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Document Title: Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials-Requirements for U.S. Laboratories		

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1.0 PURPOSE

- 1.1 The purpose of this policy is to describe specific requirements for laboratories processing and testing biologic samples from participants enrolled in clinical trials supported and/or -sponsored by the NIAID DAIDS in the United States.

2.0 SCOPE

- 2.1 This policy applies to US laboratories performing testing for clinical trials where: 1) the clinical trial is conducted by a DAIDS-funded clinical trials network; or, 2) the non-Network clinical trial is conducted by a DAIDS-funded Principal Investigator and DAIDS is the IND holder. In some cases, for clinical trials that are supported, in part or in whole, by DAIDS, but where DAIDS does not hold the IND, these requirements may also apply.

3.0 DEFINITIONS

For additional definitions, see [DAIDS glossary](#).

- 3.1 DAIDS Clinical Laboratory Oversight Team (DCLOT):

A cross-DAIDS team that includes staff from the Vaccine Research, Prevention Sciences, and Therapeutic Research Programs. DCLOT develops, evaluates, coordinates, communicates, and oversees the implementation of harmonized guidelines, standards, and requirements for determining the readiness and on-going ability of clinical laboratories to participate in DAIDS-supported and/or -sponsored clinical trials and clinical research projects.

- 3.2 DCLOT Points of Contact (POC)

DCLOT staff act as points of contact for laboratory oversight to investigators from the Vaccine Research, Prevention Sciences, and Therapeutic Research Programs conducting DAIDS-supported and/or -sponsored clinical trials and clinical trials and clinical research projects.

- 3.3 DAIDS Good Clinical Laboratory Practices (GCLP) Guidelines:

A comprehensive document outlining the guidelines for quality laboratory testing and operations, intended to ensure consistent, reproducible, and auditable laboratory data and results that can support study reconstruction.

4.0 RESPONSIBILITIES

- 4.1 **DAIDS Clinical Laboratory Oversight Team (DCLOT)**

- 4.1.1 This policy, and the associated policies with specific requirements for U.S. and non-U.S. laboratories, have been created by DAIDS Clinical Laboratory Oversight Team (DCLOT) whose responsibility is to oversee the laboratory component of NIAID DAIDS sponsored clinical trials. DCLOT will be responsible for updating this policy in response to changes in federal and international regulations and based on continued experience in the conduct of clinical trials. DCLOT will be responsible for working in partnership with the clinical trial network and non-network grantees and contractors to determine if laboratories have acceptable performance.

4.2 Principal Investigator of a NIAID supported grant and/or Investigator of Record (IoR)

- 4.2.1 The Principal Investigator of a NIAID supported grant and/or Investigator of Record (IoR) is responsible for ensuring that laboratories processing and testing biologic samples from participants enrolled in clinical trials adhere to the laboratory requirements identified in this policy, as well as follow specific guidance described in individual clinical trial protocols. DCLOT will be responsive to queries by investigators who need assistance with understanding this policy and with implementing the specific requirements for U.S. and non-U.S. laboratories. Please email: DCLOT (NIAIDDCLOT@niaid.nih.gov) for enquiries about the laboratory policy.

5.0 POLICY

U.S. laboratories that perform any test, including waived tests on "...materials derived from the human body for the purpose of providing information for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings" must meet certain federal requirements. Laboratories that perform tests for these purposes fall under Clinical Laboratory Improvement Amendments (CLIA) requirements. An overview of CLIA requirement can be found in the document [CLIA Application for Certification \(https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms116.pdf\)](https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms116.pdf). All laboratories performing waived tests must apply for a CLIA certificate of waiver. For more information see: [An overview of the application for CLIA certification \(https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA\)](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA).

