessment for External Laboratories

CTU/CRS that support the HPTN who wish to contract with outside laboratories for specimen testing must work with the HPTN LC and the external laboratories to ensure, as far as possible, the integrity of the results and correct handling of specimens. To fulfill this requirement, each CTU/CRS using an external laboratory must:

- Consult with HPTN LC staff to determine which assays being performed at external laboratories require inclusion of EQA, and to determine what materials should be used as controls and frequency of testing.
- Document inclusion of known controls with groups of samples submitted to external laboratories
- Maintain archival records that document the results of assays done on control samples and participant samples.
- Consult with HPTN LC staff immediately when results are unacceptable, to formulate a plan for assessing performance of the external laboratory in greater detail and to discuss possible plans for corrective action

13.4.3 Proficiency Testing

Each site will be enrolled in PT programs as appropriate for each HPTN protocol. Prior to protocol activation, the laboratory must be in good standing for the required EQA as determined by the HPTN Network Laboratory staff. After a protocol is activated at the site, the recommendations for PT are as follows:

- Any proficiency deficiency (<100%), regardless of the scoring, will require an investigational response by the CTU/CRS laboratory. The HPTN LC considers scores between 80% and 100% to be passing scores. Any non-protocol analyte that has been evaluated and scores <100% requires an internal investigation.
- If a CTU/CRS laboratory fails to report to the appropriate DAIDS contractor that a panel has not been received, this will be considered unsatisfactory.
- If the results are not graded by the proficiency provider because the results were submitted late, the appropriate DAIDS contractor will make an effort to grade the results and will document that the panel is considered late.
- If the results of an analyte are not graded by the proficiency provider for any reason, the DAIDS contractor may decide that they will determine if grading is applicable.
- When a site receives a score <80% for any analyte, the PNL will trigger a report to the site. The HPTN LC will work with the CTU/CRS lab to determine what actions should be taken with participant samples.
- For CTU/CRS laboratories that receive unsatisfactory results (failures) on two out of three consecutive panels or three panels in a row for the same analyte, the HPTN LC

will provide instructions to the laboratory on what additional measures must be taken in addition to the corrective action reporting.

- For CTU/CRS laboratories that receive unsatisfactory results on three consecutive panels, the HPTN LC may stop all testing for that analyte and implement a back-up plan at the CTU/CRS. Other LCs may communicate their decisions about testing (e.g., stop/continue) through the PNL. Determinations will be on a case by case basis, depending on the reason for the PT failure.

DAIDS contractors that provide PT support to CTU/CRS laboratories currently include:

- pSMILE (safety laboratory tests; each CTU/CRS will have a main contact)
- Virology Quality Assurance (VQA; HIV viral load, HIV DNA PCR, HIV genotyping)
- Immunology Quality Assurance (IQA; CD4/CD8, Viable PBMC)
- Pharmacology Quality Assurance (PQA)
- Microbicides Quality Assurance (MQA)

13.4.4 US CTU Laboratory Certification

CTU/CRS laboratories within the US that participate in HPTN protocols are required to have Clinical Laboratory Improvement Amendments (CLIA) certification and to provide documentation of this certification to the HPTN LC. Recertification is required every two years. Renewals must be provided to the HPTN LC.

HPTN LCs performing diagnostic assays for the HPTN protocols are required to be CLIA-certified. Other testing performed at the HPTN LC may not fall under the CLIA or GCLP guidelines because they fall under research or developmental testing.

13.5 HPTN LC Oversight of CTU/CRS Laboratories

HPTN LC staff conduct periodic site visits to assess the implementation of laboratory QC procedures, including proper maintenance of laboratory testing equipment and appropriate use of reagents as they relate to HPTN protocol testing. Each site is visited approximately annually by one of the QA/QC coordinators or Deputy Director, or more often if necessary. Annual visits for each HPTN protocol are not required. During these visits, laboratories are assessed using the HPTN Laboratory Assessment Checklists, or if a quality assessment visit is more focused, a shorter report may be generated Study Visit Assessment Report Template. The purpose and scope of the visit are discussed with site personnel prior to the visit. In addition, the HPTN LC may place an HPTN LC staff member onsite. HPTN LC staff work directly with the on-site QA/QC coordinator to address and resolve any QC or quality assessment problems identified either through PT or site visits, or by the site during study preparation or implementation.

