14. LABORATORY ISSUES

All Microbicide Trials Network (MTN) study sites are required to adhere to the standards of Good Clinical Laboratory Practice (GCLP), the Division of AIDS (DAIDS) GCLP guidelines and local Standard Operating Procedures (SOPs) for the proper collection, processing, labeling, transportation and storage of laboratory specimens. In most cases, laboratories with Clinical Laboratory Improvement Amendments (CLIA) certification may submit this as documentation of GCLP compliance.

14.1 Microbicide Trials Network Laboratory Program

14.1.1 Microbicide Trials Network Laboratory Quality Assurance Policy

The MTN Laboratory Center (LC) has developed and implemented a generic network laboratory quality assurance (QA) policy entitled "*Laboratory Quality Assurance and Quality Assessment Policy"* that is the basis for a range of QA activities carried out by the MTN LC and site laboratories. This laboratory QA policy applies to all MTN laboratories 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 staff. The Clinical Trials Units (CTUs) and their associated Clinical Research Site(s) (CRS) are responsible for implementing the QA policy at the CTU/CRS laboratories.

The objectives of the MTN laboratory QA policy (and related programs) are to:

- Ensure that QA activities are comprehensive, coordinated and that appropriate information is reviewed and reported
- Establish, maintain, support and document an ongoing QA program that includes effective and systematic mechanisms for monitoring, collecting, and evaluating information about important aspects of laboratory data to identify opportunities for improving data analysis and participant care
- Assist in improving care and identifying problems through continuous monitoring by focusing on identification, assessment, correction and follow-up of problems that affect data analysis and participant care
- Implement corrective action when problems or opportunities are identified
- Follow up on identified problems to ensure improvement and resolution

The complete QA policy is attached to this manual as Appendix II. See Appendix III for the QA policy specific to HIV testing.

14.1.2 Microbicide Trials Network Laboratory Quality Control Policy

CTU/CRS laboratory quality control (QC) activities are an integral part of the laboratory QA program. The CTU/CRS QC program is divided into the following main areas of focus:

- Internal QC (testing of known materials)
- Parallel testing (validation of new controls and reagent lots)
- Blinded or split-sample testing
- External Proficiency testing programs
- QC monitoring (corrective action logs)
- QA program feedback

- Preventative maintenance program

Further guidance for developing a site QC program that incorporates these components is contained in Appendix IV.

14.2 MTN Laboratory Quality Assessment and Quality Control Program

Each CTU/CRS involved in MTN research is expected to develop a site-specific laboratory QA/QC plan to expand on the generic *Laboratory Quality Assurance and Quality Assessment Policy* (Appendix II) and *Laboratory Quality Control Policy* (Appendix IV) instituted by the MTN LC. The site-specific QA/QC plan is designed to ensure accurate, timely and reliable test results by providing routine monitoring of the overall laboratory operation.

14.3 Assessment of Clinical Research Site Laboratory Performance

14.3.1 Non-U.S. Clinical Research Site Laboratories

DAIDS has arranged for non-U.S. local laboratories that participate in MTN research to receive proficiency panels from the College of American Pathologists (CAP), the United Kingdom National External Quality Assessment Service (UK NEQAS) and other approved proficiency providers. The panels are sent to sites based on the assays performed for the specific MTN trials in which the site is participating. Each year, the MTN LC re-enrolls sites based on the assays that are/will be done at that specific site via the Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) group, Immunology Quality Assurance Group (IQA) and Virology Quality Assurance Group (VQA). The MTN LC follows the results and communicates directly with the sites regarding any potential issues or problems with the results and works with the sites to identify corrective actions, as needed. This oversight is achieved as part of a cross-network collaboration with other U.S. National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS clinical trials networks, IQA, VQA and pSMILE as part of the Primary Network Laboratory (PNL) system. In addition, each laboratory undergoes an assessment by the Clinical Site Monitoring Group (CSMG) and receives results generally through DAIDS, including recommendations for and assistance on addressing existing or potential problems. The MTN LC reports annually on site performance in the proficiency-testing program and shipping quality to the MTN Network Evaluation Committee.

14.3.2 Non-Affiliated External Laboratories Outside the U.S.

Non-affiliated laboratories are laboratories (often commercial) that an MTN site contracts with and pays to perform tests on specimens collected during an MTN study. The MTN site may also use non-affiliated laboratories as part of a back-up plan (see *Guidelines for Use of Back-Up Equipment and Back-up Laboratories for Safety Testing in DAIDS-Sponsored Clinical Trials,* https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx). Although the use of non-affiliated laboratories is necessary, sometimes it is not encouraged because oversight is frequently difficult to manage. As such, the MTN LC has developed and implemented strategies to assess and monitor performance of non-affiliated laboratories that receive and process specimens from non-U.S. MTN sites.

