

The Total Quality Management Program for HIV Clinical Trial Network Laboratories – A Summary in Progress

Introduction

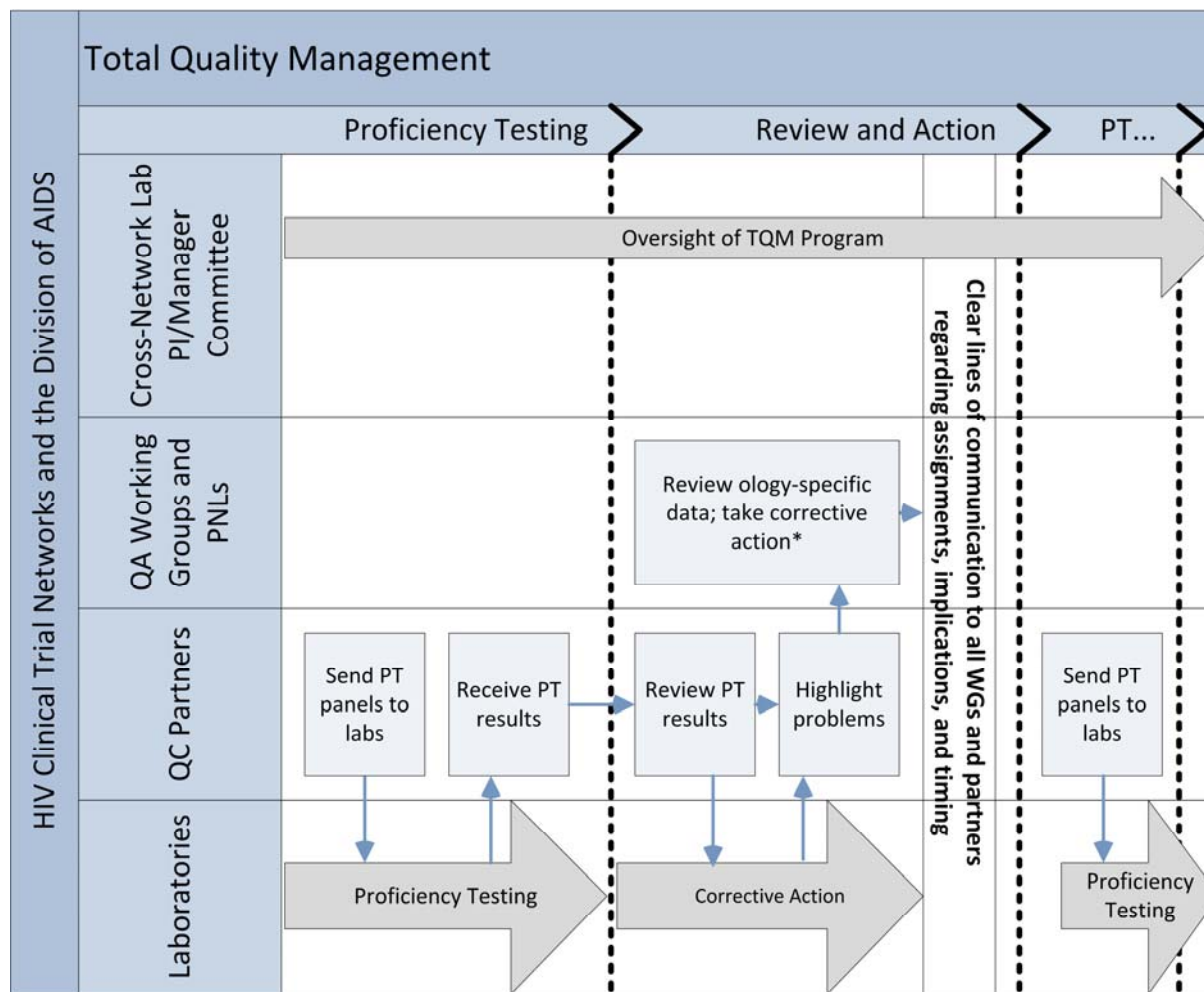
The HIV Clinical Trials Network Laboratories (NL) continually improve the quality and efficiency of protocol-related testing under a Total Quality Management (TQM) Program. Oversight of the TQM Program is provided by the Cross-Network Laboratory PI/Manager Committee and the Laboratory Focus Group (LFG). The Laboratory PI/Manager Committee will guide the working groups (WG) and participants responsible for the implementation of the TQM Program, and is comprised of representatives from DAIDS and each of the Networks. The LFG is comprised of representatives from each NL.