5.1 Laboratory Safety, Diagnosis, Eligibility and Other Tests Used for Participant Management

Tests that are used for diagnosis (e.g., HIV, CMV, HSV, Syphilis), determining enrollment eligibility (e.g., pregnancy test), monitoring the safety of the intervention (e.g., hematology, chemistry), making participant management decisions (e.g., CD4 cell count, HIV viral load, drug levels), must be performed in laboratories that are [CLIA certified](#) or have a CLIA waiver. Most of these tests will be FDA-approved methods, but fully validated laboratory developed tests (LDTs), performed in CLIA certified laboratories, may also be used for these purposes.

These tests (unless CLIA waived) must be quality assured by CLIA approved EQA providers, such as the College of American Pathologists (CAP). See: A list of [CLIA Approved EQA providers \(https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/downloads/ptlist.pdf\)](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/downloads/ptlist.pdf). When commercial or standard EQA is not available, alternative EQA plan should be devised and proposed to DAIDS for approval.

5.1.1 HIV Virology

If HIV viral load, HIV DNA or total nucleic acid (TNA) PCR or HIV genotypic drug resistance testing is a primary endpoint of the proposed trial, it is recommended that laboratories that perform these tests participate in the [DAIDS Virology Quality Assessment \(VQA\) program \(https://www.hanc.info/labs/labresources/vqaResources/Pages/default.aspx\)](https://www.hanc.info/labs/labresources/vqaResources/Pages/default.aspx).

To request enrollment in VQA EQA program(s), please contact [NIAID DCLOT CORs \(NIAIDDCLOTcORs@mail.nih.gov\)](mailto:NIAIDDCLOTcORs@mail.nih.gov). The process of achieving certification takes at least 5 months.

For laboratories performing testing for NIAID (DAIDS) -sponsored clinical trials, there is no fee for participating in the VQA program. However, laboratories are responsible for test kits/reagents used to test the EQA panels. These costs should be considered when preparing the budget for conducting the trial.

5.1.2 Pharmacology

If pharmacology results will be used for participant management decisions during the trial, the pharmacology lab must be CLIA certified. Most of this testing will be performed using validated LDTs. If pharmacology outcome is a primary endpoint of the study, it is recommended that the testing be performed in laboratories that participate in the [DAIDS Clinical Pharmacology Quality Assurance \(CPQA\) program](http://www.buffalo.edu/tprc/section-2/CPQA.html) (<http://www.buffalo.edu/tprc/section-2/CPQA.html>).

For information on laboratories that participate in the CPQA program, please contact [NIAID DCLOT CORs](mailto:NIAIDDCLOTORs@mail.nih.gov) (NIAIDDCLOTORs@mail.nih.gov).

5.2 Endpoint Tests not approved by FDA

For studies that require regulatory action for approval or labeling (including tests for PK/PD), primary endpoint tests should be standardized/optimized/validated according to FDA Guidelines on Bioanalytical Method Validation and should be performed in laboratories that conduct operations in accordance with Good Clinical Laboratory Practices (GCLP). See Appendix I in POL-A-OD-002 Requirements for Laboratories Performing Testing for NIAID DAIDS-Supported and/or Sponsored Clinical Trials for DCLOT Algorithm for Determining Level of Validation Required for Endpoints Assays. Endpoint tests are performed for investigational or research purposes only and are not used for the diagnosis, treatment or management of trial participants.

GCLP embraces the research, pre-clinical and clinical aspects of Good Laboratory Practices (GLP). Complying with GCLP is an ongoing process that is central to optimal clinical research laboratory operations. DAIDS and/or DAIDS contractors may monitor the progress towards GCLP compliance through audits and/or site visits. GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results that support clinical trials will be produced in an environment conducive to study reconstruction and ensure the safety of the research subjects and those who perform the laboratory testing. See: <https://www.niaid.nih.gov/sites/default/files/gclpstandards.pdf>

5.2.1 Investigational Use Only (IUO) and Research Use Only (RUO) tests

Endpoint tests, such as non-FDA approved immunological, pharmacological and virological assays, do not require an investigational device exemption (IDE) submission to the FDA. These are classified as investigational use only (IUO) tests while clinical studies are being done to evaluate their performance. Results from these tests are not intended to be used for the diagnosis, treatment or management of participants without confirmation by other medically established procedures.

