DAIDS
Bethesda, MD USA

STANDARD OPERATING PROCEDURE

Prevention Sciences Program and Vaccine Research Program
Prevention Science Review Committee (PSRC) Procedures

Effective Date: July 16, 2012

Approved:

Emily Erbelding, M.D., Deputy Director, DAIDS, NIAID

1.0 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to provide guidance and direction regarding the responsibilities and roles of the Division of Acquired Immunodeficiency Syndrome (DAIDS) staff, as well as invitees, who attend and participate in the regularly scheduled meetings of the Prevention Science Review Committee (PSRC).

2.0 SCOPE

This SOP applies to the DAIDS staff members who participate in and/or attend the regularly scheduled meetings of the DAIDS PSRC. Also, this SOP is applicable to NIAID and other NIH Institutes and Centers staff who serve as primary reviewers for PSRC protocols on an ad hoc basis.

3.0 BACKGROUND

DAIDS is responsible for the oversight of clinical research activities that it sponsors through grants and contracts. This responsibility includes assessing the scientific merit, plans to ensure participant safety, and compliance with ethical and regulatory requirements. Support of the clinical research proposal is weighed in relation to the HIV/AIDS scientific priorities of the National Institute of Allergy and Infectious Diseases (NIAID) and in relation to other planned or ongoing clinical studies.

The DAIDS PSRC is a reviewing body instituted by DAIDS to review protocols supported by DAIDS through the Prevention Sciences Program (PSP) and the Vaccine Research Program (VRP). The Deputy Director of DAIDS is responsible for the oversight of PSRC activities. PSRC formally evaluates the clinical research proposals of the HIV Vaccine Trials Network (HVTN), HIV Prevention Trials Network (HPTN), Microbicides Trials Network (MTN), and other prevention and vaccine trials supported by DAIDS, as well as those with the U.S. Military HIV Research Program (MHRP). All clinical trials supported by DAIDS and other clinical research studies with components that are greater than minimal risk must be reviewed and approved by the PSRC prior to implementation. Determination of greater than minimal risk is the responsibility of Program to be made in consultation, as needed, with other members of PSRC. Other studies may be submitted for PSRC

review and approval at the discretion of the Program through which they are supported.

3.1 Key Parties in PSRC activities:

3.1.1 PSRC Committee Membership

3.1.1.1 Chair, Non-Voting Member

3.1.1.2 Scientific Program Representatives, Voting Members

Director, VRP, DAIDS
Director, PSP, DAIDS
Chief, Vaccine Clinical Research Branch (VCRB), VRP, DAIDS
Chief, Preclinical Research and Development Branch (PRDB), VRP, DAIDS
Chief, Clinical Prevention Research Branch (PRB), PSP, DAIDS
Chief, Clinical Microbicide Research Branch (MRB), PSP, DAIDS
Chief, Preclinical Microbicide and Prevention Research Branch (PMPRB), PSP, DAIDS
Chief, Biostatistics Research Branch (BRB), Division of Clinical Research, NIAID

3.1.1.3 Subject Matter Experts, Non-Voting Members

Chief, Pharmaceutical Affairs Branch (PAB), Office of Clinical Site Oversight (OCSO), DAIDS
Chief, Regulatory Affairs Branch (RAB), Office for Policy in Clinical Research Operations (OPCRO), DAIDS

3.1.2 Deputy Director (DD), DAIDS

The DAIDS Diretor or Deputy Director has the right to temporarily re-assign responsibilities when a position is vacant. The PSRC Committee Members will be notified when a reassignment has occurred or PSRC membership has changed.

3.1.3 DAIDS Protocol Medical Officer (DPMO)

3.1.4 Reviewers

3.1.4.1 Primary Reviewer(s)

Is recommended by the Branch Chief or his/her designee and approved by the Chair. Additional reviewer(s) may be requested by the Director of PSP or VRP, the Branch Chief, the Chair, the Primary Reviewer, the DAIDS Protocol Medical Officer (DPMO), or an Institute or Center (IC) that is a joint sponsor of the protocol

3.1.4.2 Standing Reviewers (PSRC members)

Chief, BRB, Division of Clinical Research (DCR), NIAID
Chief, PAB, OCSO, DAIDS
Chief, RAB, OPCRO, DAIDS

The standing reviewers may designate someone else from his/her branch with the needed subject matter expertise to conduct the review.

3.1.4.3 MHRP reviewer(s) for joint protocols with MHRP

3.1.5 The Henry M. Jackson Foundation (HJF) PSRC Coordinator

3.1.6 HJF Administrative Assistant

3.1.7 Regulatory Support Center (RSC) PSRC Coordinator

3.1.8 Representatives of other U.S. Government institutions that are joint sponsors of the protocol [e.g., National Institute of Child Health and Human Development (NICHD), National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), MHRP]

4.0 DEFINITIONS

See DAIDS glossary

5.0 OBJECTIVES

5.1 Assess the scientific merit, especially the primary objectives and the study design (see Appendix IV, PSRC Procedures - Guidance for PSRC Reviewers)

5.2 Assess plans to ensure participant safety based on the eligibility requirements, study evaluations, toxicity management, and data and safety monitoring plans

5.3 Assess operational feasibility

5.4 Assess compliance with Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations and guidelines with respect to human subjects protection

5.5 Assess the statistical plan including the proposed analysis

6.0 RESPONSIBILITIES

6.1 Deputy Director (DD), DAIDS

- Oversees all PSRC activities
- Signs official PSRC review and approval letters
- Designates a signatory when needed

6.2 PSRC Committee Members

- Attend all meetings of the PSRC
- Review the protocols scheduled
- Identify and discuss major issues
- Prepare written comments of major issues as appropriate, specifically issues critical to the Program/Branch represented and forward an electronic copy of all major and minor comments within 24 hours of the meeting to the RSC PSRC Coordinator
- Vote on the approval status of the protocol
- Work with the DD and the PSRC Chair to improve the PSRC review process
- If needed, delegate responsibilities to someone from the same Program/Branch

6.3 PSRC Chair

- Manages the review schedule
- Approves DAIDS Primary Reviewer(s) suggested by the DPMO and/or Branch Chief. If the PSRC Chair(s) does not approve of the suggested DAIDS Primary Reviewer(s), then the Director for the Program responsible for the protocol will be involved in the final decision for the DAIDS Primary Reviewer(s)
- As needed, works with the DPMO and MHRP to identify reviewers for joint protocols
- Reviews submitted protocol materials and submitted review comments Discusses review issues, as appropriate, with reviewers or DPMO
- Attends all PSRC review meetings. If unable to attend, identifies a senior member of DAIDS to chair the meeting and complete other PSRC activities
- Chairs the meetings to ensure that each document receives an appropriate review and that Committee Members and other reviewers are provided adequate opportunity to present their major comments. When relevant, sees that a decision is reached regarding the approval status of the protocol
- Reviews, revises, and approves, within 10 business days of the review meeting, the drafts and final letter that detail the PSRC comments, recommendations, and decisions. Discusses with the relevant parties ambiguities, inconsistencies or other issues to improve the review document
- Participates as needed in resolving disagreements between the Study Chair and the PSRC via document review, letters, conference calls with the investigators, etc.
- Is the main point of contact for all inquiries about PSRC activities. Resolves issues and consults with the DD as appropriate
- Provides PSRC orientation to new personnel, such as medical officers or new reviewers
- Periodically reviews PSRC procedures and identifies improvements
- Identifies mechanisms for modifying the procedures when indicated
- Refers issues regarding poor performance and tardiness of reviewers or committee members to the DD for consideration of appropriate action
- Requests supplemental documents from investigators as requested by the Primary Reviewer(s)

6.4 DAIDS Protocol Medical Officer (DPMO) [or Medical Officer (MO) for Department of Defense (DoD)/DAIDS joint protocols]