13.6 Laboratory Monitoring by the Clinical Site Monitor

DAIDS Clinical Site Monitors will periodically conduct a complete laboratory audit prior to or during the conduct of an HPTN protocol. Peripheral blood mononuclear cell (PBMC) specimens should NOT be disturbed during such laboratory audits.

13.7 Specimen Handling and Processing

Each CTU/CRS laboratory should have documented procedures for handling and processing of specimens to be used in DAIDS-sponsored clinical trials. In addition, each laboratory is required to utilize the Laboratory Data Management System (LDMS) for collection, testing (specific to HIV RNA), storage, and labeling of certain biological samples identified by the HPTN LC for each HPTN protocol, as described below.

13.7.1 Laboratory Data Management System

Each CTU/CRS is required to utilize the LDMS. LDMS training may be provided at annual meetings, regional meetings, at the Frontier Science and Technology Research Foundation (FSTRF), or onsite. Each CTU/CRS is required to maintain the training records of their staff members and is fiscally responsible for the training. The CTU/CRS is responsible for maintaining their LDMS system, including hardware and software upgrades. HPTN LC staff will provide LDMS codes for each protocol so that specimens are entered correctly into the system. Additional details are included in the SSP Manual for each HPTN protocol and on the FSTRF website.

All sites must establish SOPs for weekly reconciliation and verification of all archived specimens including (but not limited to): plasma, serum, whole blood, PBMCs, dried blood spots (DBS), tissue, breast milk, amniotic fluid, and genital secretions. These SOPs must be followed throughout the study.

On a periodic basis (at a minimum, monthly), the SDMC will send each CTU/CRS laboratory that is storing samples for an HPTN protocol a missing sample report. This report is an Excel file that lists samples that were indicated as collected on the Case Report Form (CRF) and are missing from the LDMS. This could include samples that are logged in incorrectly, not stored, or not received by the laboratory.

13.7.2 Specimen Shipping

HPTN specimens must be transported in accordance with International Air Transport Association (IATA) regulations and with US federal, international, and local laws and regulations. This applies to transportation of specimens on-site, to and from clinics and laboratories, from CTU/CRS to the HPTN LC, or from sites or external laboratories to other laboratories or sites, including the HPTN LC. Study staff who transport, ship or receive infectious substances and diagnostic samples must receive adequate and appropriate training to ensure compliance with guidelines and regulations. Documentation of the appropriate training must be filed onsite, and a copy must be sent to the HANC.

IATA regulates the safe transportation of dangerous goods by air in accordance with the legal requirements of the International Civil Aviation Organization. IATA requires training and certification for those involved with shipping Class 6.2 infectious substances and diagnostic specimens. IATA regulations define infectious substances, cultures and stocks, biologic products, and diagnostic specimens and specify the requirements for the handling and shipping of each. Diagnostic specimens and infectious substances are further separated into risk groups based on the organism that is known or suspected to be present within the sample.

IATA shipping certification renewal is required every two years with a review of the IATA Dangerous Guidelines annually to check for any new or changed requirements. Each staff member who handles shipments must be trained and certified. Each CTU/CRS is responsible for obtaining the appropriate training and annual IATA dangerous goods guidelines.

Each site should follow local regulations regarding transportation of samples by dedicated couriers. The US Department of Transportation (DOT) regulates the transportation of infectious substances within the US. Sites within the US must follow the DOT requirements (see 49 CFR Part 171). Sites outside the US are subject to their own country's government regulations for transportation of infectious substances.

Importation of human pathogens to the US from abroad requires an importation permit from the US Centers for Disease Control and Prevention (CDC). The HPTN LC maintains a worldwide importation license that covers all materials sent from CTU/CRS sites to the HPTN

LC at Johns Hopkins University. Specimens sent from the sites to other locations within the US are not covered under this importation permit.

