


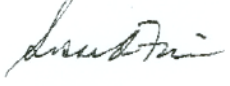
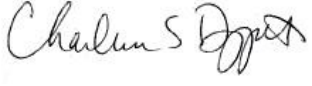


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## 1 Purpose

The purpose of this standard operating procedure (SOP) is to define the process for the monitoring of virology external quality assurance.

## 2 Scope

This SOP applies to:

- Virology Quality Assurance (VQA) personnel
- Personnel of VQA subcontractors
- Network testing laboratories (TLs) participating in the VQA program and performing testing for the National Institute of Health (NIH)-funded HIV/AIDS Clinical Trials Networks (AIDS Clinical Trials Group [ACTG], HIV Prevention Trials Network [HPTN], HIV Vaccine Trials Network [HVTN], International Maternal Pediatric Adolescent AIDS Clinical Trials Group [IMPAACT], and the Microbicide Trials Network [MTN])
- Network personnel responsible for the monitoring of laboratory performance in the VQA program.

This SOP does not apply to other programs that utilize the VQA program, including but not limited to: Women’s Interagency HIV Study (WIHS), Multicenter AIDS Cohort Study (MACS), Center for HIV/AIDS Vaccine Immunology (CHAVI), Comprehensive International Program of Research on AIDS (CIPRA), NIH Research Project Grants (R01s) and other Division of AIDS (DAIDS) programs.

## 3 Definitions

Abbreviation	Definition
ACTG	AIDS Clinical Trials Group
ARman	Abbott RealTime HIV-1 Assay, manual extraction
ARauto	Abbott RealTime HIV-1 Assay, automated extraction
CHAVI	Center for HIV/AIDS Vaccine Immunology
CIPRA	Comprehensive International Program of Research on AIDS
DAIDS	Division of Acquired Immunodeficiency Syndrome
DCLOT	DAIDS Clinical Laboratory Oversight Team
DNA	Deoxyribonucleic acid
EQA	External quality assurance
FSTRF	Frontier Science and Technology Research Foundation
HANC	Office of HIV/AIDS Network Coordination
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IR	Investigation report
LFG	Cross-Network Lab Focus Group
MACS	Multicenter AIDS Cohort Study
MTN	Microbicide Trials Network

<b>Abbreviation</b>	<b>Definition</b>
Network	One of the NIH-funded HIV/AIDS Clinical Trials Networks participating in the VQA Program: ACTG, HPTN, HVTN, IMPAACT or MTN
NIH	National Institutes of Health
NL	Network Laboratories, organizations within each network that provide EQA oversight for network site-affiliated laboratories.
PNL	Primary Network Laboratory
PT	Proficiency testing
QCM	Quality Control Materials
RNA	Ribonucleic acid
R01s	NIH Research Project Grants
RTI	Research Triangle Institute International
SDAC	Statistical & Data Analysis Center
SOP	Standard Operating Procedure
TQM	Total Quality Management Program
VQA	Virology Quality Assurance; the DAIDS contract partner that conducts the VQA program, based at Rush University Medical Center
VQAAB	VQA Advisory Board
WIHS	Women’s Interagency HIV Study

## 4 Background

The validity of diagnostic and monitoring tests 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. To this end, the Network Laboratories (NLs), which oversee the activities of all network testing laboratories (TLs), endeavor to 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 Lab Focus Group (LFG). The LFG will guide the VQA Advisory Board (VQAAB) and participants responsible for the implementation of the TQM Program, and is comprised of key NL personnel of each network. These NL personnel serve as network contacts and are responsible for monitoring external quality assurance (EQA) results within each network.

The VQAAB is comprised of representatives from the VQA program, DAIDS, Statistical & Data Analysis Center (SDAC), the VQA Data Management Group at Frontier Science and Technology Research Foundation (FSTRF), the VQA Statistical Analysis Group at the Research Triangle Institute (RTI) International, and each of the respective networks. The VQAAB holds monthly and ad hoc calls to:

1. Review and approve proposed scoring from virology assay proficiency testing analyses.
2. Establish monitoring standards that differentiate between missing data, transcriptional or computational errors, and technical problems.
3. Review and approve proposed changes in policies or procedures to promote quality assurance in virology assay testing.
4. Review and approve proposed implementation of external quality control standards for use in virology assay testing.
5. Review and approve changes in VQAAB approval status for protocol testing for TLs.

