MTN Manual of Operational Procedures (MOP)

APPENDIX I: Laboratory Quality Assurance and Quality Assessment Policy

Prepared by	Date Adopted	Supersedes Procedure #
Adapted from HPTN Policy		N/A

Review Date	Revision Date	Signature

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1 SCOPE

This policy applies to all laboratories performing clinical laboratory testing for the Microbicide Trials Network (MTN).

2 PURPOSE

The MTN Laboratory Center (LC) has an ongoing Quality Assessment (QA) Program that is designed to monitor, evaluate and improve the quality of laboratory performance; ensure the reliability of test data; and evaluate the competency of the laboratory staff. The LC will identify and resolve any problems that may affect laboratory performance and thus patient care.

Any work area in which testing of patient samples occurs is subject to the same sets of guidelines and policies as the MTN LC. This includes clinic areas and off-site locations. Any individual who performs testing on patient samples must adhere to the contents of this policy.

Additional QA procedures may also be listed in the Study-Specific Procedures Manual developed for each study.

Manufacturer recommendations must be followed. If this document or other documents give conflicting information on QA, please contact the MTN LC (mtnnetworklab@mtnstopshiv.org).

3 OBJECTIVES

The objectives of the policy are to:

- Ensure that QA activities are comprehensive and 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 performance to identify opportunities for improving patient care
- Assist in improving care and identifying problems through the use of ongoing monitors by focusing on identification, assessment, correction and follow-up problems that affect laboratory performance
- Implement corrective action when problems or opportunities are identified
- Follow up on identified problems to ensure improvement and resolution in a timely manner with documentation of corrective action

4 QUALITY ASSURANCE MONITORS

The following QA Monitors are actively evaluated to maintain an established standard of laboratory performance and compliance. Data from each monitored area are collected, recorded and analyzed. The findings are evaluated to detect trends and overall compliance. When required, appropriate corrective action will be implemented and documented. Monitoring will be continued to ensure that the action taken was appropriate and resulted in correction of any problems found. It is recommended that site laboratories hold quarterly meetings to review the reports of the monitored areas.

4.1 Proficiency Testing

Proficiency programs are used as an external check on the quality control (QC) and QA of a test system. Generally, analytes should be tested a minimum of twice per year — three times per year, when possible. The laboratory will participate in external proficiency panels/surveys, which are blind assessments of the laboratory's performance. Where possible, the laboratory will participate in a proficiency program for each test performed in the lab/clinic area.

Note: *Please also refer to the Instructions for Handling CAP Proficiency Surveys Guidelines:* http://www.cap.org/web/home/lab/proficiency-testing?_adf.ctrl-state=pidpsfp9l_77&_afrLoop=360379839010715#!.

- For testing where no external proficiency program samples are available, other methods of proficiency checks will be used, if possible.
- Proficiency samples are tested in the same manner as any routine specimen submitted to the laboratory.
- All staff involved in patient testing should rotate testing proficiency samples.

- The laboratory supervisor or designee will review the final results form and send it to the testing agency in a timely manner.
- A copy of the final results form will be kept in the External Proficiency Testing file.
- When the survey results are returned, the Laboratory Supervisor and Director will review and sign the results.
- If there are any noted deficiencies, the deficiencies will be investigated by the Laboratory Supervisor and Director. Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) will send an Investigation Report (IR) to the laboratory on all failed or missed analytes. The Primary Network Laboratory (PNL) for each site may perform more frequent reviews and notify the site earlier to initiate corrective action.
- A report of the findings and corrective action will be written. The Laboratory Supervisor and Director will sign this report. The IR form should be completed.
- The report will be sent to the PNL for review. After review, the PNL may request further follow-up from the site or forward the report to pSMILE for final disposition.
- A copy of the response will be filed with the survey results.
- All proficiency program reports should be reviewed, signed and dated by the Laboratory Supervisor and Director as soon as possible upon receipt. The signed copy should be filed with the original results. The Laboratory Supervisor and Director must review any deficiencies cited by any proficiency program or accrediting organization in which the laboratory participates.
- The Director or designee must submit in writing a plan of corrective action within two weeks of notification of any deficiencies to pSMILE, to the attention of the Domestic QA/QC Coordinator.
- For immunology quality assurance (IQA) or virology quality assurance (VQA) proficiency panels, please submit the corrective action plan to the appropriate contact person for those agencies as well as the MTN LC.
- The deficiency report will include an explanation of the likely cause(s) of the deficiency along with appropriate corrective action, if indicated.
- These deficiency reports will be filed in the proficiency test result manual with the original report.