The validity of diagnostic and monitoring tests used by an NL is entirely dependent on the quality of the measures employed before, during, and after each assay. The consistent production of valid results will more likely occur when an overall program that includes Quality Assurance (QA) and Quality Control (QC) is utilized. QA includes planned and systematic actions that are established to ensure that lab tests are performed and data are generated, documented (recorded), and reported in compliance with the applicable regulatory requirement(s). QC includes the operational techniques and activities undertaken within the QA system to verify that the systems in place are performing according to expectations. Proficiency Testing (PT) provides external quality assessment in support of the overall QA program. The scope of the TQM Program is broad and will respond to the needs of the Networks as the field of HIV research evolves.

The TQM Program will provide quality management for all of the protocol-specified assays conducted in the DAIDS-sponsored Network clinical trials. Those assays that are monitored through PT from an NIH-supported contract resource (e.g. Virology QA) will continue to be supported by these partners. Exploratory assays will be monitored by an NL or other designee. The TQM Program will develop, review, and modify as needed guidelines for laboratory quality management including but not limited to performance criteria and mechanisms for restricting protocol testing based on poor PT performance. The TQM Program may use a database to track laboratory performance for both U.S.-based and international NLS.

The TQM Program (Figure 1)

Figure 1. TQM Program Flowchart



*This may involve input from the PNL.

TQM Quality Assurance Partners

In addition to the HIV Clinical Trial Networks and the Division of AIDS, participants in the TQM program will include the current Quality Assurance (QA) partners who provide QA support for the NLs. These partners include:

- IQA – Immunology and PBMC Cryopreservation QA
- PQA – Pharmacology QA
- SMILE – Safety Evaluation QA
- VQA – Virology QA

Exploratory or novel assays may undergo QA by a Network or other contractor (e.g. through the CRS contract with PPD), in which case their participation in the TQM program may be requested. Additional

participants may be required as the TQM Program matures and is at the discretion of the Lab PI/Manager Committee.

Quality Assurance Working Groups

QA Working Groups in support of the TQM Program will be constituted under the guidance of the Cross-Network Lab PI/Manager Committee. QA Working Groups will be comprised of the critical QA Partners relevant to each specific quality assurance area, representatives from DAIDS, and representatives from the Networks. Their function will include:

1. Review data posted by the QA Partners, particularly highlighted problems.
2. Coordinate PT panels and shipping support.
3. Establish monitoring standards for each specialty area, which should differentiate between missing data, transcriptional or computational errors, and technical problems. The standards should take into consideration the following situations and the consequences of unacceptable performance for each:
 - a. Protocol start-up
 - b. Protocol continuation
 - c. Cessation of testing for a specific analyte or instrument if established criteria are not met
 - d. Resumption of testing – If testing has been suspended, the QA Working Group will determine what must be accomplished before sites are able to resume testing.
4. A communication plan has been established for communicating Network responses to PT failures/problems. This communication plan includes the Primary Network Laboratories (PNL), the relevant site lab(s), other Networks active at the site(s), and QC Partners. The current plan takes into account that individual Networks may differ in their responses to a PT failure or problem, and that the individual Network responses may also be protocol-specific (e.g. based on whether an analyte is used for endpoint determination, etc.).
5. Establish procedures for each specialty area, including:
 - a. Instrument and method validation for new analyzers:
 - i. All new analyzers will need to have validation performed, which may include precision, accuracy, linearity (reportable range) and comparison between similar or different instruments running the same analyte. Requirements will vary depending on the type of analyzer.
 - ii. Validation of test method must be performed on samples that span the dynamic range of the test method
 - b. Instrument and method validations needed for an “older” analyzer:
 - i. An “older analyzer” is defined by CLIA (42 CFR part 493.1253): Laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003.
 - ii. The proficiency data should be acceptable and current, with linearity being performed and instrument comparisons kept on file.
 - c. Assay selection - Determine the number of testing events for each analyte that must be passed to achieve qualification as a new analyte.
 - d. Reference ranges may be required for quantitative assays
 - i. Validating manufacturer suggested or published reference ranges
 - (1) Sites will either use established reference ranges which may require validation with at least 20 patient samples, or conduct a full reference range study.