- After discussion and agreement with the Branch Chief, requests a PSRC review date from NIAID PSRC Coordination
- Decides, in consultation with his/her Branch Chief or designee, the adequate number of and the specific reviewers for the PSRC review and recommends reviewers to the PSRC Chair
- Coordinates with the Protocol Team (PT) to provide the NAID PSRC Coordination with the protocol materials at least 10 business days prior to the scheduled PSRC review and sends confirmation that he/she has reviewed the protocol, that all needed materials are included, and that he/she approves the

submission for PSRC review. Informs NAID PSRC Coordination when other IC staff are expected to attend the PSRC review meeting

- Reviews Sample Informed Consent (SIC) comments from the RSC regulatory review. Works with Primary Reviewer to include as a part of his/her review any comments in the PSRC letter that warrant a written response from the PT. Forwards to NAID PSRC Coordination any SIC comments that the MO wishes sent as an Attachment to the PSRC review letter to assist the PT in preparing for the regulatory review
- Following the PSRC review meeting, interacts with the Study Chair to review PSRC comments and answer questions
- Forwards the Study Chair's response to the PSRC review to the NAID PSRC Coordination
- Ensures that changes in response to the PSRC comments are incorporated into the protocol prior to final approval
- For protocols approved contingent upon addressing major concerns with a written response from the PT sent to the DPMO (see section 7.3.2), the DPMO will determine if the response adequately addresses the concern. The DPMO will review the responses and the revised protocol and consult with the reviewers as needed
- If PT response is adequate, sends an e-mail to PSRC Chair and NAID PSRC Coordination within one week stating that reviewers have been consulted and that the responses are adequate so that a PSRC letter of final approval can be sent. Provides a tracked and a clean copy of the revised protocol and the written response from the PT to the concerns enumerated in the PSRC review
- If the DPMO has been unable to receive approval of the response from a PSRC reviewer within one week, notifies the PSRC Chair and Branch Chief for assistance
- If response is not adequate, the MO must send a summary of remaining issues that need to be addressed to the PSRC Chair and NAID PSRC Coordination so that the Study Chair can be informed

There will be no exceptions to these procedures regarding the review response unless the MO receives authorization from his/her Branch Chief

6.5 MHRP Clinical Operations Officer (COO)

- Works with DPMO to ensure readiness of protocol for PSRC review. Provides feedback to DoD Principal Investigator (PI)
- If ready, forwards the protocol document to NAID PSRC Coordination
- Assists in identifying DoD reviewer(s) and informs DoD participants of the review date

6.6 Reviewers

6.6.1 Primary Reviewer(s)

- The Primary Reviewer(s) must be an MO or Science Representative not directly involved in the project. The DPMO or Primary Reviewer may request that an overview of the proposal is presented to the PSRC
- Receives a copy of the protocol and accompanying documents from NIAID PSRC Coordination

- Requests supplemental documents as needed from investigators through the PSRC Chair
- May request input from other Government reviewers [e.g., NICHD, Vaccine Research Center (VRC)] as needed
- Alerts PSRC Chair(s), other reviewers, and the DPMO to critical issues 24 hours prior to the PSRC review meeting
- Seeks consultations from Protection of Participants, Evaluation and Policy Branch (ProPEP), the Research Ethics Team (RET), and/or the Training and Safety Branch, as appropriate, about issues related to humans subjects, ethics, or safety. Incorporates this information into the PSRC review as appropriate.
- Presents the major comments during the PSRC review meeting and interacts with the PT and the PSRC for clarification and discussion of the protocol materials
- Submits an electronic copy of his/her review document organized into major (to be discussed at the PSRC review meeting) and minor (to be conveyed to the PI in writing) comments to NAID PSRC Coordination no later than close of business (COB) one business day prior to the meeting. Submits his/her revised comments to the RSC PSRC Coordinator by COB on the next business day after the meeting so that they can be considered for inclusion in the draft of the letter to the investigator
- Reviews drafts of the letter to the PT
- If requested by the DPMO, reviews the PT's response to the PSRC review and verifies that the response satisfactorily addresses the PSRC's concerns

6.6.2 Secondary Reviewer(s)

- The Secondary Reviewer(s) provides an independent review and has the same responsibilities as described above for the Primary Reviewer

6.6.3 Standing Reviewers: BRB, PAB, RAB (and MHRP where applicable)

- Hold primary responsibility for reviewing the protocol sections related to his/her Branch's area of expertise
- Alert the PSRC Chair and other reviewers to major issues at least 24 hours prior to the PSRC review meeting
- The BRB Reviewer and MHRP Reviewer(s) if a joint DAIDS/MHRP protocol submit an electronic copy of his/her review comments to NAID PSRC Coordination no later than COB one business day prior to the meeting
- Present at the PSRC review meeting the major comments concerning the protocol, specifically identifying those critical to his/her Branch
- Forward to the RSC PSRC Coordinator an electronic copy of both major and minor comments by COB on the next business day following the meeting
- Review drafts of the PSRC review letter to the PT

- If requested by the DPMO, reviews the PI's response to the PSRC review and verifies that the response satisfactorily addresses the PSRC's concerns or assists in reaching a resolution
- If required, the COO within the MHRP will host a teleconference or arrange a face-to-face meeting between the Walter Reed Army Institute of Research (WRAIR) reviewers/chair and the PSRC Chair to coordinate the review

6.7 PSRC Coordinator

- Works with the DPMO to ensure document readiness of protocol for PSRC review and confirms DPMO's approval of documents for review
- Ensures that a DAIDS-ES number has been given to the protocol
- Verifies that all required sections of the protocol and required accompanying documents have been submitted (Appendix I, PSRC Document Submission Checklist)
- Notifies DPMO and PSRC Study Chair(s) of missing documents
- Renames files, if needed, for standardization and forwards protocol and accompanying documents to the RSC PSRC Coordinator at least 9 business days prior to the review for distribution to the PSRC distribution list
- Forwards protocol and accompanying documents to the Primary Reviewer(s) when received from the DPMO
- Assists the PSRC Chair as needed

6.8 PSRC Administrative Assistant

- Manages teleconferencing activities for PSRC
- Receives documents and obtains appropriate signature
- Forwards signed PSRC documents to RSC PSRC Coordinator for distribution

6.9 Regulatory Support Center (RSC) PSRC Liaison

- Emails PSRC documents to appropriate recipients at least 9 business days prior to the review
- Forwards the comments from the Primary Reviewer(s), upon receipt, to the reviewing members of the PSRC prior to the PSRC review meeting
- Makes copies and distributes to the PSRC attendees a viewing packet per protocol that includes the cover page of the protocol, protocol schema, and comments from the Primary Reviewer(s), the BRB Reviewer, and MHRP Reviewer(s) where appropriate
- Attends PSRC meeting and takes notes
- Receives PSRC written comments from reviewers
- Collates comments into a draft document that identifies the reviewer who made the comment and that states the decision made by the PSRC. Submits the document to the PSRC Chair within 3 business days of the PSRC review meeting for review and revision prior to further circulation
- Revises PSRC review document and forwards to reviewers and MHRP COO (for joint DAIDS/MHRP protocols) within 5 business days of the PSRC review meeting for review and revision

- Revises draft of the PSRC review document and forwards to the PSRC Chair within 7 business days of the PSRC review meeting for final review and approval
- Finalizes review document
- Forwards the final draft without the identification of reviewers to the PSRC Chair and Program Director (PDs) for final review and approval within 8 business days of the PSRC review meeting
- Forwards the approved review document to the NIAID PSRC Coordination to obtain appropriate signature within 9 business days of the PSRC review meeting
- Distributes the signed letter to the Study Chair(s), DPMO or DAIDS Clinical Representative, PSRC members, NIAID PSRC Coordination, DoD DAIDS Coordinator, and other appropriate individuals or committees within 10 business days of the PSRC review meeting
- Maintains electronic files of final PSRC review and protocol
- Forwards the review responses from the PT, when received from NIAID PSRC Coordination, to the PSRC, and to reviewers who provided comments for the previous PSRC review of the protocols
- Upon request from NIAID PSRC Coordination prepares other PSRC communications, such as PSRC final approval letter or letter granting an extension of time within which enrollment can begin

6.10 DAIDS Consultants

Any reviewer or PSRC Committee member may request a consultation from ProPEP, Training and Safety Branch, and/or the RET regarding safety and human subjects issues. When the information is received, the requester can use it for informational purposes or can include part or all of the comments in his/her PSRC review either as received or modified. These will then be included as a Major or a Minor comment(s) in the PSRC review letter.