14.3.2.1 Requirements for Sites Using Non-Affiliated External Laboratories

DAIDS has specific requirements for sites that send samples to external non-affiliated laboratories. Sites may periodically include blinded positive and negative specimens (controls) along with test specimens that are sent to these laboratories. This provides a basis for monitoring the performance of external non-affiliated laboratories and assists those laboratories in identifying possible problems with their assay procedures. Site staff should consult the MTN LC Manager or their PNL about which assays to monitor, which control materials to use and what range of external laboratory results to anticipate and consider acceptable for a particular assay. When necessary, MTN LC staff will assist in obtaining the required control materials. Results are monitored as part of the proficiency panels submitted to UK NEQAS and CAP, as described above.

The MTN LC staff may visit external non-affiliated laboratories that are (or will be) receiving and processing specimens collected during MTN studies. Early visits, prior to initiation of a specific study, will focus on a laboratory's capability to perform required tests. When LC staff travel to MTN sites, they also visit external laboratories when possible and document these visits.

14.3.2.2 Responsibilities of Sites for Quality Assessment of Non-Affiliated External Laboratories

MTN sites that contract with external laboratories for specimen testing must work with the LC and external laboratories as much as possible to ensure the integrity of the results and handling of specimens. Each MTN study site that uses an external laboratory must:

- Consult with LC staff to determine which assays conducted at external laboratories will require the inclusion of periodic controls and which materials should be used as controls
- Consult with LC staff to determine the minimal frequency for including control samples in assays conducted at external laboratories
- Document the incorporation of known controls into groups of samples submitted to external laboratories
- Collate results of assays done on these controls and fax information to LC monthly (or more often, if requested)
- Maintain archival records of all of the documentation of results for assays performed on control samples
- Consult LC staff immediately in case of unacceptable results to determine a plan for assessing the external laboratory's performance in greater detail and discuss possible plans for corrective action

14.3.3 Proficiency Testing

Each site laboratory must complete proficiency testing specifically applicable to a particular study's design and laboratory needs. The laboratory must generally pass one round of proficiency testing prior to study activation; blinded external validation panels can fulfil this requirement. Laboratories are subject to repeat proficiency testing as the study is being conducted. Possible outcomes include:

- Any deficiency, regardless of the scoring, will require corrective action by the site laboratory
- A site laboratory's failure to report to the pSMILE group that a panel has not been received may be considered unsatisfactory

- If the proficiency provider does not grade the results because they were submitted late, pSMILE will make an effort to grade the results and document that the panel is considered late
- When a site laboratory receives unsatisfactory results on two panels in a row, or two out of three panels, the LC and pSMILE will provide instructions to the laboratory on what corrective action needs to be taken in addition to reporting the corrective action
- When a site laboratory receives unsatisfactory results on two panels in a row, or two out of three, the laboratory's back-up plan may go into effect, in which case the laboratory cannot perform protocol testing for those particular analytes. The site laboratory, LC, DAIDS Clinical Laboratory Oversight Team Point of Contact and pSMILE will confer to decide on a corrective action plan that may include additional panel testing
- For the HIV viral load, HIV DNA and CD4 proficiency panel results, the LC will follow the recommendations of the appropriate governing QA partner — pSMILE, VQA or IQA — and take appropriate action based on these recommendations

14.3.4 Certification of U.S. Study-Site Laboratories

Laboratories within the U.S. that participate in MTN research and generate results that are used for the clinical management of patients are required to have CLIA certification and to provide documentation of this certification to the LC. Recertification is required every two years. The CLIA certification may serve as proxy for certain documentation requirements of the GCLP. The MTN may request to review GCLP documentation from U.S. CTU/CRS laboratories. Certain documentation (such as laboratory normal ranges and study-specific SOPs) will be required for study activation.

14.4 Laboratory Center Oversight of Study-Site Laboratories

The LC staff may conduct periodic site visits and/or "for cause" site visits to assess the implementation of laboratory QC procedures, including the proper maintenance of laboratory testing equipment and appropriate use of reagents. The purpose and scope of the visit is discussed with site personnel prior to the visit. In addition, the LC may place a temporary laboratory technician/advisor on site if the need is indicated. Whether on site or centrally located, the LC staff work directly with the MTN CTU/CRS staff to address and resolve any QC or QA problems that are identified by the site through proficiency testing, site visits or by the site during study preparation or implementation.