Useful websites with information concerning specimen handling and shipment are provided in Section 13.15

13.8 Laboratory-related Site-specific Protocol Activation Requirements

A specific set of protocol activation requirements will be created for each HPTN protocol. Requirements may vary between studies and sites. Examples of these requirements are:

- HPTN LC approval of PT for protocol-related testing
- Quality Assessment/QC procedures at the site
- Site SOP for establishing/maintaining reference intervals
- Appropriate validation for protocol-specified tests
- Appropriate laboratory assay SOPs
- Appropriate HIV algorithm validation
- Local laboratory back-up arrangements, if necessary
- IATA specimen shipping certification
- Site Specimen Management Plan for the appropriate collection, processing and handling of protocol-related samples, as well as “chain of custody” for samples used for primary study endpoints
- Laboratory manager curriculum vitae
- LDMS utilization, provided by FSTRF, including training documentation

The HPTN LC notifies the LOC Clinical Research Manager (CRM) for the study when the site’s laboratory-related procedures, facilities, and staff are deemed ready for study activation. This HPTN LC approval constitutes local laboratory certification for CTU/CRS laboratories outside of the US. The HPTN LC verifies annually that the laboratories are meeting the necessary protocol-specified laboratory requirements for each protocol. Certification can be rescinded at any time for failure to maintain key systems or requirements, such as failure to appropriately use the LDMS.

Prior to protocol activation, each site is required to establish a Specimen Management Plan for local specimen handling and maintenance of “chain of custody” related to testing for primary endpoints. This plan must be approved by the HPTN LC. The plan should specify:

- How a sample is obtained
- How a sample is transported from the clinic to the laboratory
- What documentation accompanies each sample
- How a sample’s departure from one place and arrival at another is documented
- The temperature at which a sample is transported
- Any time requirements for the delivery of the sample
- How a sample is handled and processed once it reaches the laboratory
- How discrepancies and rejected samples are handled

Specific information that must accompany each specimen includes the participant identification number (PTID), collection date, and visit code. Specimen labels provided by the SDMC include this key information. Accountability for the samples must be maintained with requirements for signatures of each individual who handles the specimen. The site SOP should also detail:

- How the results are returned from the laboratory to the clinic
- How problem samples are reported back to the clinic
- How critical values are handled
- How to dispose of samples that arrive in unsuitable or unusable condition

13.9 Validation of HIV Antibody Testing Algorithms

The HPTN LC may require validation of HIV testing algorithms at a CTU/CRS site. For a given protocol, the HPTN LC will determine if a validation study is needed, and if so, what type of validation study is needed for each site/algorithm. The Cross Network Guidelines for Diagnosing HIV-1 Infection in DAIDS-sponsored Clinical Trials Protocols is available on the HANC website.

13.10 Centralized Testing

The HPTN LC will oversee any non-standardized or specialized testing (e.g., testing that must be standardized across the sites or across HPTN protocols) and any QA/endpoint confirmation testing, unless prior approval has been granted by the HPTN LC for another arrangement. Endpoint QA testing and specialized assays will be performed at the HPTN LC, or at a laboratory designated by the HPTN LC.

13.11 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all study personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC SOP for post-exposure follow-up.

13.12 QA Testing

The HPTN LC will develop a plan for each protocol to verify the HIV infection status of clinical trial participants. This will include QA testing at the HPTN LC and may include specialized testing. The plan may change during the conduct of a protocol and may vary among study sites (e.g., if testing problems at one or more sites are identified, if sites are using different testing algorithms). These assessments are typically performed at the end of enrollment (e.g., for each study site), but may occur earlier in larger studies or studies in which problems in site testing or sample/data management are suspected or identified. QA testing continues during the course of the study, in batched assessments and/or evaluation of specific participants, sites, or sample subsets.

