Table of Contents

1.0 PURPOSE 2
2.0 SCOPE 2
3.0 DEFINITIONS 2
4.0 RESPONSIBILITIES 2
5.0 POLICY 2
6.0 REFERENCES 5
7.0 APPENDICES 6
8.0 REVISION SUMMARY 10

1.0 PURPOSE

1.1 The National Institute of Allergy and Infectious Diseases (NIAID), Division of Acquired Immunodeficiency Syndrome (DAIDS), has established specific requirements for laboratories processing and testing biological samples from participants enrolled in NIAID DAIDS - Sponsored and/or Supported clinical trials. These requirements relate to general laboratory operations, quality assurance and quality control procedures, management of specimens, and management of laboratory data. The purpose of this policy is to ensure the reliability and validity of all laboratory measurements made to determine eligibility, identify and manage adverse events, and assess outcomes during the course of the clinical trial and to safeguard participants enrolled in clinical trials and individuals who perform laboratory testing.

2.0 SCOPE

2.1 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 non-network clinical trial is conducted by a Principal Investigator of a NIAID supported grant and/or Investigator of Record (IoR).

3.0 DEFINITIONS

For additional definitions, see DAIDS glossary

4.0 RESPONSIBILITIES

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

This policy, and the associated policies with specific requirements for U.S. and non-U.S. laboratories, have been created by DCLOT whose responsibility is to oversee the laboratory component of DAIDS-Sponsored and/or Supported 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)**

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 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

This policy aligns with the DAIDS laboratory oversight framework for monitoring laboratories participating in DAIDS-Sponsored and/or Supported clinical trials that require laboratory oversight to ensure compliance of laboratories with the Code of Federal Regulations (CFR) and the DAIDS Good Clinical Laboratory Practice (GCLP) Guidelines.

5.1 The DAIDS GCLP concept possesses a unique quality, as it embraces both the research/pre-clinical and clinical aspects of Good Laboratory Practice (GLP). DAIDS GCLP Guidelines encompass applicable portions of 21 CFR part 58 or GLP, and 42 CFR part 493, or Clinical Laboratory Improvement Amendments (CLIA), and enhanced by standards from accrediting bodies such as the College of American Pathologists (CAP), South African National Accreditation System (SANAS) and International Organization for Standardization (ISO). Compliance to these regulations and standards promote good laboratory practices, reliable and reproducible laboratory results and documentation/records, and ensure that laboratory data and results will be acceptable to regulatory agencies (e.g. Food and Drug Administration (FDA) and European Medicines Agency (EMA).

5.2 DAIDS-Sponsored and/or Supported clinical trials must be conducted in a manner to assure the sponsor, and regulatory agencies, that all data submitted are a true reflection of the results obtained during a study, and that this data can be relied upon when making risk, safety, or advancement assessments of study products.

5.3 In addition to maintaining operations in compliance with GCLP Guidelines, DAIDS has established, and maintains, specific requirements for laboratory performance in five areas.

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

Tests that are used for diagnosis, determining eligibility, monitoring the safety of the intervention, and making participant management decisions, should be performed in laboratories that conduct operations in accordance with GCLP Guidelines. These tests should be quality assured by External Quality Assurance (EQA) surveys. When commercial or standard EQA is not available, alternative EQA plans should be devised and proposed to DAIDS for approval. U.S. laboratories must be Clinical Laboratory Improvement Amendments (CLIA) -certified or waived as appropriate for certain testing.

5.3.2 **Study Endpoint Tests**

A primary endpoint establishes the effects of the intervention. These are the basis for concluding that the study meets its objective and will be the main data evaluated for future decision making and/or regulatory approval. A secondary end point may extend understanding of an effect related to the primary endpoint or provide evidence of a distinct clinical benefit. An Exploratory endpoint maybe included to explore new hypotheses.

Primary endpoint tests should be documented as fit-for-purpose. If the purpose is to submit to a regulatory agency for decision making, then full validation may be required according to FDA Guidance on Biomedical Method Validation. If the purpose is exploratory and the data would not be submitted for decision-making, then optimized or qualified assays demonstrating the desired results (i.e. it is fit-for-purpose) may be sufficient. See **Appendix I** DCLOT Algorithm for Determining Level of Validation Required for Endpoints Assays. EQA should be applied to primary study endpoint tests. If existing EQA surveys are not available, a suitable form of alternative EQA should be devised and proposed to DAIDS for approval.