14.5 Laboratory Monitoring by the Clinical Safety Monitoring Group

DAIDS CSMG monitors periodically conduct complete laboratory audits prior to or during an MTN study. The Statistical and Data Management Center (SDMC) provides the CSMG monitors with site-specific laboratory information to enable them to conduct the expected monitoring of specimen processing and storage of study-specific archived samples.

More information about laboratory monitoring may be found on the following Web sites:

- U.S. Food and Drug Administration (FDA): http://www.fda.gov
- College of American Pathologists (CAP): http://www.cap.org
- U.K. National External Quality Assessment Service: http://www.uknegas.org.uk

- Oneworld Accuracy (OWA): http://www.oneworldaccuracy.com/HealthMetrx/public/prepareHome.do
- Westat: http://www.westat.com
- Laboratory Data Management System (LDMS): https://www.fstrf.org/apps/cfmx/apps/ldms/index.html
- HIV/AIDS Network Coordination (HANC): http://www.hanc.info
- pSMILE: https://psmile.org/

14.6 Specimen Handling and Processing

Only properly trained personnel can perform specimen collection. It is essential that staff is aware of proper collection techniques, container types, special requirements and proper care for research participants. Specimens must be transported to the laboratory under proper conditions and within predefined time limits. In addition, each laboratory is required to use the LDMS for storing and labeling certain biological samples designated for each study.

14.6.1 Lab Specimen Labels Provided by the Statistical and Data Management Center

Lab specimen labels provided by the SDMC include the Participant Identification Number (PTID) and a space to write the date and visit code for the visit at which it was collected. The labels are intended for use only on original specimen “containers” (such as vacutainers and slides). If a specimen is to be processed, then the LDMS labeling system will be used to generate container labels after the information has been entered into the LDMS.

14.6.2 Laboratory Data Management System

The Frontier Science and Technology Research Foundation (FSTRF) and the MTN LC provides training and support to local laboratory staff on the use of the LDMS; however, each CTU/CRS laboratory is financially responsible for training its staff members. The CTU/CRS laboratory is responsible for maintaining its LDMS program, including hardware and software upgrades. The MTN LC develops code sheets for each protocol to ensure that specimens are entered correctly into the system. Additional details are included in each Study-Specific Procedures (SSP) Manual.

The MTN SDMC and LC offer pre-printed labels and specimen-tracking sheets to sites to facilitate the entry of specimens into the LDMS database. For each study, the protocol and SSP manual will indicate which specimens will be stored locally and which will be shipped to the MTN LC for testing. The SSP manual also will indicate, with instructions, which specimens must be entered into the LDMS.

14.6.3 Specimen Shipping

Specimens will be transported in accordance with International Air Transport Association (IATA) regulations, U.S. federal laws and regulations, and any and all laws and regulations that govern specimen transport to and within the receiving country. This applies to transporting specimens, test supplies and reagents on site; to and from the clinic and the laboratory; and from the site to the LC. Study and laboratory personnel who are involved with packaging and transporting specimens must receive adequate and appropriate training to ensure compliance with all applicable guidelines and regulations. Documentation of training must be filed on site and a copy sent to the LC.

The IATA regulates the safe transportation of dangerous goods by air in accordance with its legal requirements. The IATA requires training and certification for individuals who are involved with shipping Class 6.2 infectious substances and diagnostic specimens. The IATA regulations define infectious substances, cultures and stocks, biologic products and diagnostic specimens. The regulations also specify the requirements for handling and shipping each of these substances. 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.

Definitions of key terms follow:

Class 1: Explosives
Class 2: Gases
Class 3: Flammable Liquids
Class 4: Flammable Solids
Class 5: Oxidizers/Organic Peroxides
Class 6: Toxic and Infectious Substances