## **5 Authority and Responsibility**

- 5.1 The Network Laboratory Directors (or his/her designee) have the authority to establish, review and update this procedure with input from the VQAAB and VQA program.
- 5.2 The Office of HIV/AIDS Network Coordination (HANC) is responsible for the maintenance and control of SOP documentation.
- 5.3 The VQA, VQA subcontractors, members of the VQAAB, NLs, and testing laboratory Directors are responsible for the implementation of this SOP.
- 5.4 All participants are responsible for reading and understanding this SOP prior to performing the procedures described.

## **6 Procedure**

- 6.1 Validations
  - 6.1.1 The VQA produces Quality Control Materials (QCM) that may be used for assay or run validation. The VQA will continue to work with NL(s) to develop new strategies for validating new and existing assays. The VQA currently provides validation support for the following:
    - 6.1.1.1 Instrument validations (HIV RNA, HIV DNA, HIV genotyping)
    - 6.1.1.2 Assay validations (HIV RNA, HIV DNA, HPV DNA)
    - 6.1.1.3 Linearity Reports (HIV RNA)
    - 6.1.1.4 Kit version validation (Version 1.0 vs. version 2.0 of the Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test)
    - 6.1.1.5 Sample extraction validation (Manual vs. automated extraction of the Abbott RealTime HIV-1 Test)
    - 6.1.1.6 Dilution studies (HIV RNA only)
  - 6.1.2 Procedure for currently supported validations
    - 6.1.2.1 The NL, PNL or testing laboratory will contact the VQA Manager if a testing laboratory needs assistance with existing validation. The PNL is copied on all communications that may impact multiple networks.
    - 6.1.2.2 The VQA Manager will send validation documents to the testing laboratory and NL; arrange for a shipment of QCM to the TL.
    - 6.1.2.3 The testing laboratory will perform the testing and submit the validation data to the VQA Data Management Group.
    - 6.1.2.4 The VQA Statistical Analysis Group will retrieve the data, perform the analysis, and send a report to the VQA Manager for review.
    - 6.1.2.5 The VQA Manager will review the report and:
      - 6.1.2.5.1 Send it to the VQA Director and VQA Project Officer if it is acceptable.

- 6.1.2.5.2 Send it to the testing laboratory as a preliminary report if major problems exist that warrant additional testing.
- 6.1.2.6 A final report will be sent to the testing laboratory for final review and sign-off by the testing laboratory Director.
- 6.1.2.7 The testing laboratory must send the final report to the affiliated NL(s) for review.
- 6.1.3 Procedure for currently non-supported validations
  - 6.1.3.1 The NL or PNL will send requests for new QCM productions for purposes of validation to the VQA Manager, VQA Director, or VQA Project Officer.
  - 6.1.3.2 All requests for new QCM productions must be approved by the VQA Project Officer.
  - 6.1.3.3 Adequate notice must be given for the production, validation and distribution of new QCM.
  - 6.1.3.4 The VQA Manager will coordinate documentation, implementation, and distribution of new QCM for purposes of validation.
  - 6.1.3.5 Implementation of new validation plans will follow the pattern of existing plans.

## 6.2 Proficiency Testing (PT)

The delineation of roles and responsibilities among the VQA, VQA subcontractors, VQAAB, NLs, and TLs follows the flow diagram of general roles and responsibilities in Figure 1.

The following are the steps for each round of PT:

- 6.2.1 The NLs will notify the VQA of specific testing laboratory PT needs.
  - 6.2.1.1 New TL
    - 6.2.1.1.1 The NL(s) will submit requests for new TL(s) to the VQA Project Officer for approval; the requests will include:
      - 6.2.1.1.1.1 A justification for adding the new lab, including why another lab already in the VQA program could not be used, and;
      - 6.2.1.1.1.2 The address and contact information for the responsible person(s) at the lab.
      - 6.2.1.1.1.3 The NL(s) should be prepared to identify an existing lab to be removed from the VQA program if funding cannot be identified to add the new lab.
    - 6.2.1.1.2 The NL(s) will submit to the VQA Manager a list of assays for which EQA is needed for each new TL.