4.2 Specimen Management

Specimens sent to the local laboratory are monitored to determine the effectiveness of the collection procedures as well as the integrity of the specimens received. The following areas will be monitored, recorded and investigated in a timely manner:

- Lost specimens (that is, specimens lost at point of collection, in transit to the laboratory or within the laboratory)
- Rejected specimens (that is, unsuitable specimens)
- Missed testing (that is, test missed by lab)
- Specimen integrity (that is, specimens too old to test or stored at wrong temperature)

4.3 Reporting of Results

Results released to the clinician or study personnel are monitored to determine the effectiveness of the laboratory review and reporting system. The following are examples of areas used to monitor the accuracy of released results:

- The number of modified or amended results is to be documented with the reason for the change and any corrective action taken.
- The laboratory must have a policy in place to deal with the reporting of amended results.

4.4 Technical Delays

Technical delays are monitored to evaluate the overall effectiveness of the laboratory. Any delay in reporting of patient test results due to a technical problem in the laboratory needs to be documented. This includes such parameters as scheduled and unscheduled instrument downtimes, acute or chronic staff shortages, contaminated cultures, failed reagents, failed QC and supply back orders. Clinic staff need to be notified when downtime causes delays of routine reports if the delay is to exceed the established turn-around time (TAT). If the delay will adversely affect the study, the laboratory should discuss the issue with the clinic staff and the MTN LC to determine if the backup plan needs to be implemented.

TAT is a measurement of technical delays and it can be affected by items such as specimen transport difficulties or the above-mentioned technical problems in the laboratory. Maximum acceptable TATs must be available to the laboratory's clients. The Laboratory Director mandates the TAT for each test. Monitoring of pre-analytical, analytical and post-analytical processes help to identify potential problematic areas within the laboratory.

4.5 Complaints

Complaints received by the laboratory are monitored for response, corrective action and follow-up. The Laboratory Supervisor or designee will respond to any written or significant oral complaint concerning the quality of service or results. Patient care, well-being and clinical study support are taken into consideration in designing and responding to the corrective action. It is the responsibility of the laboratory to define the timeline for responding to complaints. Responses to complaints will be forwarded to the Laboratory Director for review and any additional recommendations of appropriate action.

4.6 Performance Improvement Monitoring/Quality Improvement Program (QIP)

The laboratory will identify potential problems or areas of improvement within the laboratory. These areas will be monitored for frequency, possible causes, corrective action and improvement. The information will be documented by the Laboratory Supervisor or designee and reviewed by the Laboratory Director.

5 TRAINING

Laboratories must maintain rosters of which staff are certified to perform testing.

New Employee: Laboratory-specific job descriptions that list specific duties for each employee are kept in the individual personnel files. Each employee must read and sign off on his or her

particular job description. A checklist for the training of new personnel has been established for the assays in the laboratory. Trainees and their trainers must sign each section on the checklist. These records are kept in the personnel file and should be available for inspection.

New Procedures/New Equipment: Each employee must be trained on new procedures or new equipment. The training must be documented and signed by the employee and the trainer. These records are kept in the employee's personnel file and should be available for inspection.

6 CONTINUING EDUCATION

Continuing education provides personnel an opportunity to review and expand their knowledge of laboratory procedures, policies and any other subjects pertinent to successful laboratory operations.