RUO assays, such as Enzyme-linked Immunosorbent Spot (ELISpot), Intracellular Cytokine Staining (ICS), monoclonal antibody PK assays and quantitative viral outgrowth assays (QVOA), cell-associated HIV RNA (caRNA), are intended to advance product or perform basic scientific research and are not considered to be effective diagnostic tools. See Appendix I in POL-A-OD-002 for determination of the level of assay verification for endpoint IOU and ROU tests.

Where possible, External Quality Assurance (EQA) should be applied to such tests. DAIDS has established an EQA program, [EQAPOL \(https://eqapol.dhvi.duke.edu/\)](https://eqapol.dhvi.duke.edu/), for laboratories performing immunogenicity assays as part of NIAID (DAIDS)- sponsored clinical trials.

Please contact [NIAID DCLOT CORs \(NIAIDDCLOTcORs@mail.nih.gov\)](mailto:NIAIDDCLOTcORs@mail.nih.gov) for more information on [EQAPOL](#).

If existing EQA surveys are not available for these tests, a suitable form of alternative EQA assessments should be devised and proposed to DAIDS for approval. Results from these assays are not to be used for making clinical decisions.

5.2.2 Instrument and Method Validation

For tests that are used for diagnosis, determining eligibility, monitoring the safety of the intervention, making participant management decisions and for most primary study endpoints and products on a regulatory approval track, DAIDS requires laboratories to perform qualification, verification or validation as appropriate prior to placing a new method or instrument into use, whenever conditions for which the method has been validated change or if the change is outside the original scope of the method, after major maintenance or service of equipment used, or after relocation of equipment. To minimize validation requirements, the use of FDA-approved methodologies is strongly encouraged. If non-approved methods are considered, these should be validated in a study that compares a proposed method to a FDA-approved method if available. For information on guidelines for conducting a validation study refer to DAIDS guidelines for GCLP standards (<https://www.niaid.nih.gov/sites/default/files/gclpstandards.pdf>).

5.3 Specimen Management Plan

Procedures for the management of trial specimens must be documented and followed to ensure the integrity and chain of custody of specimens and their timely testing. Each study should have a Specimen Management Plan that describes study specific sample acquisition, recording, testing, retention, storing, shipping and disposal; including specimen flow chart, quality assurance (QA) oversight and corrective action (the latter two may be included in the Laboratory Quality Management plan). Details may be included in Manual of Operations for the trial and/or in study protocol appendices.

If shipments of specimens are to occur, they must be done according to the most current International Air Transport Association (IATA) shipping regulations and comply with local/state regulations.

Note: For clinical trials where DAIDS is not the IND holder, the Specimen Management Plan is the responsibility of the IND holder.

5.4 **Laboratory Data Management Plan**

Procedures for the management of laboratory data must be documented and followed to ensure data integrity and timely reporting of results. Studies must include a Laboratory Data Management Plan that describes the study specific systems and processes for acquisition, data entry, recording, exporting, reporting, modification, security and archiving of laboratory test results. The plan should describe the QA oversight and corrective actions, and how all laboratory test results will be integrated into the general study database and data transmitted to the data center.

If the laboratory plans to use a Laboratory Information Management System (LIMS) or a laboratory data management system, computerized laboratory systems should be validated and compliant with 21 CFR Part 11 [\[7\]](https://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm) (<https://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm>).

Note: For clinical trials where DAIDS is not the IND holder, the Laboratory Data Management Plan is the responsibility of the IND holder.

5.5 **Laboratory Quality Management Plan**

Quality management is a systematic approach to achieving quality objectives. The Laboratory Quality Management Plan (QMP) is comprised of Quality Assurance (QA) and Quality Control (QC) processes.

The lab QMP describes the laboratory's approach to management of quality and study-participant safety by providing guidance for the operation of a laboratory. It must describe procedures for monitoring, assessment, and correction of problems identified in pre-analytical, analytical and post analytical aspects of all lab operations.