7.0 PROCEDURE

7.1 REVIEWS

All protocol-related documents to be reviewed by the PSRC must be submitted through the DPMO to NIAID PSRC Coordination at least ten business days prior to the scheduled review and must meet the PSRC Guidelines (See Appendix I, PSRC Document Submission Checklist).

7.1.1 Reviews of Protocols for Approval

7.1.1.1 Protocols Ready-for-Implementation

These are protocols that the Protocol Team (PT) and the DPMO deem, from a scientific perspective, to be ready for implementation. Most protocols that are reviewed by PSRC are those from an HIV/AIDS Clinical Trials Network. Protocols must have all completed sections, including the informed consent(s), the Investigator's Brochure where available, and, where applicable, written reviews from the appropriate network committees. If the version submitted does not contain the changes recommended by the network committee review(s) and the

DPMO, an explanation for a lack of these changes should be included.
Non-network interventional trials funded or sponsored by NIAID/DAIDS must be approved by the PSRC prior to implementation using submission processes similar to those described for DAIDS network protocols. The Program Officer, in coordination with the DPMO, or Protocol Specialist, must request the review by contacting NIAID PSRC Coordination.

7.1.1.2 Subsequent Protocol Revisions
If there are significant concerns, the PSRC may decide that a revised protocol needs to be submitted to PSRC for re-review before its approval for implementation is given (see section 7.3.2).

7.1.1.3 Additional Protocols Related to the Parent Protocol
Program determines when an ancillary or substudy to the parent protocol needs PSRC review. PSRC will review it as a "Ready-for-Implementation" protocol (see 7.1.1.1) even though it may be closely linked to the parent study (e.g., use the infrastructure, same participants, or utilize data from the parent study).

7.1.1.4 Protocols in Development
Although seldom used, a PT may submit a protocol for PSRC review that is in development. The request is for PSRC approval to continue development of the proposed plans.

7.1.2 Reviews of Amendments to Approved Protocols
The PT should submit all amendments to Program. If Program decides that the amendment is significant, the DPMO requests a PSRC review through NIAID PSRC Coordination and submits a summary of all protocol changes since the previously approved version that PSRC approved. Otherwise, Program forwards a copy of the amendment and informs PSRC of Program's approval. Amendments must be approved by the appropriate network committee(s) prior to PSRC review. The written review from the network committee should accompany the amendment, and the revised protocol submitted should contain the changes prompted by the network committee review(s). Otherwise, the response from the PT should explain why any such changes were not incorporated.

7.1.3 Requests for Time Extensions
Enrollment should begin within 12 months of the date of the PSRC's final approval of the protocol. This final approval is usually after the PT's response to the PSRC's concerns has been accepted. If there has been a justifiable delay, the Study Chair sends a letter to Program requesting an extension of the time within which enrollment can begin. The letter should explain the delay and address any changes since the prior PSRC review in participant risk and in the scientific importance of the study.

If Program agrees to the extension and so notifies PSRC, PSRC sends a letter of approval to the Study Chair for an extension of time within which enrollment can begin.

7.1.4 Other Reviews

PSP, VRP, or DAIDS leadership can request that a non-DAIDS protocol in which it has an HIV prevention interest be reviewed by PSRC. Such a review is a non-binding, courtesy review and PSRC forwards written comments to the PT but does not approve or disapprove the protocol.

7.2 PSRC MEETINGS

7.2.1 Schedule

Review meetings are scheduled twice a month for 1½ hours and a quorum of members or their representatives is required for the meeting to be held. Generally, a 45-minute review period is scheduled for each of two protocols or amendments. Times are sometimes adjusted to review three submissions. Extra review meetings are arranged if needed to prevent long delays between a protocol's being ready for review and the availability of a review date. The PSRC Chair will request extra review meetings with the agreement of the Directors of VRP and PSP when an available slot exceeds two regular review dates or four calendar weeks whichever is less.

Other items, such as discussions of PSRC procedures, are scheduled as needed.

In addition to in-person meetings, PSRC business can be conducted, if appropriate, by conference call or by another medium.

7.2.2 Format

The meeting consists of an open session during which PT members can be present in person or by teleconference. Major comments on the protocol are first presented by the primary reviewer, the secondary reviewer(s), and standing reviewers and then by the PSRC members. The PT is given an opportunity to make any responses or provide any clarifications that will help PSRC's deliberation. The PT is not excepted to address all the major concerns that were raised. The open session is ended and the closed session without the PT follows. During the closed session, the PSRC continues the discussion of the protocol and votes on the approval of the protocol (see 7.3.1).

Within approximately two weeks, major and minor written review comments are provided to the PT. For protocols accepted as submitted, PSRC sends a letter to the PT stating its approval of the protocol for enrollment within a one-year window. For protocols with contingent approvals (see 7.3.2), the PT responds in writing to the review comments and submits a revised protocol. When it has been determined that the PT has adequately addressed the PSRC concerns, a letter is sent to the PT stating final approval of the protocol for enrollment within a one-year window.

7.2.3 Attendance

PSRC meetings are not public meetings. The meeting is open only to DAIDS staff and to other IC or U.S. government staff if the proposal is jointly supported by their IC.

Others who wish to attend must receive permission from the PSRC Chair at least 24 hours prior to the meeting.

7.3 PSRC DECISIONS

7.3.1 Votes

Motions and amendments to motions regarding the approval of the protocol are offered. When a motion is seconded, a vote is taken on the motion. A representative of a voting member may vote if he/she states that the member has given specific instructions regarding the vote to be taken. The motion carries if 2/3 or more of voting members or their representatives who are present vote in favor; otherwise, a different motion is entertained. In the event that a decision cannot be reached, the DAIDS DD in consultation with the Director of the Program sponsoring the protocol will make the decision.

7.3.2 Types of Decision

- Approved.
- Approved contingent upon the PT's adequately addressing in writing the major concerns with the DPMO's determining the adequacy of the PT's response and the revised protocol.
- Approved contingent upon the PT's adequately addressing in writing the major concerns with the PSRC's reviewing the responses and the revised protocol.
- Disapproved. If a protocol is disapproved, the PSRC will review a submitted revised protocol. If the revised protocol is disapproved, an additional submission will require prior approval from the Director of the Program sponsoring the protocol.

7.4 SPECIAL ISSUES

7.4.1 Vaccine Proposals

Appendix III (Preventive HIV Vaccine Protocols) summarizes DAIDS policy regarding whether and how a protocol of a preventive HIV vaccine candidate product should be reviewed by PSRC.

8.0 REFERENCES

None

9.0 INQUIRIES

Questions and comments regarding this SOP may be directed to NIAID PSRC Coordination: NIAIDPSRCCoordination@niaid.nih.gov

10.0 AVAILABILITY

This SOP is available electronically on the PSRC Community within the DAIDS Portal

11.0 CHANGE SUMMARY

This SOP supersedes all previous versions of the PSRC SOP.

12.0 APPENDICIES

12.1 Appendix I: PSRC Documents Submission Checklist
12.2 Appendix II: Written Responses to PSRC Comments
12.3 Appendix III: Preventive HIV Vaccine Protocols
12.4 Appendix IV: Guidance for PSRC Reviewers

13.0 APPROVAL: Approved by the Deputy Director, DAIDS, NIAID

Appendix I: PSRC Documents Submission Checklist

Protocols

The following items are required:

- Protocol with all completed sections, including the Informed Consent document(s). The version submitted must contain the changes prompted by the network committee review(s) and the DAIDS Medical Officer, where applicable.
- Written review(s) from the appropriate Network committees, where applicable.
- If re-review, written response to the previous PSRC review(s).
- Investigator's Brochure when applicable.