5.3.3 Specimen Management

Procedures for the management of trial specimens must be documented and followed to ensure the integrity of specimens and their timely testing. Procedures must address specimen acquisition, receipt, processing, testing, storage, and shipping according to regulations (e.g. International Air Transport Association (IATA)) and under conditions that preserve specimen integrity (e.g. maintaining the cold chain) and tracking as applicable.

5.3.4 Laboratory Data Management

Procedures for the management of laboratory data must be documented and followed to ensure data integrity and timely reporting of results and are required to include appropriate procedures for data quality assurance (QA) and corrective actions. Procedures should address data acquisition, recording/entry, data modification, signatures, export, archiving and security, as well as integration of the laboratory data with the main study database.

Computerized laboratory systems should be validated and compliant with 21 CFR Part 11**.**

5.3.5 Laboratory Quality Management Plan

Laboratories must have a documented Quality Management Plan (QMP) that describes the overall quality management program of the laboratory. For additional information please refer to the DAIDS GCLP Guidelines. DAIDS recommends laboratories designate a senior staff member to be responsible for executing the laboratory QMP.

5.4 DAIDS Laboratory Oversight Framework

DAIDS Laboratory Oversight framework involves four key components, namely: QA oversight, GCLP Audit, GCLP Training, and Lab Quality Improvement. The oversight framework is guided by the GCLP Guidelines, and other applicable regulatory guidelines and requirements. Laboratories performing testing for clinical trials should maintain satisfactory performance in all applicable aspects of the lab oversight framework activities

5.4.1 QA oversight

The DCLOT representatives work closely with DAIDS external laboratory partners to oversee quality assurance performance in compliance with GCLP Guidelines.

5.4.2 GCLP Audit

Laboratories participating in NIAID DAIDS-Sponsored and/or Supported clinical trials may be subject to DAIDS GCLP audits in accordance with the GCLP Guidelines. The audit activities involve three phases, namely: pre-audit, audit, and post-audit. The pre-audit phase involves activities related to the planning and scheduling of GCLP audits. The audit phase involves on-site or remote activities and assessment of GCLP compliance of the laboratories. The post-audit phase involves activities related to the review and resolution of GCLP audit reports.

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 satisfactory performance standards.

For the types of audits performed and the report resolution process please refer to **Appendix II**. Please email DAIDS Clinical Laboratory Oversight Team (NIAIDDCLOT@niaid.nih.gov) for inquiries about the DAIDS-sponsored GCLP audit and report resolution processes. Refer to specific requirements for U.S. and non-U.S. laboratories.

5.4.3 GCLP Training

DAIDS GCLP Training component involves the online and face-to-face formats. The DAIDS GCLP online training is offered through GCLP eLearning modules available on the DAIDS Learning Portal. DAIDS face-to-face GCLP training is offered on an as needed basis, with DCLOT approval, based on lab quality performance and improvement outcomes. Refer to specific requirements for U.S. and non-U.S. laboratories.

Laboratory management should ensure that training frequency is sufficient to ensure that personnel remain familiar with the GCLP requirements applicable to them. For additional information, please refer to the DAIDS GCLP Training Related FAQs .

5.4.4 Lab Quality Improvement

DAIDS Laboratory Quality Improvement component involves activities to assess the overall quality improvement of laboratories participating in DAIDS-Sponsored and/or Supported clinical trials. DCLOT, with support from DAIDS laboratory partners and in alignment with GCLP Guidelines, monitor lab performance throughout the life cycle of the clinical trial.

6.0 REFERENCES

6.1 U.S. Code of Federal Regulations, Title 21, Parts 11 and 58

6.2 U.S. Code of Federal Regulations, Title 42 CFR Part 493

6.3 CLIA Program – Clinical Laboratory Improvement Amendments

6.4 International Air Transport Association (IATA) Dangerous Goods Shipping Regulations

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

6.6 DAIDS GCLP Guidelines

7.0 APPENDICES

7.1 Appendix I: DCLOT Algorithm for Determining Level of Validation Required for Endpoints Assays

7.1.1 SCOPE

Applies to any laboratory developed test (LDT) used for endpoint determination that may be submitted to the FDA in support of licensure or used to advance a product to subsequent clinical trial phases.