- It is recommended that sites have their technical employees fulfill a minimum of 10 hours of continuing education per year.
- Continuing education may be earned through reading, audiovisual learning, online training, departmental lectures, teleconferences, training seminars, workshops, tech sample reviews or safety training (for example, fire safety, universal precautions or blood-borne pathogens).
- Dangerous Goods Shipping certification is required every 24 months.
- Each employee should keep a record of his or her continuing education activities. Any supporting documents should be given to the supervisor to maintain in the personnel file.

7 QUALITY CONTROL

Each procedure outlines the required control materials and analysis frequency for the tests performed in the laboratory or other testing location. It is the responsibility of every technologist to ensure that the required controls have been performed and satisfactory performance has been obtained prior to the release of any patient results. Please refer to Appendix III*: Laboratory Quality Control Policy* of this Manual for further information.

8 NEW REAGENT LOT VALIDATION

Reagent kits and controls used by the laboratory have a limited shelf life. It is important to ensure that test kits and reagents are not used beyond their expiration date. New lot check-in of reagents is done to validate the lot-to-lot variability.

HIV Enzyme Immunoassay (EIA) Assay: To validate the lot-to-lot variability with the HIV EIA assay, a minimum of three patient samples — negative, low positive and high positive — identified by the Laboratory Supervisor are run using the new lot and the in-use lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other HIV EIA runs.

HIV RNA PCR Quantitative Assay: To validate lot-to-lot variability, three patient samples (not detected, a mid-range viral load and a high viral load) are assayed on the in-use lot and the new lot of reagent/kit. The Laboratory Supervisor or Director will sign off on the validity check. These

results will be recorded in chart form and filed with the QC records for this assay by the Laboratory Supervisor. As the laboratory is starting to perform the assay, lot-to-lot variation should be less than 0.5 $\log_{10}$ — any variation greater than a 0.3 $\log_{10}$ difference should be investigated and documented. After the laboratory is established, this difference may be tightened, but the ultimate decision is made by the Laboratory Director. Please note that commercial standards or those provided through the VQA can be utilized in place of patient samples.

PCR (HIV, GC, Chlamydia) Qualitative Assay: To validate lot-to-lot variability, a minimum of three patient samples (negative, low positive and high positive) are run using the in-use lot and new lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other PCR runs.

GeneXpert (GC/ Chlamydia) Qualitative Assay: To validate lot-to-lot variability, a minimum of two patient samples (negative, positive) are run using the in-use lot and new lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples in the GeneXpert specimen log.

p24 ELISA: To validate lot-to-lot variability with the p24 ELISA, a known positive supernatant from a previous run is assayed. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other p24 ELISA runs.

CD4/CD8 Assay: To validate lot-to-lot variability of reagents, a minimum of two patients (one with a CD4/CD8 ratio <1.0 and one with a CD4/CD8 ratio >1.0) are run using both the in-use lot and the new lot of reagent/kit. The patient results should be reproducible (that is, based on manufacturer guidelines for sample-to-sample, lot-to-lot variation) between the two lots. Typically, the results should be within 15 percent of each other. The Laboratory Supervisor or Director should sign off on the validity check. The patient samples will be marked as validation samples and filled with the other CD4/CD8 runs. It is also important to check expiration dates and perform lot testing on primary and secondary antibodies used for this purpose.

Complete Blood Count/Full Blood Count (**CBC/FBC) Controls:** To validate new CBC/FBC controls, the new lot of controls will be run in parallel with the old lot of controls for three to five days when possible. The Laboratory Supervisor or Director will sign off on the validity check before the old lot is finished.

Chemistry Controls: To validate new chemistry controls, the new lot of controls will be run in parallel with the old lot of controls until the mean and standard deviation are obtained for the new lot of controls. The Laboratory Supervisor or Director will review and sign off on the mean and standard deviations for the new lot of controls before being put into use.