Amendments

The following items are required:

- Protocol with all completed sections, including the Informed Consent document. A copy of the protocol with tracked changes and a clean copy must be submitted.
- Written review(s) from the appropriate network committees, where applicable.
- The version submitted must contain the changes prompted by the Net Work committee review(s).
- Letter from the investigator outlining the major changes and the rationale for the changes

Appendix II: Written Responses to PSRC Comments

The PT must provide (a) a written response that addresses the Major and Minor concerns specified in the PSRC review letter and (b) a revised protocol that incorporates the appropriate changes. Both a clean and a tracked version of the protocol should be submitted. If the protocol was disapproved, the PSRC will consider the responses in the re-review. If PSRC gave contingent approval and responses were to be submitted to the

PSRC, PSRC will review them for adequacy. If the responses were to be submitted to the DPMO, the DPMO will consult with the PSRC reviewers to determine if the responses are adequate. If any are deemed to be inadequate, the DPMO will work with the PT, the reviewers, and, if needed, the PSRC Chair and PD to resolve the inadequacy.

Appendix III: Preventive HIV Vaccine Protocols

This Appendix summarizes DAIDS policy regarding whether and how a protocol for a preventive HIV vaccine candidate product should be reviewed and approved by PSRC. PSRC approval is required prior to protocol implementation. However, there may be instances when PSRC approval is not binding to the organization that submitted the protocol and the trial may proceed in the absence of PSRC approval. When PSRC review occurs, whether or not it binds the submitting organization, all established review procedures, scope, criteria, and standards should be followed. The need for PSRC review should be noted both in contracts and in grants (Clinical Terms of Award) when advancement into a clinical trial is expected during the term of the award. Detailed instructions that address different scenarios are provided below.

DAIDS-HELD IND: PSRC REVIEW/APPROVAL REQUIRED

All preventive HIV vaccine trial protocols for which DAIDS will hold the Investigational New Drug Application (IND) are subject to PSRC review and approval, regardless of the source of support for product development or conduct of the clinical trial. While DAIDS does not generally hold the IND for preventive HIV vaccine trials that are not supported by DAIDS or the Vaccine Research Center (VRC), it is conceivable that DAIDS may receive requests from other groups within the NIH (e.g., DMID, NCI, NICHD, NIDA, NIMH, NIAID DIR), or from close collaborators (e.g., USMHRP, CDC, IAVI, EuroVacc), particularly if DAIDS staff have been involved in product development and/or would be involved in trial implementation. Requests to hold the IND for non-NIAID trials must be approved by the DAIDS OPCRO Director, and if approved, such protocols must be reviewed and approved by PSRC prior to implementation.

DAIDS SUPPORT: PSRC REVIEW/APPROVAL REQUIRED (except in limited circumstances as determined by PSRC Chair and VRP Director)

All preventive HIV vaccine trial protocols that DAIDS financially supports and/or that require substantial DAIDS medical staff support are subject to PSRC review and approval, regardless of who holds the IND. However, when DAIDS support for a trial is not substantial, the PSRC Chair and VRP Director should decide based on the level and directness of DAIDS' involvement whether PSRC review and approval should be required.
Examples of trials that require PSRC review and approval:

- Clinical protocols conducted by and supported by VRC where DAIDS holds the IND and/or provides medical officer and other regulatory support but does not provide financial support
- Clinical protocols conducted by DAIDS-supported Networks (e.g., HVTN, USMHRP)
- Clinical protocols funded under the IPCAVD program
- Clinical protocols funded under R01, R03, R34, IAA or other grant or contract mechanisms
- Clinical protocols conducted by partners (e.g., IAVI, EuroVacc) where DAIDS holds the IND, even if DAIDS does not provide direct monetary support for the trial

Examples of trials that may not require PSRC review and approval:

- Clinical protocols in which DAIDS provides laboratory support to test specimens, statistical input, or data management input

PRODUCTS DEVELOPED UNDER DAIDS GRANT/COOPERATIVE AGREEMENT; PSRC REVIEW POSSIBLE, NO FORMAL PSRC APPROVAL/DISAPPROVAL, PSRC COMMENTS NOT BINDING WHEN DAIDS WILL PLAY NO SUBSTANTIVE ROLE IN THE SUPPORT, CONDUCT, OR OVERSIGHT OF THE TRIAL
At the request of a grantee or contractor, PSRC may review clinical protocols involving a product whose development was supported under a DAIDS grant or

cooperative agreement even though DAIDS will play no role in the support, conduct, or oversight of the clinical trial. In such cases, DAIDS will review the protocol and provide major and minor comments according to customary PSRC procedures. DAIDS will not provide formal approval or disapproval, and the PSRC comments will not be binding. DAIDS has no standing to require that the product or clinical trial sponsor(s) obtain PSRC review unless: a) the terms of the contract or cooperative agreement have given DAIDS ownership of the candidate vaccine (e.g., transfer of master file) or b) a clinical trial agreement or other Memorandum of Understanding (MOU) related to the conduct of the trial with the product explicitly requires PSRC review/approval.

When a candidate vaccine whose development was supported under DAIDS contract or grant mechanism will be evaluated in a clinical study in which DAIDS plays little or no role in the study's support, conduct, or oversight, the Project Officer should strongly encourage the the sponsor to submit the protocol for PSRC review unless there is a document to the contrary (e.g., contract terms, Terms of Award, MOU). In such cases, PSRC review will be conducted according to customary practice, but PSRC approval will not be required prior to protocol implementation.

Examples of trials where PSRC review should be requested but approval is not binding:

- Non-DAIDS supported clinical protocols of products whose development was supported in full or in part under a Preclinical HIV Development Team Contract
- Non-DAIDS supported clinical protocols of products whose development was supported in full or in part under the IPCAVD program

PRECLINICAL ASSESSMENT: REQUIRED BEFORE PSRC REVIEW

Prior to the PSRC review, a designated member from the Preclinical Research and Development Branch (PRDB) Vaccine Translational Research Team must confirm that the preclinical/non-clinical studies (e.g., toxicity studies) support the clinical protocol. The PRDB member should review and comment on the preclinical protocols to ensure they are supported by the safety testing and check for compliance with regulatory requirements such as cGMP manufacturing, vialing and release. The penultimate draft of the PSRC review protocol and all supporting documents will be distributed to PRDB by the study's DPMO at least 2 weeks prior to the PSRC submission (i.e., 4 weeks prior to the PSRC review) to allow for PRDB review. DPMO confirmation that the protocol is ready for PSRC review implicitly includes acknowledgement that the PRDB assessment of the preclinical studies has taken place.

Appendix IV: Guidance for PSRC Reviewers

Background Rationale and General Considerations for PSRC Reviewers

1. Has language been included in the background and rationale section of the protocol that describes the purpose of the study?

2. Are the rationale and content adequately presented?

3. If applicable, are the preclinical data presented on safety and immunogenicity sufficient to justify a clinical trial (data must be presented in the protocol)?

4. If applicable, are the criteria/rationale for the dosage level, number of doses, and schedule defined for all treatment groups in the clinical protocol and supported by preclinical data?

5. If applicable, are all the preclinical studies mentioned in the clinical protocol included and adequately described in the Investigator's Brochure?

6. If there is previous human experience with the product under study or with the class of products, are the data adequately described to support the current study?

7. For studies with a part A and a part B, is a rationale adequately described and are instructions provided for moving from part A to part B?

8. Are ethical considerations adequately discussed in the clinical protocol?

9. Are provisions for care of injured participants contained in the protocol?

10. As a summary of this section: Are the risks of the proposed study acceptable?

Study Design

11. Is the study design appropriate for the research question that is addressed? Are an adequate description and rationale for the design provided?

12. Is there a rationale for the study sample size?

13. Is a control group necessary; if yes, is the control group appropriate?

14. Are the study participant registration procedures adequately described?

15. For randomized studies, is the randomization adequately described in the protocol, including the details of time of randomization relative to the first visit, any stratification factors, and type of randomization employed?

16. If the protocol includes stratification, are the criteria for participant stratification (e.g., gender, HLA subtype, presence and level of antibodies to vector/component of vaccine) adequately described?

17. If the study is blinded, is the blinding appropriate for the study design?

18. For dose exploration studies, are the proposed dose cohorts adequate to assess each dose?

19. Is the duration of the study treatment phase specified in the clinical protocol and appropriate to the study aims?

20. Is the duration of the study follow-up phase specified in the clinical protocol and appropriate to evaluate potential safety issues?