7.1.2 Notes on the use of this algorithm:

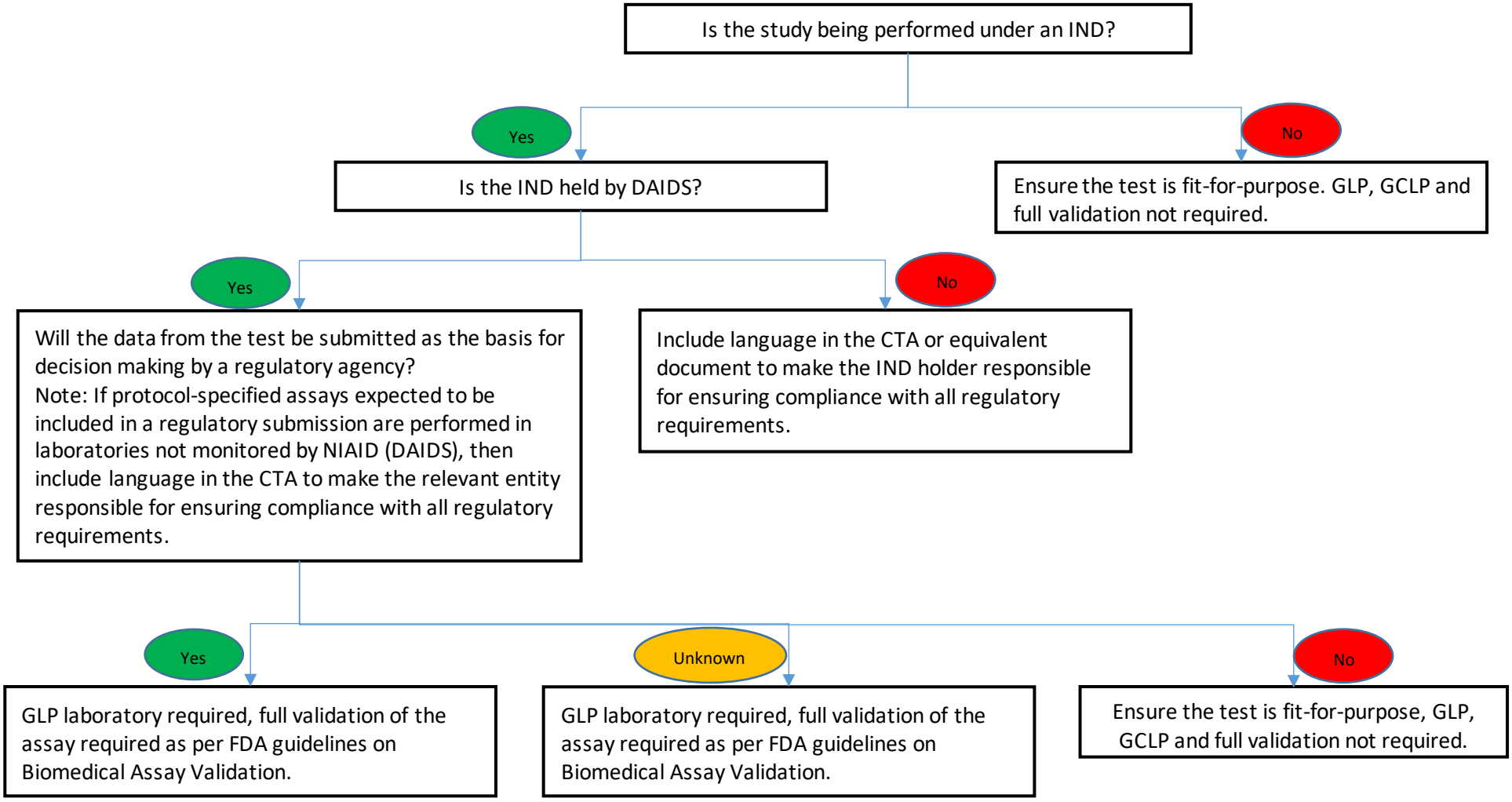
7.1.2.1 This algorithm is separate from CLIA certification or GCLP compliance of a laboratory. If CLIA or GCLP is required for testing, the laboratories would also need to be in compliance with those requirements in addition to the requirements described in the algorithm.

