

DAIDS

Bethesda,MD USA

ARCHIVED APPENDIX I

Guidance to Investigators Participating in DAIDS-Supported and/or -Sponsored Clinical Trials

This document outlines the DAIDS laboratory-related requirements and deliverables for U.S. laboratories.

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 \(link is external\)](#)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 \(link is external\)](#).

Laboratory Safety, Diagnosis, and Food and Drug Administration (FDA)-Approved Primary Endpoint Tests

Tests that are used for diagnosis (e.g., HIV, CMV, HSV, Syphilis), determining eligibility (e.g., pregnancy test), monitoring the safety of the intervention (e.g., hematology, chemistry), making patient management decisions (e.g., CD4, viral load, drug levels), must be performed in laboratories that are [CLIA certified \(link is external\)](#) or have a CLIA waiver.

These tests (unless CLIA waived) must be quality assured by CLIA approved Proficiency Testing (PT) providers, such as the College of American Pathologists (CAP). See: [A list of CLIA Approved PT providers \(link is external\)](#)pdf.

1.1. CD4 Testing

CD4 determinations should be done using standard flow cytometric measurements, or protocol-mandated technology. Consideration should be given to the Centers for Disease Control and Prevention (CDC) guidelines that describe dual-platform technology - [Morbidity and Mortality Weekly Report \(MMWR\) 1997;46 \(No. RR-2\) \(link is external\)](#), or single-platform technology – [MMWR 2003; 52\(RR-02\) \(link is external\)](#).

If CD4 is a primary endpoint of a proposed trial, in addition to being CLIA-certified, it is recommended that the laboratory that performs CD4 testing participate in the DAIDS Immunology Quality Assessment (IQA) CD4 proficiency testing (PT) program. [Information about the IQA CD4 PT program \(link is external\)](#) .

Enrollment in this program will have to be requested from DAIDS. There is no fee for participating in the IQA CD4 PT program or for receiving assistance from the IQA. However, laboratories are responsible for the cost of test kits/reagents used to test the proficiency panels. These costs should be taken into account when preparing the budget for conducting the trial.

Please contact [Daniella Livnat \(link is external\)](#) to discuss.

If HIV viral load, HIV DNA 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). [More information about this program \(link is external\)](#).

To request enrollment in VQA PT program(s), please contact [Joe Fitzgibbon \(link is external\)](#). The process of achieving certification takes at least 5 months.

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

Non-FDA Approved End Point Tests

This section covers all research tests not approved by FDA nor validated by International Conference on Harmonisation (ICH) or US Pharmacopeia. Generally, the endpoint tests should be performed in laboratories that conduct operations in accordance with Good Clinical Laboratory Practices (GCLP).

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 toward 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.pdf](#).

This guidance document is provided to define the standards that encompass GCLP which include applicable portions of 21 Code of Federal Regulations (CFR) part 58, or GLP, and 42 CFR part 493, or CLIA rules. Due to the ambiguity of some parts of these regulations, these GCLP standards also include guidance from accrediting bodies such as the College of American Pathologists (CAP), and other agencies with deemed status and ISO 15189 Certification, e.g. South African National Accreditation System.

2.1. Investigational Use Only

Endpoint tests, such as new non-FDA approved 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 patients without confirmation by other medically established procedures. There is no existing DAIDS-supported Proficiency Testing Program for these tests, therefore, a suitable form of alternative proficiency assessments should be devised and proposed to DAIDS for approval. IRB review (21 CFR part 56) and human subjects regulations (21 CFR parts 50) apply.

2.2. Research Use Only (RUO)

RUO assays, such as Enzyme-linked Immunosorbent Spot (ELISPOT) and Intracellular Cytokine Staining (ICS), are intended to be used for performing product advancement or basic scientific research, are not considered to be effective diagnostic tools and must be appropriately labeled "for Research Use Only, Not for use in diagnostic procedures". External Quality Assurance should be applied to such tests. DAIDS has established an external quality assurance (EQA) program,

[EQAPOL \(link is external\)](#) , for laboratories performing immunogenicity assays as part of NIAID (DAIDS)-supported and/or -sponsored clinical trials.

Please contact [Jim Lane \(link is external\)](#) for more information on EQAPOL.

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

2.3. Instrument and Method Validation

DAIDS requires laboratories to perform validation prior to placing a new method or instrument into routine use, whenever the conditions change for which the method has been validated or if the change is outside the original scope of the method. If non-approved methods are considered, these should be validated in a study that compares a proposed method to a FDA-approved method. For information on guidelines for conducting a validation study refer to [DAIDS guidelines for GCLP standardspdf](#).

Study specific-Specimen Management Plan

Procedures for the management of trial specimens must be documented and followed to ensure the integrity of specimens and their timely testing. Each study should have a specimen management plan that describes study specific sample acquisition, recording, testing, storing and shipping; 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 study/Network Manual of Operations and/or in study protocol appendices. Please refer to the [SOP Checklist-Study Specific Management Plan](#) doc for an example and guidance on required elements.

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

Study Specific-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.

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 \(link is external\)](#) for Investigational New Drug (IND)-enabling studies. For non-IND studies, computerized laboratory systems should be validated and the elements of 21 CFR Part 11 should be taken into consideration.

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 supported and/or -sponsored by the NIAID (DAIDS) 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 patient 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](#)pdf. For information on required elements that must be included in the QMP, please refer to the [Lab Quality Management Checklist](#)doc as an example.

GCLP Training

An interactive GCLP training, sponsored by the DAIDS and delivered by online and face to face methods, is intended to give participants an introduction to GCLP and their relation 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 assuring 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 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)-supported and/or -sponsored clinical research sites. Information on [GCLP eLearning modules \(link is external\)](#).

At this time, GCLP training is not a DAIDS requirement. However, it is recommended that laboratory personnel receive training in GCLP. The frequency of this training must be sufficient to ensure that employees remain familiar with the GCLP requirements applicable to them.

Laboratory-Specific Auditing

DAIDS and/or its contractors may conduct laboratory-specific audit visits to determine GCLP compliance. 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.

DAIDS reserves the right to conduct for-cause or ad-hoc audits at any of the U.S. laboratories participating NIAID (DAIDS)-supported and/or -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/non-Network, 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](#)pdf.

Please note that DAIDS is not an accreditation body and does not issue GCLP certificates.

Please email [DAIDS Clinical Laboratory Oversight Team \(DCLOT\)](#) (link sends e-mail) for enquiries about the DAIDS-sponsored GCLP audit and report resolution processes.

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