21. If appropriate, is the follow-up long enough to assess and capture data on pregnancies (and their outcomes) that might have occurred in relation to the last vaccination or treatment?

22. If appropriate, are risk factors for HIV infection being measured at baseline and during follow-up?

23. As a summary of this section: Is the study design adequately detailed?

Study Objectives

24. Are the primary objectives of the study clearly stated?

25. Are the secondary objectives of the study clearly stated?

26. Are the methods and associated endpoint(s) for assessing the primary objective(s) clearly defined? Are novel assays validated and described in detail?

27. Do all objectives have data collected/patient assessments to support those aims and do all patient assessments have clearly associated objectives?

28. If applicable, are behavioral risk assessment and an adherence measure included in the study evaluation?

29. As a summary of this section: Are the study objectives clear and based on a sound rationale?

Study Population and Eligibility Criteria

30. Are the study population clearly defined and recruitment strategies discussed, including number and location of study sites?

31. Is the expected time needed for accrual discussed?

32. Are the inclusion and exclusion criteria clear and consistent with the preclinical toxicology data?

33. If appropriate, are participants allergic to vaccine components excluded from the study?

34. Are the appropriate contraindicated concomitant treatments and medications included in the eligibility criteria?

35. Are participants with high/low-risk sexual behavior appropriately included/excluded in the study?

36. Are eligibility criteria based upon age, pregnancy or lactation status described and are they justified?

37. Are contraceptive measures appropriate for the risks associated with the investigational product?

38. As a summary of this section: Are the eligibility criteria adequate to address the study aims?

Study Product

39. Is the product information in the clinical protocol consistent with the information provided in the Investigator's Brochure?

40. Is the study product(s) adequately described? Are dose, formulation, and dosing frequency for each product given?

41. Are the procedures for preparation and administration of the product, including3 special precautions, adequately described? Is blinding, if applicable, maintained?

42. Is there a plan for how the study product will be distributed, including participation of a product distribution facility and plans for final disposition of study product?

43. Is the following contact information provided for each pharmaceutical company supplying study product(s): Name, address, telephone, fax, and e-mail?

44. Are the vaccine diluents(s) and placebo (when applicable) adequately described?

45. Are contraindicated or precautionary medications, interventions, and/or behavior described?

Study Procedures

46. Are the study procedures adequately described?

47. If applicable, are there provisions for restriction of the number of participants/day for products that are entirely new or products with an anticipated toxicity profile?

48. Is the interval between dose cohorts adequate for the class of product under study?

49. Are all protocol laboratory evaluations listed with the specification of the exact test components and type of specimen needed?

50. Does the protocol specify the lab that will be performing each assay or evaluation?

51. Are special instructions for the preparation, handling, and storage of specimens clearly explained?

52. Does the protocol describe the procedures for biohazard containment to be used?

53. If applicable, is there a discussion of specimens and consent for future use of specimens?

54. Does the protocol include a table summarizing all planned dose levels?

55. Are the procedures listed in the table mentioned above consistent with the procedures defined in the text?

56. Is the total amount of blood needed for the safety and immunological studies less than or equal to 500 mL/8weeks?

57. Are the possible reasons and procedures for early withdrawl and/or termination of treatment clearly discussed in the protocol, including whether such subjects will be replaced, whether follow-up will continue, and how such subjects will contribute to the analysis?

Safety Monitoring

58. Is safety monitoring adequately described and sufficient to meet the aims of participant protection?

59. Is the safety monitoring period (duration) adequately defined and appropriate?

60. Does the protocol make adequate provision for following subjects who become pregnant post study enrollment in terms of monitoring, documenting and reporting AEs?

61. Are the safety monitoring procedures consistent with indications from the preclinical toxicity profile?

62. Are specific organ toxicities addressed?

63. Are provisions for grading of adverse events adequately described?

64. Are there adequate provisions for assessing and reporting adverse events that fall outside of those specified in the Manual for Expedited Reporting to DAIDS?

65. Has the decision to use or not use a Safety Monitoring Committee (SMC) or Data Safety Monitoring Board (DSMB) been adequately justified?

66. If an SMB or DSMB is monitoring the study, are the roles and membership eligibility adequately described in the protocol?

67. As a summary of this section: Are the risks adequately appreciated?

Toxicity Management

68. If applicable, are management guidelines for reactogenicity included in the protocol?

69. Are there management guidelines for potentially serious adverse events suspected for the product under study?

70. Does the toxicity evaluation plan contain rules for appropriate description, attribution, and expectedness/unexpectedness of the adverse events?

71. Is the issue addressed of providing antiretroviral therapy for participants who become infected during the study?

72. Are there criteria for treatment modifications in response to toxicities included in the protocol?

73. Are criteria for removal of individual participants (participant escape rules) from the study listed and clearly defined in the protocol?

74. Are criteria for stopping the study adequately described in the protocol?

75. For the 3 points above: Is the information presented in a consolidated fashion?

76. Are adverse event reporting guidelines to DAIDS and other relevant regulatory agencies and bodies, including appropriate time frames, described in the protocol?

77. As a summary of this section: Are adequate precautions being taken?

Immunogenicity Assessment – If Applicable

78. Is the number of visits to assess immunogenicity appropriate to address the study objectives?

79. Are all assays needed to evaluate immune response listed and adequately described in the protocol?

80. For phase II studies, are the assays being utilized in this study validated? If not, is a justification provided?

81. Does the protocol include a list of post vaccination/treatment evaluations?

82. Does the protocol include a table summarizing all the evaluations and procedures planned for the study?

83. Are the tests and procedures listed in the table consistent with the tests and procedures described in the text of the protocol?

84. In the case of multiple immunogenicity assessments (assays and timepoints), does the protocol specify which immunogenicity timepoint and measure will be used for the primary immunogenicity endpoint and analysis?

Statistical Considerations

85. Are all primary and secondary endpoints clearly defined including safety, immunogenicity, and efficacy?

86. Are the analytical methods to evaluate the data adequately described and appropriate to address the objectives of the study?

87. Is the primary analysis adequately specified in the protocol, including the primary endpoint and if appropriate (i.e. an efficacy study): the choice of statistical test, alpha level, methods for addressing missing data, and any issues of multiplicity addressed?

88. Is the justification for the sample size adequate?

89. For studies with multiple dose levels, are procedures for advancing to the next dose level described?

90. Are the potential biases and strategies to address them included in the data analysis section?

91. For blinded studies, are the procedures for emergency unblinding addressed in the protocol?

92. Are there provisions for interim safety analysis addressed in the protocol?

93. For any planned interim analysis, are the timing, who will conduct the analysis, whether or not the analysis would be blinded, and guidelines for related decision processes adequately described in the protocol?

94. As a summary of this section: Is the statistical plan adequate to achieve the study objectives? More detailed guidelines for making this judgement can be found in the Biostatistics Research Branch (BRB) Statistical Guidelines for PSRC Scientific Review. This document is available from the BRB Branch Chief upon request.

Informed/Assent Consent

95. Is the purpose of the study clearly identified in the informed consent/assent document?

96. Is the treatment plan, as described in the informed consent/assent , consistent with the clinical protocol?

97. Are all the test and procedures to be performed during the study, including the risks associated with such procedures, clearly described in the informed/assent consent document?

98. Are all potential risks associated with participation in the trial (physical, psychological, social, legal, or other) adequately addressed in the informed consent/assent document?

99. If applicable, are the risks of testing positive for HIV with conventional tests clearly described in the informed consent document?

100. Are potential toxicities suggested by the preclinical toxicity profile or prior human experience adequately described in the informed consent/assent document?

101. Are provisions for care of injured participants adequately explained in the informed consent/assent document?

102. Are procedures for maintaining participant confidentiality, data security requirements, and any record retention requirements that the sponsor has been adequately described?

103. If appropriate, has a plan been described for participants to continue therapy at the completion of the study or its discontinuation?