All laboratories performing testing that supports a clinical trial sponsored by the NIAID (DAIDS), where data will be submitted for regulatory decisions, must have a documented QMP that describes the overall quality management program of the laboratory.

The QMP should describe the following; the laboratory's plan to ensure overall quality and participant safety, corrective action and preventive action (CAPA) activities, risk assessment activities, QC and EQA activities, monitoring of key indicators and continuous improvement plans. For additional information, please refer to [guidance in preparing and implementing a QMP](#).

5.6 **Laboratory Auditing**

Laboratories participating in NIAID (DAIDS)- sponsored clinical trials are audited periodically by a NIAID contract and/or by other organizations (e.g. CAP, the International Organization for Standardization – ISO) to document the ability of Laboratories to conduct activities in accordance with GCLP, CLIA and other regulations or standards. Compliance will ensure that

consistent, reproducible, auditable, and reliable laboratory results that support clinical trials will be produced in an environment conducive to study reconstruction.

DAIDS reserves the right to conduct for-cause or ad-hoc audits at any of the U.S. laboratories participating NIAID (DAIDS) -sponsored clinical trials. After an audit, a report will be distributed to the laboratory. The laboratory is responsible for working with DAIDS and/or its contractors and the Network staff, to resolve the audit report findings. These audit report findings must be adequately addressed by the laboratory to maintain a satisfactory performance standard.

For the types of audits performed and the report resolution process please refer to **Appendix 1**.

Please email [DAIDS Clinical Laboratory Oversight Team \(NIAIDDCLOT@niaid.nih.gov\)](mailto:NIAIDDCLOT@niaid.nih.gov) for enquiries about the DAIDS-sponsored GCLP audit and report resolution processes.

5.7 **PBMC EQA:**

Laboratories that process and cryopreserve viable PBMCs, critical to the integrity of planned and/or future testing as part of NIAID (DAIDS) -sponsored clinical trials, must participate in an Immunology Quality Assessment (IQA) Cryopreservation EQA Program.

An example of such a program can be found [here \(https://iqa.center.duke.edu/programs/cryopreservation\)](https://iqa.center.duke.edu/programs/cryopreservation).

For laboratories performing testing for NIAID (DAIDS)-supported and/or -sponsored clinical trials, there is no fee for participating in the IQA program. However, laboratories are responsible for the cost of shipping to IQA. These costs should be taken into account when preparing the budget for conducting the trial.

Please contact [NIAID DCLOT CORs \(NIAIDDCLOT CORs@mail.nih.gov\)](mailto:NIAIDDCLOT CORs@mail.nih.gov) to discuss enrollment for this IQA program.

For laboratories enrolled in or planning to enroll in other QA programs for PBMCs, these programs should be proposed to DAIDS for approval.

5.8 **GCLP Training**

An interactive GCLP training, sponsored by the DAIDS and delivered online (and occasionally face-to-face), is intended to give participants an introduction to GCLP and their relationship to clinical research. The course provides participants with an understanding of the differences between FDA and CLIA regulations. In addition, other guidance and accreditation information is presented to augment and clarify GCLP. The topics presented would be most appropriate for the Laboratory Managers/Supervisors, QA/QC Coordinators, training supervisors or other laboratory staff working, or planning to work, in a GCLP environment. Participants attending the training will get an understanding of key components of GCLP, and the role they play in ensuring the validity of studies. The importance of documentation is stressed throughout the training.

Online Training: The GCLP eLearning modules (self-guided training) are available on the DAIDS Learning Portal (DLP) and can be completed at any time from any internet-accessible location.

DLP is a web-based software that offers sites the capability to assign, track, and monitor the completion of required training; thereby, increasing the efficiency and effectiveness of training management, administration, and coordination across NIAID (DAIDS)- sponsored clinical research sites. Information on [GCLP eLearning modules](https://daidslearningportal.niaid.nih.gov/) (<https://daidslearningportal.niaid.nih.gov/>).

Clinical laboratory staff involved in specimen processing and testing may take GCLP training, available on the DAIDS learning portal. Refer to [GCLP guidelines](#) for more detail on requirements.