- *Division 6.1: Toxic Substances*
  - Guanidinium (chemical preservative)
- *Division 6.2*: *Infectious Substances*
  - Category A Infectious Substances–Packing Instruction 620 - An infectious substance which is transported in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Indicative examples of substances that meet these criteria are given in Table 3.6.D of the IATA Dangerous Goods Regulations. Category A substances that affect humans are assigned to UN2814. This includes viral isolates from cultures of HIV and Hepatitis B.
  - Category B Biological Substances, UN3373–Packing Instruction 650 - An infectious substance which does not meet the criteria for inclusion in Category A. Substances in Category B must be assigned to UN3373. For shipping purposes, these are considered to be Category B biological specimens and must be assigned to UN3373. Patient Specimen (this is the definition for a patient specimen) refers to any human or animal material including, but not limited to, excreta; secretions; blood and its components; tissue and tissue fluids; body parts being transported for research diagnosis, investigational activities or disease treatment or prevention.
  - Exempt Human Specimens– no specific packing instruction – definition- Specimens for which there is minimal likelihood that pathogens are present. These specimens are not regulated provided the specimens are packed in packaging which will prevent leakage and is marked “Exempt human specimen” or “Exempt animal specimen”.

Class 7: Radioactive Material
Class 8: Corrosives
Class 9: Miscellaneous Dangerous Goods:

- Dry Ice, UN(1845)–Packing Instruction 954

Renewal of IATA shipping certification is required every two years with an annual review of the IATA Dangerous Goods Regulations to check for any new or changed requirements. The CTU/CRS laboratory personnel are responsible for obtaining the appropriate training and annual IATA Dangerous Goods Guidelines. Each staff member who handles shipments must be trained and certified. New staff must be trained within 90 days of their start date. Site personnel should review IATA regulations, which are updated annually.

Each site should follow local regulations regarding the transportation of samples by dedicated couriers. MTN study sites within the U.S. must follow the U.S. Department of Transportation requirements, which regulate the transportation of infectious substances within the U.S. (See U.S. Code of Federal Regulations [CFR] 49 CFR, Part 171). Sites outside the U.S. are subject to in-country government regulations for transportation of infectious substances.

Importation of human pathogens to the U.S. from abroad requires an importation permit from the U.S. Centers for Disease Control and Prevention (CDC). The LC maintains a worldwide importation license that covers all materials sent from MTN sites to the LC at Magee-Womens Research Institute in Pittsburgh, PA, USA. Specimens sent from the sites to other locations within the U.S. are not covered under this importation permit.

Specimen shipping may require Specimen or Material Transfer Agreements (MTA). Sites need to notify the LC during study activation of these requirements so they can be completed before specimen shipping is required.

More information on specimen shipping and shipping materials is available on the following web sites:

- CDC Shipping Regulations: http://www.cdc.gov/od/ohs/biosfty/shipregs.htm
- Code of U.S. Federal Regulations: http://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
- U.S. Department of Transportation: http://www.dot.gov/
- U.S. Postal Service: http://www.usps.com
- Saf-T-Pak: http://www.saftpak.com
- IATA: http://www.iata.org/index.htm
- CDC Biohazard Policy: http://www.cdc.gov/od/ohs/biosfty/biosfty.htm
- World Health Organization (WHO) Transport of Infectious Substances: http://www.who.int/ihr/publications/laboratory/en/

To learn more about risk-group assessments, visit these web sites:

- American Biological Safety Association: http://www.absa.org/riskgroups/index.html
- CDC Select Agent Program: http://www.cdc.gov/od/sap/
- U.S. National Institutes of Health (NIH): http://osp.od.nih.gov/office-biotechnology-activities/oba/rac/guidelines_02/APPENDIX_B.htm
- U.S. Department of Agriculture (USDA) Plant and Animal Pathogen Select Agent Program: http://www.aphis.usda.gov/programs/ag_selectagent/downloads/BR-9cfr121-7cfr331.pdf

14.7 Policy for Testing of Stored Specimens

Some specimens that are collected as part of an MTN clinical trial may be stored for future use and testing, including as part of an ancillary study (see Section 21 of this manual). If not used by the protocol team to address study objectives, an Ancillary Study *A*pplication (http://www.mtnstopshiv.org/resources) may be required. Non-MTN investigators must also complete an *MTN Materials Transfer Agreement for Specimens from MTN Clinical Studies* form (http://www.mtnstopshiv.org/resources) for the use of stored specimens from MTN studies.

All proposed testing of stored specimens must be reviewed and approved by the relevant MTN protocol team, MTN Working Groups, and MTN Executive Committee (EC). Assuming approval is obtained, the investigator proposing to test the specimens is responsible for ensuring that the following steps are followed:

1. All primary study endpoints must be ascertained prior to any testing of stored specimens. In addition to ascertaining primary endpoints, all protocol-specified laboratory testing that involves the stored specimens at issue (including QA/QC testing to be performed by the LC) must be completed prior to any other testing of the specimens.
2. All protocol-specified data analyses must be completed and considered final by the protocol team prior to any testing of stored specimens. Retesting of samples for participant safety and clinical management, QA purposes or ambiguous endpoints may be done at the discretion of the LC or site.