104. If applicable, are contraceptive measures appropriate for the risks associated with the investigational product adequately described for the participants?

105. As a summary of this section: Are participants adequately informed through the informed consent/assent document?

Special Populations

106. If volunteers include special populations, such as children, adolescents, prisoners, pregnant or breastfeeding women, are adequate protections described in accordance with 45 CFR 46 and other Federal Guidelines?

107. If subjects are or might become pregnant or breastfeeding, are plans described for changes in study procedures, such as discontinuation in the study, discontinuation and re-start of study product, follow-up visits.

108. Are appropriate contraceptive requirements and advice presented clearly to women of child-bearing age?

Other Considerations

109. Is there consistency (e.g., implementation of the objectives and safety endpoints) across all sections of the protocol including the synopsis, tables, footnotes, etc.?

110. Does the document contain “boilerplate” language that does not apply to this protocol?

111. Has the protocol adequately considered feasibility/futility plans?

112. Are there any considerations regarding implementation of the study that have not been adequately addressed?

General Scientific Merit of the Protocol
(to be discussed in closed session)

113. Does the protocol address an important scientific question(s) that is within the NIAID/DAIDS mission?

114. Are the study objectives and scope appropriate given the current stage of development of the product under study?

115. Is it possible to address the question(s) by better means?

116. Are there other trials underway investigating similar products or similar combinations of products? If so, is this protocol redundant?

117. Are the preclinical immunological data for the product under review similar or better than data available with similar products?

118. Will it be possible to pool relevant data obtained from the study under review with data obtained from other studies with similar products if that would be scientifically desirable?

119. Will the study as written provide data to support the use of this product in combination with other products in a multivalent vaccination strategy?

120. Can enrollment be expanded for potential benefit/indications among other populations such as adolescents, pediatric, elderly?

APPENDIX II: LABORATORY QUALITY ASSURANCE AND QUALITY ASSESSMENT POLICY

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

Review Date	Revision Date	Signature

Distributed to	# of Copies	Distributed to	# of Copies

1 SCOPE

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

2 PURPOSE

The 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 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 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 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 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 VI: Laboratory Quality Control Policy 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 V: Method Validation Policy 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 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 LC for approval before implementation. These changes must also be communicated to the 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

APPENDIX III: HIV-TESTING 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

- For Phase IIb-IV studies, at the Laboratory Center's (LC) discretion or for studies enrolling HIV-positive participants, baseline plasma/serum samples from 50 participants or 10 percent (whichever is greater) of randomly selected, enrolled adult participants at each site will be retested for HIV antibody by the LC, using U.S. Food and Drug Administration (FDA)-licensed tests. Samples from all participants will be retested if there are less than 50 total study participants. In the event of a false-positive or false-negative result that changes the infection status of the participant, an additional 100 samples or 20 percent of samples (whichever is greater) from enrolled participants will be retested.

- Baseline and seroconversion plasma/serum samples from all seroconverting adult participants and an equal number of randomly selected samples from uninfected participants matched by a follow-up visit will be retested by the LC, using FDA-licensed tests (that is, HIV antibody, HIV DNA PCR or HIV RNA, if necessary). If not otherwise specified in the protocol, specimens will be retested at the end of the study. In the event of an unexpected result (that is, positive baseline sample or negative endpoint sample in a seroconverter), retesting of additional aliquots or time points may be performed as determined by the LC.

- For prenatal trials, the LC will retest (using FDA-licensed tests) plasma/serum samples from all HIV-infected infants and an equal number of randomly selected uninfected infants.

2 PURPOSE

As a site-specific Quality Assessment measure to verify the HIV-infection status of clinical study participants, the Microbicide Trials Network (MTN) LC will perform the relevant protocol-related testing at the end of enrollment. Specimens from seroconverters and an equal number of HIV-negative participants will also be tested to verify site results. This testing will be done to verify local laboratory test results and, in special circumstances, samples will be tested at a non-MTN centralized location (that is, a local commercial laboratory). The LC will use the same test method as used for the original test. Discrepancies may be resolved using test methods with different sensitivities.

3 RESPONSIBILITIES

The Statistical Data Management Center (SDMC) is responsible for the following:

- Generating participant identification numbers (PTIDs) for retesting
- Providing retest PTIDs to the sites
- Providing PTIDs and HIV test results from participant case report forms (CRFs) to the LC

The LC is responsible for the following:

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

4 PROCEDURES

4.1 Generating and Distributing Retest PTIDs

The SDMC provides the LC with regular updates on study enrollment status and seroconverters and notifies the LC when retesting is due for a protocol. The SDMC generates a retest list containing PTIDs and associated specimen collection dates for retesting, following the guidelines, specified under the SCOPE section above, and sends the list to the LC and to the site(s) along with instructions to pull and ship specimens to the LC.

4.2 Retesting Specimens

Retesting is conducted as follows:

- The site pulls and ships specimens to the LC, using the PTIDs and collection dates.
- The LC conducts the retesting and informs the SDMC when retesting has been completed.
- The SDMC provides the LC with a retest list containing retest PTIDs, collection dates and the HIV test results performed at the site's local laboratory and documented by the site's on study CRFs.
- The LC matches the HIV retest results to the site's local laboratory results and identifies any discrepancies. The LC and SDMC will follow up on discrepancies, as appropriate.

Following completion of study retesting, the LC sends a report to the SDMC that contains:

- PTIDs with discrepant results, associated visit codes and collection dates
- PTIDs with results that were unavailable for retesting with associated visit codes and collections dates

The SDMC files the discrepant-results report and incorporates and documents the retest results.

APPENDIX IV: LABORATORY QUALITY CONTROL POLICY

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

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1 SCOPE

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

2 PRINCIPLE

Quality control (QC) is an important part of every lab test. Appropriate QC practices will maximize the accuracy of results reported as well as provide early information about potential problems. This procedure is intended to give a summary of the QC program to be followed in the laboratory. A detailed description of the QC procedures for individual assays is included in the QC sections of the individual procedures.

The laboratory recognizes that the institution and maintenance of a rigorous QC program can ensure the reliability of patient laboratory data. As the spectrum of the tests offered is broad, so are the QC procedures and the way in which data from various types of QC material are handled and presented.

3 PROCEDURES

The QC Program can be divided into the following main areas of focus:

- Internal QC — testing of known materials
- Parallel testing — validation of new controls and reagent lots
- Internal proficiency testing — blind or split-sample testing
- External proficiency testing programs
- QC monitoring — corrective action logs
- Quality assessment program
- QC through preventative maintenance programs

3.1 Internal QC — Testing of Known Materials

Qualitative test systems include the following:

- QC of assay reproducibility is achieved by testing materials of known reactivity.
- Qualitative procedures are checked by at least one positive and one negative control.
- The frequency of controls is dependent on the manufacturer's recommendation as well as the laboratory confidence/experience with each method.
- The number of controls and the frequency of control runs are specified in each test procedure.
- The testing technologist is responsible for reviewing and recording the QC results on the assay worksheet (or equivalent).
- If the QC results are within the established guidelines and the patient test results appear valid, the testing technologist will sign and forward the results to the Laboratory Supervisor or designee for final review.
- If the QC results and patient test results are acceptable, the Laboratory Supervisor will sign and release the test run.
- All results (QC and patient) must be reviewed, evaluated and signed by the Laboratory Supervisor or designee before the patients' test results can be released.
- In the event that the Laboratory Supervisor or designee is unavailable and the release of results will be delayed, peer review is allowed for release of results. Peer review results must be documented by signature. The Laboratory Supervisor or designee review must be done as soon as possible and documented.
- If the QC results are not within the established guidelines or a potential problem is noted, the testing technologist will review the results with the Laboratory Supervisor or designee.
- All QC results must be documented, including any out-of-range results.
- Out-of-range results and follow-up action will be documented on the test-system, corrective action log.
- When a control result falls outside the established range or potential problems are noted, the Laboratory Supervisor or designee will make the final decision on the disposition of the run.
- If the run is considered invalid based on review of the QC results, all tests must be repeated.
- Patient results cannot be turned out until the QC is resolved and the test run is repeated, if necessary.
- The Laboratory Supervisor or designee will review and sign off on the corrective action logs once per month. If potential problems exist, the QC results will be reviewed more frequently.

