

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

I. SCOPE

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

II. APPENDIX

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 \(https://www.cms.gov/cmsforms/downloads/cms116.pdf\)](https://www.cms.gov/cmsforms/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 \(https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/\)](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/).

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 \(https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/\)](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/).

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

[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.

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>).

To request enrollment in VQA EQA program(s), please contact [NIAID DCLOT CORs \(NIAIDDCLOT CORs@mail.nih.gov\)](mailto:NIAID DCLOT CORs (NIAIDDCLOT CORs@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 taken into account when preparing the budget for conducting the trial.

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](#) (<https://www.buffalo.edu/tprc/section-2/CPQA.html>).

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

2. Endpoint Tests not approved by FDA

For pivotal studies that require regulatory action for approval or labeling (including tests for PK/PD), primary endpoint tests should be

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

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 III 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: [DAIDS guidelines for GCLP standards \(https://www.niaid.nih.gov/sites/default/files/gclp.pdf\)](https://www.niaid.nih.gov/sites/default/files/gclp.pdf).

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 III 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

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

assays as part of NIAID (DAIDS)- sponsored clinical trials.

Please contact [NIAID DCLOT CORs \(NIAID DCLOT CORs@nida.nih.gov\)](mailto:NIAID_DCLOT_CORs@nida.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.

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 \(https://www.niaid.nih.gov/sites/default/files/gclp.pdf\)](https://www.niaid.nih.gov/sites/default/files/gclp.pdf).

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. Please refer to the Checklist-Study Specific Management Plan [custody checklist](#) for an example and guidance on required

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

elements.

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.

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 (<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. 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

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

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](#). For information on required elements that must be included in the QMP, please refer to the [Lab Quality Management Checklist](#) as an example.

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 the [GCLP Lab Audit Information Document](#).

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

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

and report resolution processes.

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 \(NIAIDDCLOTCORs@mail.nih.gov\)](mailto:NIAIDDCLOTCORs@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.

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

Appendix I
Guidance to Investigators Participating in DAIDS-Sponsored Clinical Trials
Requirements for U.S. Laboratories

Effective Date: 09/10/19

Document No.: **APP-A-OD-001.01**

on the DAIDS Learning Management System (LMS) and can be completed at any time from any internet-accessible location. DAIDS LMS 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. This should include laboratory staff as well as study nurses and any other non-lab staff performing testing in the clinical laboratory.

The frequency of this training must be sufficient to ensure that employees remain familiar with the requirements applicable to them.

REFERENCES

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

III. REVISION HISTORY

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.

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 I that was inadvertently missing when the document was submitted to the QMS.