Chemistry, Hematology and Coagulation — New Reagent Lot Check-In: New lot numbers of reagents must be validated before being introduced into routine use. QC should be acceptable for old and new lots. Samples should be assayed by both lots within a time period in which there has been no loss of integrity to the sample or analyte. Results should be compared to the old lot. Acceptability criteria should be set by the Laboratory Director.

9 VALIDATION STUDIES

Any time an instrument or methodology is changed within the laboratory, validation studies must be performed. Please refer to Appendix IV*: Method Validation Policy* of this Manual for details.

10 METHOD COMPARISON

This is performed semiannually between similar instruments or methods. A minimum of 10 samples should be run and compared. There must be a back-up method available for protocol-related safety and endpoint assays. The comparisons should be run in-house, but may be performed at a back-up laboratory, if necessary. Primary and back-up methodology must be compared during initial validation and semiannually thereafter. The Laboratory Director sets the acceptable limits of the method comparison.

11 PROCEDURE REVIEW

All procedures used in the laboratory must be documented and reviewed. All laboratory procedures are reviewed in accordance with U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) policies. Procedure reviews are done by the Laboratory Supervisor and Director at least every two years. Any changes that occur at that time need to be communicated to the staff. Each procedure is preceded by the documentation of review (that is, the signature page).

Modifications of a procedure can occur at any time due to newly published guidelines, revised package inserts or changes in central policy. All revisions should be documented in ink on the original copy with initials of the Laboratory Supervisor or designee and the date of change. This superseded/obsolete copy must be kept for at least five years.

- The revised procedure should include the revision number and effective date to identify it as the current procedure.
- All changes must be documented and communicated to the technical staff.
- Appropriate version control must be maintained.
- Any copies of procedures must be pulled and replaced with the updated version.
- Documentation for all MTN protocol-related procedures must be approved by the MTN LC prior to study activation.

12 COMPETENCY

New employees are checked for competency twice during their first year of performing a given assay and annually thereafter. The first competency check should be completed before the new employee reports any patient results. Existing employees are checked annually and as needed. Competency may be checked by one of the following (list not exhaustive):

- Direct observation (use standard operating procedures or a checklist to ensure no steps are omitted)
- Review of QC results

- Repeat- and split-sample testing
- Review of unusual patient or control results
- Proficiency testing review
- Blind-specimen analysis
- Written or oral examinations

Any employee that fails a competency check must complete a re-training procedure and pass a further competency evaluation before being allowed to test patient samples.

13 BLIND OR SPLIT-SAMPLE TESTING (INTERNAL PROFICIENCY TESTING)

As part of the laboratory's internal proficiency-testing program, personnel-proficiency testing is done periodically during the year. Coded samples, blind samples or split samples may be given to the technologists or clinic staff to assess the reproducibility of the assays as well as the technologist-to-technologist variability and accuracy.

- The Laboratory Supervisor or designee (for example, the QA/QC technologist) will be responsible for assigning the samples, documenting the results and reviewing the results.
- The acceptable range of reproducibility will be determined by the test and documented on the result form.
- The documentation must include the results by the technologist and whether the results were acceptable for accuracy and reproducibility.
- The Laboratory Supervisor or Director must sign off on the results.
- The results will be filed as internal proficiency testing records.

14 STORAGE OF LABORATORY RECORDS

All laboratory records, inclusive of requisitions, patient results, QC logs, maintenance logs and QA logs, are retained indefinitely per NIAID/DAIDS requirements.

- Records are to be stored in an organized manner that allows for retrieval within 24 hours.
- Records may be stored off site and on site in locked and secure storage.

15 RESULT MODIFICATION/AMENDMENT

Any data that appear to be incorrect must be verified. Incorrect data must be modified and the correct data entered. Discrepancies are to be resolved immediately.

- All modified results must be brought to the attention of the ordering physician/clinic and documented.
- The modified report must include the initials of the Laboratory Supervisor as well as a brief explanation, if appropriate.
- Modified (amended) reports will be documented under the QA monitoring.