6.0 REFERENCES

- 6.1 [U.S. Food and Drug Administration, Guidance for industry: bioanalytical method validation, 2018.](#)

7.0 APPENDICES

7.1 **Appendix 1: Laboratory Audits Conducted by NIAID HIV and Other Infectious Diseases Clinical Research Support Services (CRSS) Contractor**

The CRSS Core Team is contracted by the Division of AIDS (DAIDS) to perform laboratory audits for Good Clinical Laboratory Practice (GCLP) compliance throughout the world. The DAIDS Laboratory Program staff is responsible for requesting audits. These audits may be triggered due to an immediate need or may be driven by an established audit visit schedule. CRSS auditors contact the site staff to schedule the date(s) for the audit. An e-mail is then sent to the site staff to introduce the auditor and confirm the audit date(s). After the audit date(s) are set, a pre-visit letter is provided to the site staff at least 10 calendar days prior to the audit date(s), which describes the agenda for the visit. In addition, a copy of the appropriate audit checklist is provided with the pre-visit letter to the site staff and all appropriate parties specified in the distribution list provided to the CRSS by DAIDS are copied (DAIDS, Network/Non-Network staff, and Lab QA contractor).

The types of audits performed by CRSS include: General Laboratory, Central/Endpoint Laboratory, Peripheral Blood Mononuclear Cell (PBMC) Processing Laboratory, Histology/Cytology Laboratory, Tuberculosis/Acid-fast bacilli (TB/AFB) Laboratory, and Specimen Repository audits. The customized laboratory audit checklists utilized for each of these audits were developed using GCLP standards and cover regulations from 21 CFR Part 58 (GLP) and 42 CFR Part 493 (CLIA) and are augmented by guidelines from other organizations and accrediting bodies such as the Clinical Laboratory Standards Institute, the College of American Pathologists (CAP), and the International Organization for Standardization (ISO). The checklists take approximately two to three working days for a laboratory auditor to complete during the audit visit. The following GCLP Principles are covered, as applicable, in each document:

- External Quality Assurance
- Organization and Personnel

- Equipment
- Testing Facilities Operation
- Test and Control Articles
- Test Method Validation and Verification
- Records and Reports
- Physical Facilities
- Specimen Transport and Management
- Personnel Safety
- Laboratory Information Systems
- Quality Management

In addition, an audit of practice versus procedure (Vertical Audit) is conducted during each audit visit, where applicable. This exercise evaluates the accuracy of a particular laboratory in following their established standard operating procedure (SOP) for a particular assay that the auditor selects at the time of the visit or is requested by DAIDS. When the audit visit is completed, a report is sent to the staff on the distribution list provided by DAIDS within 21 business days. The Distribution list will include DAIDS Clinical Laboratory Oversight Team (DCLOT) members, Network/Non-Network staff and Lab QA contractor. The resolution of identified deficiencies found during the audit is then conducted between the site, DCLOT, Lab QA contractor, and the Networks/Non-Networks as appropriate.

Laboratory Audit Checklists

There are six different checklists (audit shells) that are used by CRSS laboratory auditors. All six of the checklists are similar in that they cover the same GCLP principles consistently for each facility type. This construction is in place to assist in the ongoing efforts to establish a global GCLP standard for all DAIDS-supported and/or sponsored laboratories. To that end, there are subtle differences to be noted. These differences are due to the distinct variation in the scope of services provided by each laboratory type. A summary of each audit approach is listed and found along with the corresponding checklists below.

General Laboratory

The General Laboratory Checklist was developed mainly for safety laboratories. This checklist is used globally for clinical trial site-operated, contracted, satellite, and back-up laboratories. It incorporates all of the aforementioned GCLP principles, and requires the auditor to address each principle for all testing activities supported and/or -sponsored by DAIDS. This checklist is also used for Point-of-Care (POC) audits.