   Note: *There may be circumstances in which it is acceptable for the testing of stored specimens to proceed before approval has been obtained and the conditions in items 1 and 2 have been met. In such cases, the Protocol Chair(s), Protocol Statistician, LC Representative and the EC may approve an exemption to these requirements and allow the testing to proceed. The Protocol Chair(s), Protocol Statistician, LC Representative and the EC must be unanimous in their approval of such exemptions.*
3. Any residual specimens remaining in storage from participants who did not consent to long-term storage and/or possible future research testing of their specimens will be destroyed after all primary endpoints have been ascertained, all protocol-specified laboratory testing involving the stored specimens at issue has been completed and protocol-specified data analyses have been completed and determined to be final.
4. After all primary endpoints have been ascertained, all protocol-specified laboratory testing involving the stored specimens at issue has been completed and protocol-specified data analyses have been completed and considered to be final, investigators wishing to perform further testing of stored specimens will inform the MTN prior to performing the proposed testing. (Please review Section 21 Ancillary Studies, of this manual, for information regarding access to stored specimens.) If approval is granted, the investigators may begin work on their proposal.
5. Copies of the submitted notification form, MTA and proposal will be maintained in the Leadership and Operations Center (LOC University of Pittsburgh) files. The proposing MTN investigator will also retain copies of these documents on site, together with copies of all other relevant approvals and communications regarding the proposed testing. Minimally required documentation is indicated in Section 21 of this manual.
6. All data analyses, presentations and publications resulting from the testing of specimens collected and stored for possible future research testing in MTN studies will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. (See Section 20 of this manual.)
7. Investigators wishing access to specimens in long-term storage will need to fill out an Ancillary Study Application and MTA (see Section 21 of this manual). These are sent to the indicated personnel and will be reviewed by the protocol team, the MTN Working Groups, and the MTN EC.

14.8 Destruction of Samples

The CTU/CRS laboratory is responsible for storing samples collected in any MTN study taking place at the site, although some of these samples may be sent out to other laboratories for other required testing as mandated by the specific protocol. If a site is storing specimens after the completion of a study, a determination is made whether to destroy the specimens in question or continue to store them. In certain situations, specimens must be destroyed (for example, specimens from improperly enrolled participants who have been removed from a study, or specimens that should not have been stored per the protocol). The specific protocol team(s) will notify the laboratory via the LC if specimens need to be destroyed. The LC will notify the CTU/CRS laboratory if specimens need to be destroyed, and which samples are to be destroyed, per the study team's directive.

Each site will draft a Sample Destruction SOP, which should include a form to use to maintain the chain of custody of the samples throughout the destruction process. Laboratory staff should complete the form with the following information: date and time of destruction, protocol number, notifying authority, the nature of the samples, the laboratory staff member's signature and date, and the Laboratory Director or designee's signature and date. Final sign-off is required from the CRS leader or designee. These records should be kept in the appropriate folder. Specimen inventories should be checked prior to destruction. Any discrepancies should be noted and documented on the table. The LC will provide the laboratory with a date by which the specimens must be destroyed. This notification also may include any special requirements for destruction or documentation. Confirmation of destruction will be sent out as requested by the LC. Specimens will be removed from the specimen storage section of the LDMS.

***Note**: In some cases, it may be necessary to store specimens from participants during the screening process before they enroll in a study. If the participant is deferred from the study during a failed screening attempt, the specimens may be destroyed without MTN's authorization. These specimens may be destroyed in real time or batched at the end of the study. Site laboratories are encouraged to verify deferral against their site's screening and enrollment logs to avoid destroying specimens from enrolled participants in error. Specimens from failed screening attempts cannot be shipped away from the site without written approval from the MTN LC or the protocol team.*

14.8.1 Destruction of Samples Not Consented for Long Term Storage

Study participants who decline long term storage will be referred to as non-consenters. Samples from non-consenters are destroyed once all protocol-defined testing is complete. Protocol-defined testing may take several years. During the study close-out process, the SDMC will contact the LC before generating lists of non-consenters. The lists will generally contain PTIDs and location of samples identified by the LDMS laboratory ID. For samples that have been shipped to a non-LDMS laboratory, the storage site will not be available and show as "Pending" on the reports. When "Pending" is indicated, the report will include the LDMS laboratory ID of the shipping lab and the LDMS shipping batch number.