In most HPTN protocols, baseline plasma/serum samples from 50 participants, or ten percent (whichever is greater) of randomly-selected enrolled adult subjects at each site are evaluated at the HPTN LC to determine/confirm HIV status. Samples from all subjects enrolled at a site will be evaluated if there are fewer than 50 trial subjects at that site. If testing problems are identified (e.g., in the event of a false positive or false negative result that changes the infection status of the subject), samples from additional participants will be evaluated at the HPTN LC. In some HPTN studies, 100% of study samples will be retested at the LC (e.g., if significant testing problems are suspected or identified, if different testing assays or algorithms are used at different sites that may differ in sensitivity or specificity). Additional QA testing will be performed to confirm HIV seroconversion events. This may include testing samples prior to seroconversion for evidence of acute HIV infection. In some cases, QA testing may include assays such as ABO blood group back-typing (to detect sample mix-ups) or antiretroviral drug screening (to explain viral loads that are low or undetectable).

The SDMC is responsible for:

- Notifying the HPTN LC when QA testing is due for a protocol, if this testing is planned on a specific schedule, or is triggered by specific milestones, such as completion of site enrollment
- Generating a list of PTIDs for QA testing, with associated specimen-collection dates
- Providing QA testing list to the HPTN LC in standard format
- Receiving the QA test results from the HPTN LC
- Comparing the retest results with the results collected on CRFs
- Notifying the HPTN LC of any discrepancies and the need for further testing
- Creating and distributing a report of discrepancies for External Advisory Committee (EAC) review, if necessary

The HPTN LC is responsible for:

- Working with sites to ship samples to LC for retesting
- Conducting the QA testing
- Providing the SDMC with all QA test results
- Working with CTU/CRS laboratories to determine causes of any discrepancies
- Working with the SDMC to collate necessary material for an EAC, if necessary

13.13 HIV Endpoint Determination

The HPTN LC is responsible for specifying HIV testing algorithms in HPTN protocols that are scientifically appropriate for the study population and study objectives. Testing algorithms will be designed in consultation with the study team and will be described in the SSP Manual. HPTN Investigators of Record (IoRs) will make every effort to ensure that protocol-specified HIV testing algorithms are followed throughout the period of study implementation.

The HPTN LC performs QA and confirmatory HIV testing for HPTN studies as specified in HPTN protocol documents and/or the SSP Manual. The QA testing plan and the extent of QA testing (e.g., the proportion of study samples evaluated at the HPTN LC) are determined by the HPTN LC PI and HPTN LC QA/QC Core Director. QA test results are reviewed by the HPTN LC QA/QC Core Director and the HPTN LC QA/QC Coordinator for the protocol. Complex cases or cases where there are incomplete and/or discrepant results are also reviewed by the HPTN LC PI.

Protocol teams will refer all issues and questions related to HIV endpoint determination to the HPTN LC. The SDMC statistician for each study (or designee) will provide data reports to the HPTN LC as needed to support review and decision-making by the HPTN LC. For blinded studies, data provided to the HPTN LC will not include participants' treatment assignments or information regarding treatment failures.

13.14 External Advisory Committee (EAC)

In some cases, the HPTN LC may choose to convene a protocol-specific External Advisory Committee (EAC) to review cases where there are incomplete HIV test data (e.g., due to missed testing or loss-to-follow up at study sites) or where results from site and/or HPTN LC testing do not clearly define the infection status of one or more study participants. An EAC may also be convened to address issues such as:

- Failure of one or more study sites to follow a protocol-specified HIV testing algorithm
- Indeterminate test results persist at study exit
- An unusual pattern of test results is observed

The EAC is typically composed of the HPTN LC PI, the HPTN LC QA/QC Core Director and three or four additional virologists who are not HPTN LC investigators and have experience and expertise in HIV testing. For each study, the external EAC members will have no scientific affiliation with the study (e.g., protocol team members may not serve as committee members). Protocol team members including DAIDS Prevention Sciences Program (PSP) representatives and study operations staff from the LOC, SDMC, and LC may take part in EAC meetings as non-voting discussants or observers. Decisions of the EAC are considered final for purposes of primary analyses of HIV endpoints.

If an EAC is convened, the SDMC statistician for each study (or designee) will provide data reports to the EAC as needed to support review and decision-making. For blinded studies, data provided to the EAC will not include participants' treatment assignments.