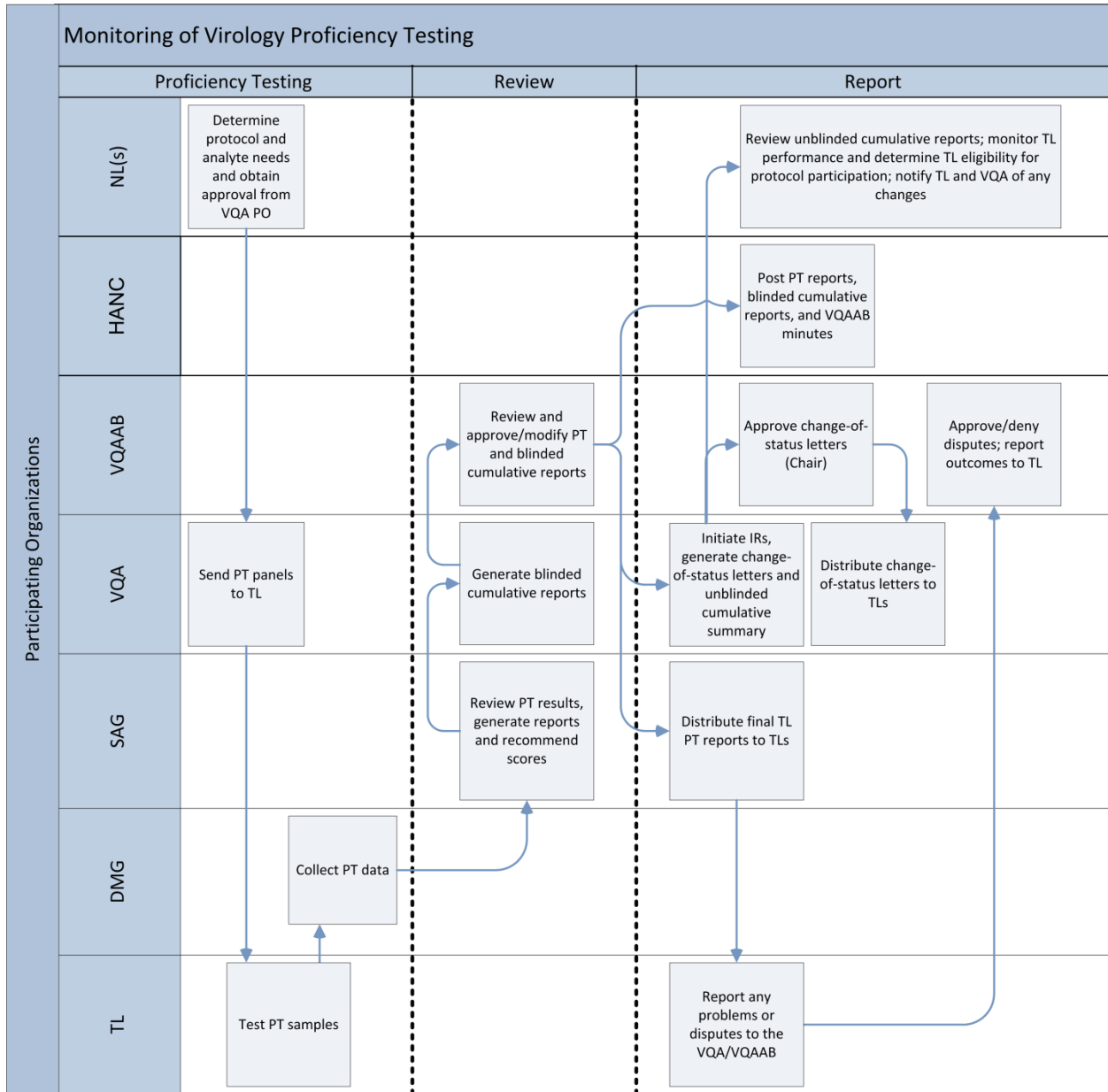
- 6.2.1.2 Current TLs  
The NLs will notify the VQA Manager when there are any changes to the list of assays for which a testing laboratory requires EQA.
- 6.2.1.3 New PT Programs
  - 6.2.1.3.1 The NL(s) will submit requests for new PT programs and/or production of new QCM for proficiency testing to the VQA Project Officer.
  - 6.2.1.3.2 If new QCM needs to be developed before protocol testing can begin, the NL(s) should submit these requests early in protocol development.
- 6.3 The VQA will ship proficiency testing panels to the TL.
  - 6.3.1 The VQA currently provides proficiency testing programs for:
    - 6.3.1.1 Qualitative HIV-1 DNA Testing,
    - 6.3.1.2 Genotypic HIV -1 Drug Resistance Testing,
    - 6.3.1.3 Quantitative HIV-1 RNA Testing.
  - 6.3.2 The VQA will maintain a Proficiency Testing Schedule and ship panels accordingly; the schedule is posted on the HANC Public Website at (<http://www.hanc.info/labs/Pages/VQAProficiencyTestingProgram.aspx>).
- 6.4 The testing laboratory will submit proficiency testing results to the VQA Data Management Group at FSTRF. The VQA program will:
  - 6.4.1 Provide support to the testing laboratory to help ensure PT panel results are correctly submitted on time; this support consists of facilitating electronic data submissions.
  - 6.4.2 Coordinate with the testing laboratory to allow delayed submittal of results via web-based exception request programs.
- 6.5 The VQA Statistical Analysis Group will download the PT data, perform the analysis and generate PT panel reports that contain recommended scores.
- 6.6 The VQA program will generate blinded cumulative reports of testing laboratory status.
  - 6.6.1 Blinded cumulative reports will contain information about kits, platforms, scores, status and comments regarding follow-up.
  - 6.6.2 The VQA will distribute blinded cumulative reports to the VQAAB.
- 6.7 The VQAAB will review and modify and/or approve proficiency panel reports and cumulative reports.
  - 6.7.1 HANC will post VQAAB reports and PT information on the HANC public website at <http://www.hanc.info/labs/Pages/VQAAB.aspx>. This will include:
    - 6.7.1.1 VQAAB roster, including all VQAAB members and their contact information