16 RESULT REPORTING CHANGE

Changes in test methodology and/or reference ranges must be communicated to the ordering staff by a laboratory note or department memo. These changes must be communicated to the MTN LC for approval before implementation. These changes must also be communicated to the MTN Leadership and Operations Center (LOC FHI 360), Clinical Research Manager and Statistical Data Management Center, Project Manager associated with the study, as changes may affect requirements for data analysis or safety reporting.

17 MAINTENANCE OF INSTRUMENTS AND EQUIPMENT

A separate manual for equipment maintenance is kept in the laboratory. Maintenance log sheets are kept on a daily, monthly, quarterly, semiannual and annual basis. These records are reviewed and signed by the Laboratory Supervisor or Director and retained for a minimum of five years. Any preventive maintenance, repairs or part-replacement records are kept for the lifespan of the equipment, or five years, whichever is greater.

17.1 Instruments

Each instrument in use has a separate maintenance procedure and time frame for performing the maintenance.

- All instruments used in the laboratory follow a preventive maintenance program that must follow the manufacturer recommendations.
- Generally, documentation of instrument maintenance, calibration, service and corrective action is found in the equipment logbooks in each area.
- The area technologist maintains these records.
- These records are reviewed and signed monthly by the Laboratory Supervisor or designee.

17.2 Equipment

Maintenance of equipment should follow manufacturers' recommendations at a minimum.

- Routine maintenance on laboratory equipment is performed according to the manufacturer's recommendations.
- The technologist performing the maintenance must document the maintenance and results.
- The Laboratory Supervisor reviews and signs off on the maintenance records monthly.
- Generally, documentation of the equipment maintenance is found in the Laboratory Maintenance Manual.

In general, preventative maintenance, monitoring or calibration covers the following equipment:

- Precision pipette calibration
- Centrifuge calibration (for example, rpm, timer and temperature, if applicable)
- Thermometers
- Timers
- Plate washers
- Plate readers
- Thermocyclers

- Incubators/water baths
- Biological/fume hoods

Temperature Monitoring: All temperature-sensitive equipment, such as freezers, refrigerators, water baths and incubators, must be monitored on a regular basis (that is, at least each working day). All test work areas and reagent storage areas must be monitored on a regular basis (that is, at least each working day). This includes room temperature monitoring where equipment and testing is done as well as where room temperature reagents are stored.

Temperature Charts: Temperature charts must include the name of the equipment (if applicable), the location, the acceptable temperature range, space to record the actual temperature and the initials of the person recording the temperature and the date. Charts may include a comments/corrective action section (or corrective action may be recorded on another form). The charts must be reviewed on a monthly basis by the Laboratory Supervisor.

17.3 Reagent Water

The following procedures and specifications are for testing water that has been purified for clinical laboratory use. There are three grades of water recognized, with the minimum specifications for bacterial count for each:

- Type I is used for the preparations of solutions, reagents (EIA testing) requiring minimum interference and maximum precision and accuracy (10 cfu/ml).
- Type II is used for general laboratory testing other than described above.
- Type III is used for glassware washing, but not final rinsing, and for feed water for the production of higher-grade water.

The preferred water is Type I, which is distilled and de-ionized. If this is not available, distilled water can be used and sterilized. If the laboratory has a water purification system, the quality of the water must be checked on a regular basis (that is, at least each working day). This must be documented on a chart that may include a comments/corrective action section (or corrective action may be recorded on another form). The charts must be reviewed on a monthly basis by the Laboratory Supervisor.

18 ATTACHMENTS

A: Corrective Action/Remarks Log for Instrument/Test System
B: Continuing Education Record Form

ATTACHMENT A: CORRECTIVE ACTION/REMARKS LOG FOR INSTRUMENT/TEST SYSTEM

Date	Problem/Comments	Initials	Corrective Action/Comments	Initials	Date

Reviewed by: _____ Date: _____

ATTACHMENT B: CONTINUING EDUCATION RECORD FORM

_____

Employee name

Date(s)	Activity Description	Hours	Supervisor's Initials