7.1.2.2 In the "fit-for-purpose" concept, the required performance characteristics of the assay are first determined for the study. Will the assay need to be qualitative or quantitative? Are positivity criteria developed for a qualitative assay? If quantitative, what range is needed? What level of precision is needed for the study? Is there a "gold standard" assay that measures the same analyte for assessing accuracy? What level of sensitivity and specificity? After the required performance characteristics are determined and pass/fail criteria set, the assay is performed with controls to confirm whether the assay meets pre-specified criteria. If one or more of the assay parameters do not meet the acceptance criteria, the assay cannot be accepted as fit-for-purpose and cannot be used for testing clinical trial samples. Additional assay optimization work is required so the assay meets all acceptance criteria before being used to test clinical trial samples.

7.1.2.3 The algorithm employs the "fit-for-purpose" concept which means:

- The level of validation should be appropriate for the intended purpose of the study.

- If data from the assay in question will be submitted to a regulatory agency for decision making for approval, safety, or labeling, then full validation is required according to the FDA Guidance on Biomedical Method Validation.
- If the endpoint is considered exploratory and the data would not be submitted for decision-making, then less stringent approaches (standardization or qualification) demonstrating that the assay can provide the desired results (i.e., it is fit-for-purpose) may be sufficient.
- For exploratory research, the methods should be documented to be fit-for purpose, since the LDT are being used to evaluate responses to interventions given to research participants, which may expose the participants to some level of risk.
- The final report should include data on the sensitivity and specificity of qualitative methods, and data on the accuracy, precision, linear range, sensitivity, and specificity of quantitative methods. The report must be signed by the lab director and kept at the lab and provided to the trial sponsor if requested.


Is the study being performed under an IND?
Yes
No
Is the IND held by DAIDS?
Ensure the test is fit-for-purpose. GLP, GCLP and full validation not required.
Yes
No
Will the data from the test be submitted as the basis for decision making by a regulatory agency?
Note: If protocol-specified assays expected to be included in a regulatory submission are performed in laboratories not monitored by NIAID (DAIDS), then include language in the CTA to make the relevant entity responsible for ensuring compliance with all regulatory requirements.
Include language in the CTA or equivalent document to make the IND holder responsible for ensuring compliance with all regulatory requirements.
Yes
Unknown
No
GLP laboratory required, full validation of the assay required as per FDA guidelines on Biomedical Assay Validation.
GLP laboratory required, full validation of the assay required as per FDA guidelines on Biomedical Assay Validation.
Ensure the test is fit-for-purpose, GLP, GCLP and full validation not required.

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

The CRSS Team is contracted by the Division of AIDS (DAIDS) to perform laboratory audits for Good Clinical Laboratory Practice (GCLP) compliance throughout the world.

The types of audits performed by CRSS include General Laboratory, Central/Endpoint Laboratory, Peripheral Blood Mononuclear Cell (PBMC) Processing 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. The laboratory is required to resolve identified deficiencies found during the audit.

7.2.1 Laboratory Audit Checks

Various checklists (audit shells) used by CRSS laboratory auditors consistently cover the same GCLP principles for each facility type. This construction is in place to assist in the ongoing efforts to establish a global GCLP standard for all DAIDS-Sponsored and/or Supported 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 the audit approach for some of the audit shells is described below.

7.2.2 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 the 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.

7.2.3 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.

7.2.4 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.

7.2.5 Specimen Repository

The Specimen Repository Checklist is unique; the focus is placed on specimen tracking and storage.

8.0 REVISION SUMMARY

8.1 POL-A-OD-002.01 is the initial version of 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.

8.2 DAIDS-OD-POL-00002 rev 01 is the first revision of this procedure within the electronic Quality Management System. The document format and document numbering have been updated to reflect current requirements. The web links have been updated as well as the inclusion of Appendix 1 as this was previously a separate document.

8.3 DAIDS-OD-POL-00002 rev 02 is the second revision of this procedure within the electronic Quality Management System. The document scope and web links have been updated, and the phrase 'DAIDS GCLP standards' has been corrected to 'DAIDS GCLP Guidelines'.

8.4 DAIDS-OD-POL-00002 rev 03 is the third revision of this procedure within the electronic Quality Management System. Changes include updated scope and web links, added Appendix II, “Laboratory Audits Conducted by NIAID HIV and Other Infectious Diseases Clinical Research Support Services (CRSS) Contractor”, removed definition section, revised the language in several sections to eliminate redundancy to align with associated documents describing U.S. and non-U.S. requirements.