- 6.7.1.2 Proficiency panel reports dating back one year
- 6.7.1.3 VQAAB conference call minutes dating back one year
- 6.7.2 HANC will post blinded cumulative reports on the VQAAB team site on the HANC Portal.
- 6.8 The Statistical Analysis Group will send reports to each TL, including:
  - 6.8.1 A report that contains the results from the PT analysis as well as the TL's resultant score for that panel
  - 6.8.2 A report that summarizes the overall scores (Certified, Provisionally Certified, or Probation) for each participating lab after every analysis
  - 6.8.3 Information about how scores are determined is posted on the HANC public website at <https://www.hanc.info/labs/labresources/vqaResources/ptProgram/Pages/participationDocs.aspx>.
  - 6.8.4 Problems or disputes will be brought to the VQAAB for discussion and recommendations for actions to be taken.
    - 6.8.4.1 The testing laboratory must contact the VQAAB chair or the VQA Manager if they would like to dispute a score received on a VQA panel
    - 6.8.4.2 The VQAAB Chair will discuss the dispute on the VQAAB call
    - 6.8.4.3 The VQAAB will vote to approve or deny the request
    - 6.8.4.4 The VQAAB Chair or VQA Manager will follow up with the testing laboratory to discuss the outcome of the discussion
      - 6.8.4.4.1 A corrected report will be sent to the testing laboratory if the VQAAB approves the dispute
      - 6.8.4.4.2 No further action will occur if the dispute is denied by the VQAAB
- 6.9 If necessary, the VQA will initiate an investigation report (IR) and send it to the testing laboratory for root cause analysis of the deficiency noted in PT. See the VQA PT Investigational Report Procedure posted at <https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesCommDataFlow.aspx> for details.
- 6.10 The VQA program will generate an unblinded cumulative tracking sheet of VQAAB-recommended testing laboratory status
- 6.11 The VQA program will send the unblinded cumulative tracking sheet to the NLS for review.
  - 6.11.1 The VQAAB recommends status and approval for testing based on the criteria in the participation documents posted on the HANC public website at <https://www.hanc.info/labs/labresources/vqaResources/ptProgram/Pages/participationDocs.aspx>.
  - 6.11.2 HANC will post the unblinded cumulative reports on the LFG team site on the HANC Portal.



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- 6.11.3 The VQA Manager will be responsible for creating Change in Status Letters that result from problems noted in PT.
    - 6.11.3.1 The VQAAB chair will review and approve the letters before they are sent to the TL.
    - 6.11.3.2 The VQA Manager will send the approved letters to the TL, and affiliated NLs.
  - 6.12 The NL(s) will monitor testing laboratory performance and determine eligibility for protocol participation
    - 6.12.1 The NL may discontinue or place protocol testing on hold at a testing laboratory in discordance with the VQAAB's recommendations if it perceives standards are not being met, in which case the NL, in consultation with the protocol team, is responsible for communicating this decision to the testing laboratory and copying the VQA.
    - 6.12.2 The NL will notify the VQA if any special assistance with troubleshooting or fast-track re-qualification is necessary.
    - 6.12.3 The NL must approve the resumption of protocol testing at a TL.
      - 6.12.3.1 The NL must establish and monitor the criteria for resumption of testing.
      - 6.12.3.2 The NL is responsible for communicating this decision to the testing laboratory and copying the VQA.

Figure 1. Monitoring of Virology Proficiency Testing



TL Testing laboratory; DMG Data Management Group; SAG Statistical Analysis Group; VQA Virology Quality Assurance; VQAAB VQA Advisory Board; HANC Office of HIV/AIDS Network Coordination; NL Network Laboratory; PT proficiency testing; PO project officer