On a study-by-study basis, the LC may request LDMS global specimen ID's or other information to expedite the destruction process. Any other study-specific requirements will be relayed at this point. The SDMC will then generate the lists and send to the LC via email or ATLAS. Before initiating sample destruction, the LC will confirm that all protocol defined testing is complete and receive approval for destruction from the Protocol Chair(s), DAIDS MO and BSWG. The LC will then be responsible to initiate and oversee the destruction process with the respective labs where samples are stored.

For CTU/CRS laboratories, the LC will instruct them to cross reference the SDMC list against their records. Any discrepancies will be referred to the SDMC for investigation. Sites may need additional information, such as LDMS global specimen ID's. The LC will relay these requests to the SDMC. Sites will perform destruction per local SOP and inform the LC when destruction is complete. Sites will be responsible for keeping local documentation of sample destruction, which must be provided to the LC upon request. The LC will notify the SDMC and the protocol team(s) when this sample destruction is complete. The SDMC will then verify that all non-consenter samples have been electronically destroyed via ATLAS. There is no mechanism for SDMC to verify samples have been electronically destroyed at non-LDMS labs.

14.9 Requirements for Laboratory-Related, Site-Specific Protocol Activation

The LC's approval of CTU/CRS laboratory readiness is required for MTN site-specific study activation. Laboratory readiness is determined when specific requirements are met, which may include the following: (See also Section 11 of this manual.)

- LC approval of proficiency in HIV testing, including validation of algorithm
- QA/QC procedures at the site
- Site-specific normal ranges
- Appropriate validation for protocol-specified tests
- Local laboratory back-up arrangements per current cross-network policy
- IATA specimen-shipping certification
- Initiation of Specimen Transfer Agreements, if required
- Site SOP for local specimen handling and chain of custody
- Laboratory manager curriculum vitae on file
- Use of LDMS
- CLIA certificates

The LC notifies the LOC (FHI 360) Clinical Research Manager for the study when the site's laboratory-related procedures, facilities and staff are deemed ready for study activation. The LC's approval constitutes local laboratory certification for CRS laboratories. Certification can be rescinded at any time for failure to maintain key systems or requirements, such as failure to use the LDMS. Sites are required to notify the LC of any changes in normal ranges or instrumentation, send updated certificates to the LC and otherwise inform the LC of any important changes or modifications.

As part of site-specific, protocol-activation requirements, each site is required to establish an SOP for handling local specimens and to maintain a chain of custody. The LC must approve the Chain of Custody SOP. Typical elements may include:

- How to obtain a specimen
- How to transport a specimen from the clinic to the laboratory
- Which documentation accompanies each specimen
- How to document a specimen's departure from one place and arrival at another
- At what temperature to transport a specimen
- How to handle and process a specimen after it reaches the laboratory
- How to handle discrepancies and rejected specimens

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

- How to return the results from the laboratory to the clinic
- How to report problem specimens back to the clinic
- How to dispose of specimens that arrive in unsuitable or unusable condition

14.10 Validation of HIV Antibody-Testing Algorithms

This validation scheme was developed by the HIV Prevention Trials Network (HPTN) LC and adapted by the MTN LC. MTN research sites that perform HIV antibody testing for MTN protocols must validate each HIV antibody-testing algorithm that they intend to use for any MTN study in which incident HIV infection is the primary endpoint. In cases of an ambiguous HIV result, the MTN LC must review the validation testing results and make recommendations. FDA-approved HIV antibody tests are sometimes required, especially for MTN protocols conducted under an Investigational New Drug application. In cases where two HIV rapid tests are used, at least one of the two tests must be FDA-approved, unless approval to waive this requirement has been received from the LC and DAIDS. Regardless of which HIV antibody test is used, each site must validate the performance of the testing algorithm that is to be used in all MTN protocols for both screening/baseline testing and follow-up testing. Validation does not need to be repeated for each study that uses the same algorithm or tests. If the protocol specifies a different algorithm, that algorithm may need to be validated. U.S.-based sites that perform HIV testing under CLIA certification or waiver must follow CLIA guidelines; MTN LC will not review a site's validation unless specifically requested.