- The Laboratory Supervisor or Director may increase the number or frequency of controls or request outside testing to resolve potential problems.

Quantitative test systems include the following:

- Quantitative procedures are checked by a low-to-high range of two to three controls, depending on the procedure.
- The frequency of controls is dependent on the manufacturer's recommendation as well as the laboratory's confidence/experience with each method.
- The number of controls and the frequency of control runs are specified in each test procedure.
- For commercial QC material, the manufacturer's ranges are used until a minimum of 20 determinations are made to establish an in-house mean +1, 2 and 3 standard deviations or 15 percent from the mean.
- The testing technologist is responsible for reviewing and recording the QC results on appropriate QC logs. The minimum requirement will include a control log. Levy-Jennings charts are required for chemistry, hematology and potentially other testing areas.
- If the test system has an automated QC record function, the control logs and Levy-Jennings charts must be checked each time the controls are run.
- Patient samples should not be run before the controls are reviewed and found to be acceptable.
- Patient samples that are included with the control run will not be reported if the controls are unacceptable.
- If the QC results are within the established guidelines and no shifts, trends, or potential problems are noted on the Levy-Jennings charts, the testing technologist will forward the patient results to the Laboratory Supervisor or designee for final review.
- If the QC results and patient test results are acceptable, the Laboratory Supervisor will sign and release the test run. Generally, patient results are considered acceptable if all QC materials fall within the established two standard deviation ranges, or 15 percent from the mean.
- All results (that is, QC and patient) must be reviewed, evaluated and signed by the Laboratory Supervisor or designee before patient test results can be released.
- In the event that the Laboratory Supervisor or designee is unavailable and result release will be delayed, peer review is allowed for release of results. Peer review results must be documented by signature. The Laboratory Supervisor or designee review must be done as soon as possible and documented.
- If the QC results are not within the expected ranges and guidelines, the testing technologist will review the results with the Laboratory Supervisor or designee.
- All QC results must be documented, including any out-of-range results.
- Any shifts or trends must be reported to the Laboratory Supervisor. Any shifts or trends must be examined.
- Out-of-range results and follow-up action will be documented on the test-system, corrective action log.
- When a control result falls outside the established range or potential problems are noted, the Laboratory Supervisor or Director will make the final decision on the disposition of the run.
- Results may be considered acceptable after review.
- The review and consideration will be documented on the assay sheet and the corrective action log.

- If the run is considered invalid based on review of the QC results, all tests must be repeated.
- Patient results cannot be released until the QC is resolved and the test run is repeated, if necessary.
- The Laboratory Supervisor or designee will review and sign off on the QC data and corrective action logs once per month. If potential problems exist, the QC results will be reviewed more frequently.
- The Laboratory Supervisor or Director may increase the number or frequency of controls or request outside testing to resolve potential problems.

Other Test Systems include the following:

- Culture Media:
  - All culture media will be checked for expiration dates before being put into use.
  - A culture media control log will be used to document the lot number and QC results.
  - Any media that appears cloudy, has a color change or shows contamination will be discarded.
  - Appropriate control organisms will be used to check selective media.
  - The control log will be initialed and dated by the technologist performing the QC.
  - The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
  - Media that fails the QC check will be documented and discarded.

- Animal Sera:
  - All animal sera will be checked for cytotoxicity before use.
  - An animal sera control log will be used to document the lot number, expiration date and QC results.
  - Acceptance criteria for cytotoxicity will be defined.
  - The control log will be initialed and dated by the technologist performing the QC.
  - The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
  - Animal sera that fail the cytotoxicity check will be documented and discarded.

- Gram Stain:
  - Gram stain reagent and procedure will be quality-controlled each day of use by including a control slide containing gram-positive and gram-negative organisms such as *E. coli* and *Staphylococcus aureus* or equivalents.
  - These control slides may be made in-house from known cultures.
  - Acceptance criteria for the gram stain slides will be defined.
  - The slide control results will be documented on a gram stain QC log.
  - The control log will be initialed and dated by the technologist performing the QC.
  - The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
  - If the control slide stain is not acceptable, check both the staining technique and the stain. Document any problems and corrective action on the gram stain corrective action log.

- Differential and/or Malaria Stain:
  - The differential stain will be checked each day of staining.
  - The first slide read after staining will be reviewed for correct color formation for the white blood cells (WBC) and red blood cells (RBC) along with excessive background debris.

- Acceptance criteria for the differential stain will be defined and documented on the control log.
- The control log will be initialed and dated by the technologist performing the QC.
- The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
- If the control slide stain is not acceptable, both the staining technique and the stain will be checked. Document any problems and corrective action on the differential stain corrective action log.

3.2 Parallel Testing — Validation of New Controls and Reagent Lots

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

HIV Enzyme Immunoassay (EIA) Assay: To validate 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 in parallel. The patient results should be reproducible between the old and new 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 old and the new lot number. 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. Any variation greater than three-fold needs to be investigated and documented.

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 in parallel. The patient results should be reproducible between the old and new 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 runs.

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 is obtained for the new lot of controls. The mean and standard deviations for the new lot of controls will be reviewed and signed off by the Laboratory Supervisor or Director before being put into use.

CD4/CD8 Assay: To validate lot-to-lot variability of reagents, a minimum of two patients (one with CD4/CD8 ratio <1.0, and one with CD4/CD8 ratio >1.0) are run in parallel. The patient results should be reproducible (that is, based on the manufacturer guidelines for sample-to-sample, lot-to-lot variation) between the old and new lots. The patient samples will be marked as validation samples and filled with the other CD4/CD8 runs. 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 Flow Cytometry runs. It is also important to check expiration dates and perform lot testing on primary and secondary antibodies used for this purpose.

Chemistry, Hematology and Coagulation — New Reagent Lot Check In: New lot numbers of reagent 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.

3.3 Internal Proficiency Testing — Blind or Split-Sample 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 to assess the reproducibility of the assays as well as the technologist-to-technologist variability and accuracy. The Laboratory Supervisor or designee will be responsible for assigning the samples, documenting the results and reviewing the results. The acceptable range of reproducibility will be determined by test and documented on the result form.

The documentation will include the results by technologist and whether the results compared acceptability for accuracy and reproducibility. The Laboratory Supervisor and Director will sign off on the results. The results will be filed as Internal Proficiency Testing records.

3.4 External Proficiency — Testing Programs

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. 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 prepare the final result forms 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. The Laboratory Supervisor and Director will investigate any noted deficiencies.

A written report of the findings and corrective action will be written. The Laboratory Supervisor and Director will sign this report. The report will be sent to the Laboratory Center for review. A copy of the response will be filed with the survey results.

3.5 QC Monitoring — Corrective Action Logs

Corrective action logs are maintained for each test and instrument. The logs are used to document QC results that fall outside the established ranges and inconsistency in results or problems with the test system (for example, reagents, controls, instruments or equipment). The testing technologist is responsible for documenting any problems and corrective action taken on the corrective action log for that test system. The Laboratory Supervisor or designee is to be notified immediately of any problems and will review the corrective action. The logs provide valuable information for troubleshooting test methods or instrument problems. The Laboratory Supervisor or designee will review and sign off on the corrective action logs once per month.

3.6 Quality Assessment Program

The main purpose of the Quality Assessment Program (QAP) is to evaluate the quality of work provided by each section of the laboratory. The QAP is another tool for monitoring potential problem areas of the laboratory that might not be detected by the Quality Control Program. Refer to the Quality Assessment Policy Procedure for more details.

3.7 QC through Preventive Maintenance Program

Instrument Maintenance: All instruments used in the laboratory follow a preventive maintenance program based on the manufacturer's recommendations. Documentation of the instrument maintenance, calibration, service, and corrective action logs is generally found in the equipment logbooks in each area. The bench technologist maintains these records. These records are reviewed and signed monthly by the Laboratory Supervisor or designee.