- (2) If established ranges cannot be validated, a full study must be conducted.*
*Note: Under CLSI guidelines, medical staff decisions regarding reference ranges are allowable.
- ii. Conducting a full reference range study if established reference ranges cannot be validated.
 - (1) A full, 120 “normals” reference range study will be conducted for the site’s population.
 - (2) Evaluation criteria will be pre-defined by the relevant QA WG.
6. Explore opportunities to establish an inventory of SOPs for each specialty area when appropriate.
 7. Delineate roles and responsibilities.
 - a. The delineation of roles and responsibilities should:
 - i. Harmonize and simplify interactions with multi-affiliated laboratories
 - ii. Use DAIDS contractual resources as “tools” to execute the Networks’ and DAIDS’ mission
 - iii. Give responsibility and accountability to Network investigators and DAIDS
 8. The delineation of roles and responsibilities may differ by QA partner and the needs of the laboratories . The QA Working Groups will:
 - a. Determine their own delineation of roles and responsibilities
 - b. Post them on their respective team sites
 - c. Share them with the Lab PI/Manager Committee
 - d. These responsibilities include:
 - i. Paying for, shipping and tracking of proficiency testing panels
 - ii. Receiving PT results from labs
 - iii. Presenting/posting data
 - iv. Highlighting problems
 - v. Reviewing PT results and communicating issues related to corrective actions to the CTU/CRS site and the PNL

Primary Network Laboratories (PNL)

A Primary Network Laboratory (PNL) will be identified to serve as the primary point of contact for each CTU/CRS laboratory for laboratory-related issues to simplify communications between CTU/CRS laboratories, NLs, and other groups, particularly at shared sites.

The PNL will be responsible for communicating relevant information from the CTU/CRS laboratories to all other NLs that are affiliated with the site. PNL affiliations will be reevaluated over time, and all relevant groups will be informed when changes are made to PNL assignments. CTU/CRS laboratories will be instructed to copy the PNL contact on all correspondence with SMILE, VQA, IQA, PQA, FTSRF, SCHARP, UK NEQAS, and DAIDS on all lab-related issues. These groups will also be asked to copy the appropriate PNL for the site using the group email alias/logon when they communicate with a CTU/CRS laboratory.

Primary contacts at each PNL are members of the Laboratory Focus Group (LFG). Therefore, any QA issue that exceeds the capacity of a single QA working group or involves multiple CTU/CRS sites will be discussed by the LFG and/or the Laboratory PI/Manager Committee, if necessary.

Data Quality, Flow and Evaluation

The Data Management Center (SCHARP or FSTRF) will track the following data management issues on an on-going basis:

- Data query-response and specimen turn-around time

- Data completeness and error rates
- The DMC will contact the PNLs when problems are identified.

Training

Sites that participate in one or more QA programs will receive the appropriate training, which may include one or more of the following:

1. IATA Certification (shipping)
 - a. Sites are responsible for obtaining training every other year by the following methods:
 - i. Regional training (either by PPD or local shipping agencies)
 - ii. Network-supported training (either regionally or at annual meetings)
 - iii. Saf-T-Pak CD
 - b. The PNLs will purchase and send IATA training materials to the sites/labs for which they are responsible.
 - c. Each PNL will track IATA shipping certification for its assigned CTU/CRS sites, and will notify site personnel prior to certification expiration.
2. Specimen processing
 - a. Sites can obtain training and assistance for specimen processing from a variety of sources.
 - b. The Laboratory PI/Manager Committee and LFG will continue to address issues related to cross-network harmonization of procedures, including test runs and certification.
3. Laboratory Information Management System (LIMS)
 - a. The initial training of site staff on the Laboratory Data Management System (LDMS) must be done by FSTRF staff either on-site or at their facilities in the US.
 - b. For subsequent trainings, FSTRF is investigating the feasibility of using an internet-based training module for sites that need to train additional or new staff. Sister or mentor sites may also provide training and assistance with LDMS issues, provided they have participated in a “train the trainer” course.
 - c. Other LIMS at study sites should not interfere with Network activity. Review by QA WGs may be required to avoid interference.
4. Good Clinical Laboratory Practice (GCLP) and Good Research Laboratory Practice (GRLP).
 - a. PPD will continue to conduct regional GCLP training for CTU/CRS laboratory staff. Participation in GCLP training will not be mandatory for all staff prior to protocol initiation, but training of critical staff positions from all laboratories (e.g. QA/QC Coordinators, lab managers, and similar positions) will be expected.
 - b. GCLP training that meets DAIDS standards and allows for tracking the training of individuals will be made available across Networks. An online program, if developed, should include:
 - i. Training for new staff without prior GCLP or LDMS training
 - ii. A refresher/update for experienced staff
 - iii. An interactive forum for posing questions and getting more personalized help
5. Additional training may include:
 - a. Blood-borne Pathogen Training
 - b. Personal Protective Equipment Training
 - c. Other Safety training requirements (e.g. electrical, fire, disaster, etc)