It is not necessary or expected that an EAC will be convened for all HPTN protocols, or that an EAC will review all HIV endpoints for a specific protocol. If the HPTN LC deems that it is necessary to have the EAC review all HIV endpoint determinations for a specific protocol, the EAC will develop written "terms of reference" to guide their review and decision-making. The terms of reference will specify, for example, considerations related to deviations from protocol-specified testing algorithms and discordance between results obtained at the HPTN LC and the local laboratories. The terms of reference will also specify the membership of the EAC for the protocol, procedures for communication with the protocol team, and the format and frequency of EAC meetings. In these cases, terms of reference must be finalized for before undertaking any data reviews and decision-making for that protocol.

If an EAC is convened, designated staff from the SDMC will provide administrative support to the EAC. Ideally, the SDMC staff will arrange and convene EAC meetings and will document EAC decisions. It may be necessary to convene the meetings through email. SDMC statisticians will incorporate EAC decisions into HPTN study databases for purposes of HIV endpoint analyses.

13.15 HPTN Sample Destruction

CTU/CRS laboratories are required to store samples for HPTN studies. Some of these samples may be sent to other laboratories for other required testing as mandated by the respective protocols. Each study should address short- and long-term storage of specimens before study initiation. At the completion of a study, when there are specimens still being stored on-site, a determination will be made by the sponsor(s) of the study or the PI(s), in consultation with the HPTN LC when to destroy specimens from participants who did not consent to long term storage and/or to continue to store the long-term specimens. The laboratory will be notified by the study team(s) via the HPTN LC if specimens must be destroyed. This process will also specify exactly which samples are to be destroyed.

Each site will draft a Sample Destruction SOP that will be reviewed by the HPTN LC. This SOP should include a form that will be used to maintain the chain of custody of the samples throughout the destruction process. All hospital and/or university policies, as well as local regulations, must be followed when handling or discarding specimens. For older studies, the executive group of the Network may make a determination to destroy or continue to store the specimens in question.

Copies of the storage reports will be kept along with the Destruction of Samples documentation logs.

13.16 Referenced or Useful Web Links

Websites for general information related to topics covered in this section, as well as those specifically cited, are listed:

Resources:

HIV/AIDS Network Coordination	https://www.hanc.info/Pages/default.aspx

Specimen Shipping, Shipping Materials and Information:

CDC Shipping Regulations	http://www.cdc.gov/od/ohs/biosfty/shipregs.htm
Code of Federal Regulations	http://www.gpoaccess.gov/cfr/index.html
US Postal Service	http://www.usps.com
Saf-T-Pak	http://www.saftpak.com
CDC Office of Health and Safety - Biosafety	http://www.cdc.gov/biosafety/
International Air Transport Association	http://iata.org/index.htm
FedEx Dangerous Goods Shipping Seminars	http://fedex.com/us/services/options/express/dangerousgoods/seminars.html?link=4
Dangerous Goods	http://www.dangerousgoods.com/profile.htm
DHL	http://www.dhl-usa.com/solutions/express.asp?nav=dhlExp
US Department of Transportation	http://www.dot.gov/
US DOT/Transporting Infectious Substances Safely	http://www.phmsa.dot.gov/staticfiles/PHMSA/Hazmat/digipak/pdfs/presentation/Infectious_Substances(04_07).pdf

Risk Group Assessments:

Risk Group Classification for Infectious Agents	http://www.absa.org/riskgroups/index.html
American Biological Safety Association	http://www.absa.org/
CDC Regulation	http://www.cdc.gov/biosafety/
CDC Select Agent Listings and Regulations	http://www.selectagents.gov/
USDA Plant and Animal Pathogen Select Agents	http://www.aphis.usda.gov/wps/portal/footer/topicsofinterest/applyingforpermit

HIV Antibody Testing Algorithm:

HPTN Requirements, Frequently Asked Questions (FAQs)	http://www.hptn.org/hptn_structure/NetworkLab/HIVABTestQA.htm