PBMC Laboratory

The PBMC Laboratory Checklist is tailored specifically for processing laboratories that work with PBMC. The questions are focused on all phases of PBMC testing, with a section dedicated to evaluating the actual performance of the PBMC processing steps versus the approved SOP.

Central Laboratory

The Central Laboratory Checklist is specific for laboratories performing endpoint assays, including non-FDA approved methods. The general checklist questions, as with all the checklists, are included as applicable along with specific topics related to endpoint testing.

Specimen Repository

The Specimen Repository Checklist is unique; although all applicable GCLP principles are covered, the focus is placed on specimen tracking and storage. The auditor is required to report more comprehensively in these areas. For example, in the other laboratory checklists, 5 to 10 random specimens are required to be audited from reception to final disposition. In this checklist, 50 randomly selected specimens will undergo this type of audit.

Histology/Cytology Laboratory

This is a comprehensive checklist specific to laboratories that specialize in Histology and/or Cytology work. It is a detailed checklist that addresses all Histology and Cytology laboratory areas of activity from specimen reception, preparation, examination, results issue, and specimen storage. The equipment section provides detailed questions on all Histology/Cytology equipment used in specimen processing and slide examination.

TB/AFB

This is a comprehensive checklist specific to laboratories performing Mycobacteriology testing such as: TB microscopy, culture, identification, and susceptibility testing. The checklist addresses specialized safety requirements for facilities performing such activities. The Quality Control, Quality Management, and Equipment sections also focus on specific requirements for TB testing.

Distribution of Audit Reports and Resolution

The final version of the laboratory audit report and the audit participation certificate will be issued 21 business days from the end date of the audit to the staff on the distribution list provided by DAIDS that includes DCLOT, Network/Non-Network staff and/or Lab QA contractor). Once distributed, the DCLOT staff request assistance from Lab QA contractor in generating the Action Plan (AP) that lists the audit findings with recommendations for corrective actions. DCLOT POC submits audit report and associated AP, and audit participation certificate to Network/Non-Network staff (if applicable) to review and label AP items with one of four designations (critical, major, minor, and recommendation) per the *Terminology Criteria and Responsibilities for Reporting DAIDS GCLP Laboratory Audits or Initial Assessments* (available upon request). DCLOT POC reviews and reconciles Network/Non-Network staff AP designations, and forwards Lab audit AP, the associated audit report, and the audit participation certificate to the lab with a request to respond within a time period deemed reasonable by DCLOT. Lab QA contractor works closely with the lab to resolve AP items and sends resolution of items to key stakeholders. AP items that support lab activation must be resolved within a short period prior to study activation. Periodic updates support key stakeholder assessment of lab readiness, lab activation, and the on-going monitoring of

laboratory performance throughout the life cycle of the study. The Lab QA contractor archives Lab audit AP and audit report.

8.0 REVISION SUMMARY

- 8.1 APP-A-OD-001.00 is the initial version of Appendix I Requirements for DAIDS Supported and/or Sponsored Laboratories in Clinical Trials Policy submitted to the DAIDS QMS. There were four previous versions of this policy published on the DAIDS Clinical Research Policies webpage prior to the implementation of the DAIDS QMS in 2018. Changes from the previous version include: the removal of 1.1. CD4 Testing section, addition of 1.2. Pharmacology Section, addition of language in 2. Endpoint Tests not approved by FDA Section, that describes level of validation required for Endpoints Assays, and addition of 7. PBMC EQA Section.
- 8.2 APP-A-OD-001.01 was revised on 06/27/19 to include additional information to the version 00 Revision History to clarify changes made to the initial version of Appendix II that was inadvertently missing when the document was submitted to the QMS.

APP-A-OD-001.01 was converted to Policy DAIDS-OD-A-POL-00004 with all hyperlinks updated and Appendix 1 added.
- 8.3 DAIDS-OD-A-POL-00004 rev 01 is the first version of this policy and was created March 29, 2022. This policy is the converted appendix, APP-A-OD-001.01. With the document type conversion all hyperlinks were updated as well as the addition of Appendix 1 (section 7.1).