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1.0 PURPOSE

1.1 This document describes specific requirements for laboratories processing and testing biological samples from participants enrolled in clinical trials supported and/or -sponsored by the NIAID DAIDS in the United States (U.S.).

2.0 SCOPE

2.1 Applies to U.S. 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)**

3.1.1 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-Sponsored and/or Supported clinical trials and clinical research projects.

3.2 **DCLOT Points of Contact (POC)**

3.2.1 DCLOT members who act as points of contact for laboratory oversight for DAIDS-Sponsored and/or Supported clinical trials.

4.0 RESPONSIBILITIES

4.1 **DCLOT**

This policy has been created by DCLOT whose responsibility is to oversee the laboratory component of U.S. laboratories participating in DAIDS-Sponsored and/or Supported clinical trials. DCLOT is responsible for updating these requirements in response to changes in federal regulations and based on continued experience in the conduct of clinical trials. DCLOT, in partnership with the clinical trial network and non-network grantees and contractors, is responsible for monitoring compliance with Clinical Laboratory Improvement Amendments (CLIA) requirements and other applicable requirements and applicable standards by collecting and verifying relevant essential source documentation.

An overview of CLIA requirements can be found in the document CLIA Application for certification

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 biological samples from participants enrolled in clinical trials adhere to the laboratory requirements identified in this document, 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 and implementing the specific requirements for U.S. laboratories. Please email: DCLOT (NIAIDDCLOT@niaid.nih.gov) for enquiries.

5.0 REQUIREMENTS

All laboratories in the United States that perform any test on material derived from the human body to assess health, or to diagnose, prevent or treat disease must meet the federal standards of the 1988 Clinical Laboratory Improvement Amendments (CLIA) (42 USC 263a) and the associated regulations (42 CFR 493). Laboratories must be certified under the CLIA program before they can accept human samples for testing and must maintain their accreditation under the CLIA program.

This document describes the specific requirements for U.S. laboratories involved in DAIDS-Sponsored and/or Supported clinical trials in regards to; 5.1) Laboratory tests for participant management; 5.2) Instrument and Method Validation; 5.3) Study Endpoint Tests; 5.4) Specimen Management Plan; 5.5) Laboratory Data management plan; 5.6) Laboratory Quality Management Plan; 5.7) Laboratory Auditing; 5.8) Peripheral Blood Mononuclear cells (PBMC) Proficiency Assessment and; 5.9) GCLP Training.

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

Laboratory tests to be used in clinical trials are described in the study protocol. Tests that are used for diagnosis, determining enrollment eligibility, monitoring the safety of the intervention, and making participant care management decisions 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. The FDA defines a LDT as an in vitro diagnostic test that is manufactured by and used within a single laboratory (i.e., a laboratory with a single CLIA certificate). See the FDA amended policy on LDTs by visiting: https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests#historical.

5.1.1 HIV Virology

Laboratories that perform HIV DNA or total nucleic acid (TNA) PCR or HIV genotypic drug resistance testing must be CLIA certified and may be required to participate in the DAIDS Virology Quality Assessment (VQA) program. 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

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

For laboratories performing testing for DAIDS-Sponsored and/or Supported 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. If a pharmacology outcome is an endpoint of the study, the testing laboratory may be required to participate in the DAIDS Clinical Pharmacology Quality Assurance (CPQA) program.

For information on laboratories that participate in the CPQA program, please contact NIAID DCLOT CORs (NIAIDDCLOTCORs@mail.nih.gov).

5.2 Instrument and Method Validation

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. If non-approved methods are considered, these should be validated in a study that compares a proposed method to an FDA-approved method if available. For information on guidelines for conducting a validation study refer to the DAIDS guidelines for GCLP standards.

5.3 Study Endpoint Tests

A study endpoint is the targeted outcome of a clinical trial that is statistically analyzed to help determine the immunogenicity, efficacy, and safety of the intervention being studied. Studies may use multiple endpoints, which are defined and described in the study protocol.

5.3.1 Investigational Use Only (IUO) and Research Use Only (RUO) Tests

Investigational Use Only (IUO) products are in vitro diagnostic (IVD) products being shipped or delivered for product testing prior to full commercial marketing. Research Use Only (RUO) products are in vitro diagnostic products that are in the laboratory phase of development. See FDA-2011-D-0305. 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 iteration or perform basic scientific research and are not considered to be effective diagnostic tools. See Appendix I in DAIDS-OD-A-POL-0002, the Algorithm for determining level of assay verification for endpoint IOU and ROU tests. Tests described in section 5.1 must be used in making medical treatment decisions during clinical studies assessing IUO and RUO tests and testing systems.

Where possible, External Quality Assurance (EQA) should be applied to such tests. DAIDS has established an EQA program, EQAPOL, for laboratories performing immunogenicity assays as part of DAIDS-Sponsored and/or Supported clinical trials. Please contact NIAID DCLOT CORs (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.

5.4 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.

5.5 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), computerized laboratory systems should be validated and compliant with 21 CFR Part 11.

If applicable, these systems must comply with the DAIDS Electronic Information Systems (EIS) policy which provides guidance and recommendations regarding the use of electronic information systems in clinical research trials supported and/or -sponsored by the NIAID (DAIDS).

5.6 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 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.

5.7 Laboratory Auditing

U.S. laboratories that fall under CLIA regulations are not required to undergo DAIDS GCLP audits. However, DAIDS reserves the right to conduct for-cause or ad-hoc audits at any of the U.S. laboratories participating DAIDS-Sponsored and/or Supported clinical trials.

For the types of audits performed and the report resolution process please refer to **Appendix II in the DAIDS-OD-A-POL-00002**. Please email DAIDS Clinical Laboratory Oversight Team (NIAIDDCLOT@niaid.nih.gov) for inquiries about the DAIDS GCLP audit and report resolution processes.

5.8 Peripheral blood mononuclear cells (PBMC) Proficiency Assessment:

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

For laboratories performing testing for DAIDS-Sponsored and/or Supported clinical trials, there is no fee for participating in the IQA program. However, laboratories are responsible for the cost of shipping samples for evaluation to IQA. These costs should be considered when preparing the budget for conducting the trial.

Please contact NIAID DCLOT CORs (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.

5.9 GCLP Training

DAIDS GCLP training is not required for clinical laboratory personnel in the U.S. laboratories under CLIA regulations. For U.S. personnel in specimen processing and endpoints laboratories, GCLP training is highly recommended. Refer to GCLP guidelines and associated FAQs for more detail on requirements.

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 for DAIDS-Sponsored and/or Supported clinical trial sites. Information on GCLP eLearning modules.

6.0 REFERENCES

6.1 U.S. Food and Drug Administration, Guidance for industry: bioanalytical method validation, 2018.

6.2 FDA-2011-D-0305

7.0 APPENDICES

Not applicable

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).

8.4 DAIDS-OD-A-POL-00004 rev 02 is the second version of this policy. Document changes include title change, updated weblinks, modified definitions, updated description of responsibilities, streamlined language in all sections to reflect current requirements, and removal of Appendix I.