Site laboratories should use the same venous specimen type (for example, plasma, serum or whole blood) as the protocol uses. If this is not feasible, the site laboratory may use one type of venous specimen to validate all venous specimen types. Finger-stick specimens may require a separate modified validation. The MTN does not allow the use of oral fluids for HIV testing.

The validation process requires testing specimens from a minimum of 20 confirmed HIV-infected individuals and a minimum of 20 confirmed HIV-uninfected individuals using an FDA-approved kit along with the kit(s) planned for use in a particular study, unless the MTN LC specifies otherwise. For cases in which some validations have already been performed, the MTN LC may require additional validation testing with a smaller sample size. If participants gave informed consent to be tested for HIV, it is not necessary to obtain additional informed consent from individuals whose samples will be used in the validation process. Because this is considered a QA activity, not a research activity, U.S. regulations do not require a review by the Institutional Review Board/Independent Ethics Committee. International sites need to refer to local or in-country regulations.

If testing reveals no more than one false-positive or false-negative result, then the testing algorithm may be considered validated and the MTN LC may grant approval for use in MTN protocols at the site. If testing reveals more than one false-negative or false-positive sample, the LC will suggest steps to resolve the discrepancy. For confirmatory methods that can also yield indeterminate results, the LC will designate appropriate acceptance criteria relative to the method.

If it is later decided to use a different algorithm for a study at the site, the validation process may be repeated as needed for that algorithm and re-submitted to the MTN LC for review before the site uses the new algorithm. Unless otherwise noted, each site should send a validation report to the LC Manager describing the validation process it used and the results. Upon review of this documentation, the LC Manager is to indicate in writing that the algorithm has been approved for use in MTN studies.

Unique circumstances at each site may require clarification or modification of this validation process. Sites are encouraged to contact the MTN LC for further guidance and to provide the MTN LC with the plan for completing this requirement in advance of implementation to ensure that the process is adequate. Any questions should be emailed to the MTN LC: MTNNetworkLab@mtnstopshiv.org.

More information on the diagnosis of HIV infection and testing algorithm can be found in the Cross Network Guidelines for Diagnosis of HIV Infection in DAIDS-Sponsored Clinical Trial Protocols document, and is available through the MTN LC.

14.11 Centralized Testing

The MTN LC will oversee any non-standardized testing for new concepts and future trials. Testing needs to be standardized across the study sites, including any QA or endpoint confirmation testing, unless the MTN Leadership Group and LC have granted prior approval. Each LC Core participating in batched testing may be required to submit testing plans (including specific timelines) to the LC Principal Investigator (PI).

14.12 Laboratory Safety

The transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood and blood products. All study personnel must take appropriate blood and secretion precautions when drawing blood and shipping and handling specimens for all MTN studies, as currently recommended by the U.S. CDC SOP for post-exposure follow-up.

14.13 Document Standards

All laboratory results must be traceable to a defined source document that is the first place a result was recorded. These must be archived based on the retention policy relevant to each study. Error correction must be performed per current DAIDS standards. Major events in the laboratory need to be documented with a *Note to File* and communicated immediately to the MTN LC representative and the DAIDS Office of Clinical Site Oversight Program Officer. Certain deviations must be documented as a protocol-deviation, as per Section 16.4 of this manual.

14.14 Training and Competency

All staff records must show education records and work experience appropriate to their job description. All employees, as well as their supervisors, must sign their own job description. All lab staff must have documented training and established competency before they are allowed to report test results or perform other laboratory activities (such as phlebotomy). Competency must

be re-assessed after the first six months, 12 months and annually thereafter. For further guidelines, refer to Appendix II, Laboratory Quality Assurance and Quality Assessment Policy.

14.15 Method Validation

All new methods, instruments or test kits must be validated. Changes to existing tests and methods may also require validation. Refer to Appendix VI for the Method Validation Policy.

14.16 Quality Assessment Testing

As a site-specific QA measure to verify the HIV-infection status of study participants, the LC reserves the right to perform relevant protocol-related testing. This testing may occur at any time during a study. Specimens from seroconverters and an equal number of HIV-negative participants will be tested to verify local laboratory test results and, under special circumstances, samples tested at a non-MTN centralized location (such as a local commercial laboratory). Discrepancies may be resolved using test methods with different sensitivities.

For Phase IIb–IV studies, or as decided by the MTN LC and the protocol team, the LC will retest baseline plasma/serum samples for the HIV antibody. Specific protocols may require random QA testing from other visits. The LC will test samples from 50 participants or 10 percent (whichever is greater) of randomly selected, enrolled adult subjects at each site. Samples from all participants will be retested if there are less than 50 study participants. Follow up for discrepant results will be study specific.