Equipment Maintenance: Routine maintenance on laboratory equipment is performed according to the manufacturer's recommendations. The technologist performing the maintenance documents the maintenance and results. The Laboratory Supervisor or designee reviews and signs off on the maintenance records monthly. Documentation of the equipment maintenance is generally found in the laboratory Maintenance Manual.

Preventive maintenance, monitoring or calibration generally 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

3.8 QC — Temperature Monitoring

All temperature-sensitive equipment, such as freezers, refrigerators, water baths and incubators, must be monitored on a daily basis. All test work areas and reagent storage areas must be monitored on a daily basis (that is, room temperature monitoring where equipment and testing is done, as well as where room temperature reagents are stored). 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 date. The temperature chart may include a comments/corrective action section. The charts should be reviewed on a monthly basis by the Laboratory Supervisor or designee.

3.9 QC — Reagent Water

The following procedures and specifications are for the testing of 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: Used for the preparations of solutions and reagents (EIA testing) requiring minimum interference and maximum precision and accuracy (10cfu/ml)
Type II: Used for general laboratory testing other than described above
Type III: 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, distilled, deionized water. If this is not available, distilled water can be used and sterilized, if necessary. Refer to the Water Procedure in the Maintenance Manual for details.

ATTACHMENTS

A: Quality Control Testing Summary
B: Corrective Action Log

ATTACHMENT A: QUALITY CONTROL TESTING SUMMARY

Test	Quality Control		Proficiency Program		Parallel Testing	Comments
	Material	Frequency	CAP	UKNEQAS		
CBC	Low, Normal, High	Daily	X		Overlap Controls	Calibrate per manufactures instructions or every 6 mos
Differential	Stain Check	Daily	X			
ESR	Low/High	Daily	X			
Malaria Smear	Stain Check	Daily	X			
CD4/CD8	Manufacturer Controls	Daily	X	X	Reagents	
Chemistry	Minimum 2 levels	Daily	X		Overlap Controls	Calibrate per manufacturer instructions or every 6 mos
HIV-1/2 EIA	Kit controls	Lot	X		Reagents	
HIV-1/2 Rapid	Commercial or In-House	Run	X			
HIV-1 Western Blot	Kit: Neg/Weak to Strong Pos	Run	X			
HIV Viral Culture		Buffy Coat				
HIV-1 P24 Ag	Kit controls	Run	X		Reagents	

Urinalysis	Commercial, Normal/Abn	Daily	X			
Urine Microscopic	Commercial, Normal/Abn	Daily	X			
Urine Pregnancy	Commercial, Neg/Pos	Kit	X			
HIV RNA PCR QT Kit Controls, Neg/L-H Pos		Run	X		Reagents	
HIV RNA PCR QL	Kit Controls, Neg/Pos	Run			Reagents	VQA
GC, Chl PCR QL	Kit Controls, Neg/Pos	Run	X		Reagents	
Bacteriology	In-house Organisms/Reag.	Weekly	X			
Gram Stain	Stain Check	Daily	X			
Media	Media Check	Per Lot				
Storage-Pla, Ser	Self Audit	As Needed				

ATTACHMENT B: CORRECTIVE ACTION LOG

CORRECTIVE ACTION/REMARKS LOG FOR INSTRUMENT/TEST SYSTEM

Date	Problem/Comments	Initials	Corrective Action/Comments	Initials	Date

Reviewed by: _____ Date: _____

APPENDIX V: METHOD VALIDATION POLICY

Prepared by	Date Adopted	Supersedes Procedure #
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1 SCOPE

This procedure applies to all Microbicide Trials Network (MTN) laboratories. Any time a new instrument or methodology is implemented or an existing instrument or method is changed within the laboratory, validation studies must be performed. Documentation of these studies must be maintained for the life of the instrument or methodology. Results of these studies must verify the performance specifications and claims of the manufacturer. This document is not a comprehensive explanation of method validation.

2 PURPOSE

The following describes assay validation studies suitable for manual and automated quantitative assays, such as for chemistry and hematology. If these procedures do not appear suitable for your assays, please contact the Laboratory Center (LC) at mtnnetworklab@mtnstopshiv.org for clarification. Results of assay validation studies must be sent to the LC for approval before that assay can be used in an MTN protocol.

3 VALIDATION PROCEDURES

Studies for quantitative assays that are U.S. Food and Drug Administration (FDA)-approved and unmodified contain the following elements:

Accuracy
Accuracy is the true value of a substance being measured. Verification of accuracy is the process of determining that the test system is producing correct, valid results. This is determined by:

- Assay materials with assigned values
- Comparing patient specimen results with a method of long-standing use
- Verifying results from inter-laboratory survey specimens
- Splitting specimens with another sufficiently accredited laboratory

Results must demonstrate that the system is accurate enough to provide clinically valid patient results. Limits of acceptability should be set by the Laboratory Director.

Precision
Precision is the reproducibility, the agreement of the measurements of replicate runs of the same sample.

Precision is the process of determining the range of random errors. The precision is measured in terms of coefficient of variation (CV) and standard deviation (SD). The smaller the CV and SD, the better the precision will be.

This can be determined by running a minimum of 20 replicates of a specimen or quality control (QC) material during a span of 10 to 20 days, if possible. The mean, CV and SD are calculated from the data obtained.

Precision data must demonstrate the assay performance, which is comparable to the performance specifications published by the manufacturer. When there are no specifications published, limits of acceptability must be set by the Laboratory Director.

Verification of Measurable Range (Linearity)
This is the range of test values over which there is a valid relationship between the instrument, kit or test systems measurement response. The response may not necessarily be linear.

- The laboratory must demonstrate a relationship between the actual and expected values of a test procedure.
- Verification must be run for assay validation and, at a minimum, annually.
- Verification determines both the lower and upper limit of reporting.
- Plot the expected values on the x-axis and the actual values on the y-axis.
- Manufacturer claims must be verified.
- If the reportable range study indicates a usable range outside the limits indicated by the manufacturer, the manufacturer-published reportable range must be used.
- If the reportable range study indicates a usable range smaller than the limits indicated by the manufacturer, the smaller range must be used.

- After verification of the measurable range, laboratories should establish their reportable range. This represents the highest and lowest values that may be reported. These may exceed the measurable range.

Reference Range Verification
Reference ranges are a measured set of values determined to occur in a healthy non-diseased population. Reference ranges can be chosen from documented literature, manufacturer-suggested ranges or existing laboratory ranges; or the laboratory may perform a full normal-value study to evaluate its own range. The laboratory must verify that their reference range is valid for their study population.

If a laboratory decides to use published ranges, these ranges must be verified. To validate or transfer this published range, the laboratory must analyze specimens from 20 healthy, non-diseased individuals for each subgroup. If two or fewer results fall outside the published range, it is validated. However, if more than two results fall outside the published range, a more extensive study should be conducted. The Laboratory Director ultimately decides which validation to use based on the study population.

Carryover Studies
Sample carryover may cause one high patient sample to affect the sample that follows it. Most of today's diagnostic analyzers take every possible precaution to avoid sample carryover. In spite of these efforts, a sample having a high result may affect one or more samples that follow it. The laboratory must show that neither its instruments nor its test system has any unacceptable carryover.

Carryover studies must be performed during assay validation, at least annually thereafter and when carryover is suspected. This can be completed in some cases using CAP panels. Follow manufacturer instructions for assessing carryover and acceptability limits.

Any deviation from the manufacturer recommendations will put that procedure into the modified category.

Studies for quantitative assays that are not FDA-approved, or are FDA-approved and have been modified, must also contain all of the previous items (one through five), as well as the following:

Analytical Sensitivity
This is the lowest measurable concentration that is distinguishable from zero. Successive dilutions of a previously analyzed patient specimen or control can be used.

Analytical Specificity
This is the ability to deal with interfering substances. At a minimum, run samples spiked with hemoglobin, bilirubin and lipids.

Any Other Applicable Performance Characteristics
Demonstration of carryover is one example.

4 ACCEPTABILITY CRITERIA

The Laboratory Director must set the limits for assay acceptability. In the absence of a Laboratory Director, a designated responsible individual from the site can set the criteria. LC staff may be able to offer guidance for setting limits.