In the event of a false-positive or false-negative result that changes the infection status of the participant, additional samples from enrolled participants will be retested, with sample sizes determined by the LC. Baseline and seroconversion plasma/serum samples from all seroconverting adult subjects, and an equal number of randomly selected samples from uninfected subjects matched by follow-up visit, will be retested by the LC using FDA-licensed tests (for example, HIV antibody, HIV DNA PCR or HIV RNA), if necessary. In the event of an unexpected result (such as a positive baseline sample or a negative endpoint sample in a seroconverter), the LC may decide to retest additional aliquots or time points.

The SDMC is responsible for:

- Notifying the LC when retesting is due for a protocol
- Generating a list of PTIDs for retesting, with associated dates for specimen collection
- Providing the retest list to the LC in standard format
- Obtaining the retest results from the LC
- Comparing the retest results with the results reported on the case report form
- Notifying the LC of any discrepancies and the need for further testing
- Creating and distributing a report of discrepancies for review by the MTN Endpoint Adjudication Committee

The LC is responsible for:

- Working with sites to ship samples to the LC for retesting
- Conducting the retesting
- Providing the SDMC with all retest results from the testing

- Working with the study sites to determine the causes of any discrepancies
- Working with the SDMC to collate necessary material for the MTN Endpoint Adjudication Committee

14.17 Endpoint Adjudication Committee

Protocol teams are responsible for specifying HIV-testing algorithms in MTN study protocols that are scientifically appropriate for the study population and study objectives. The MTN Investigators of Record are responsible for ensuring that protocol-specified HIV-testing algorithms are followed for MTN studies conducted at their sites.

The LC performs QA and confirmatory HIV testing for MTN studies as specified in MTN study protocols. The MTN Endpoint Adjudication Committee is responsible for providing guidance to the protocol teams with regard to determining HIV endpoints. The committee's decisions are considered final for purposes of primary analyses of HIV endpoints. The SDMC provides data reports to the MTN Endpoint Adjudication Committee, documents committee-meeting decisions and incorporates committee decisions into the MTN study databases.

The MTN Endpoint Adjudication Committee is composed of the MTN LC PI and up to four additional members with experience and expertise in HIV testing. The assigned committee members will have no scientific affiliation with the study. For example, protocol team members may not serve as committee members. The MTN LC PI will chair each study-specific committee unless he or she has a scientific affiliation with the study. Typically, these meetings are completed through e-mail whereby a scoring sheet is circulated. The final tallies are made by the Committee Chair and sent to the Endpoint Adjudication Committee for confirmation before being sent to the SDMC.

It is not necessary for the Endpoint Adjudication Committee to review all HIV endpoints for all MTN studies with HIV endpoints, nor is it expected. The Endpoint Adjudication Committee will instead provide guidance to protocol teams in the event that the final HIV status of one or more study participants is not unequivocal, or if the point at which one or more participants became infected is not clear. Issues or questions related to determining the HIV endpoint will arise if one or more of the following situations occur:

- A protocol-specified HIV-testing algorithm is not followed or completed
- The LC test results do not confirm local laboratory test results
- Indeterminate test results persist at study exit
- An unusual pattern of test results is observed

Protocol teams will refer all issues and questions related to HIV endpoint determination to the Endpoint Adjudication Committee. The SDMC Statistician for each study (or designee) will provide data reports to the Endpoint Adjudication Committee as needed to support the committee's review and decision making. For blinded studies, data provided to the committee will not include participants' treatment assignments.

For each study, the Endpoint Adjudication Committee will follow the terms of reference developed by the SDMC and the MTN LC Virology Core to guide its review and decision making. The terms of reference will specify, for example, considerations related to deviations from protocol-specified testing algorithms and discordance between the test results of the LC

and the local laboratory. The terms of reference will specify the procedures for communication with the SDMC and the format of Endpoint Adjudication Committee meetings. Terms of reference must be finalized for each study prior to undertaking any data reviews and decision making for that study.

Designated staff from the SDMC will provide reports and requests to the Endpoint Adjudication Committee Chair and document committee meetings and decisions. Decisions made by the Endpoint Adjudication Committee will be considered final. The SDMC Statisticians will incorporate committee decisions into MTN study databases for the purposes of analyzing HIV endpoints.