

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

I. SCOPE

This appendix applies to non-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 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

Clinical laboratories must conduct operations in accordance with DAIDS 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, as well as ensure the safety of the research subjects and those who perform the laboratory testing.

These GCLP standards must be applied to all clinical laboratories performing testing for clinical trials sponsored by the DAIDS. Institutions must also meet sponsor-specific requirements as outlined in the Sponsor Statement section of the GCLP standards document.

Accreditation by CAP or an equivalent in-country accrediting body that meets ISO 15189:2012 Standards is recommended.

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

Tests that are used for diagnosis (e.g., HIV, TB, Syphilis, HSV), determining enrollment eligibility (e.g., pregnancy test), monitoring the safety of the intervention (e.g. hematology, chemistry), or making participant management decisions (e.g.,

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

Effective Date: 09/10/19

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CD4 cell count, HIV viral load), should be performed in laboratories that conduct operations in accordance with GCLP.

These tests (including CLIA waived tests) should be quality assured by DAIDS-approved external quality assurance (EQA) providers, such as the CAP or equivalent provider. When commercial or standard EQA is not available, alternative EQA plan should be devised and proposed to DAIDS for approval. DAIDS and/or DAIDS contractors will verify participation and successful performance of the laboratory in the various EQA programs.

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 \(No. RR-2\)](#), or single- platform technology - [MMWR2003; 52\(RR-02\)](#).

The CD4 laboratory should successfully participate in the CD4 EQA program administered by the United Kingdom National External Quality Assessment Service (UKNEQAS) and must be responsive to the trouble-shooting and assistance efforts by the [DAIDS Immunology Quality Assessment \(IQA https://iga.center.duke.edu/programs/cd4\)](#) contract. (See Information about the [UKNEQAS CD4 EQA](#) program). The CD4 laboratory will have to pass at least one round of EQA before testing study subjects. Each NIAID DAIDS sponsored network may have additional requirements.

Enrollment in this program will have to be requested from DAIDS. The cost of participation may be borne by DAIDS or by the laboratory. There is no fee for receiving assistance from the DAIDS IQA. Laboratories are responsible for the cost of test kits/reagents used to test the EQA panels and these too should be taken into account when preparing the budget for conducting the trial.

To request enrollment in the CD4 EQA program, please email [NIAID DCLOT CORs](mailto:NIAIDDCLOTCORs@mail.nih.gov)

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

1.2. HIV Virology

The use of FDA-approved methods is strongly encouraged. Laboratories performing HIV viral load tests, HIV DNA or total nucleic acid (TNA) PCR and HIV genotypic drug resistance testing should 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 \(NIAIDDCLOT CORs@mail.nih.gov\)](mailto: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.

1.3. Pharmacology

If pharmacology results will be used for participant management decisions during the trial, the pharmacology laboratory must operate under GCLP. Most of this testing will be performed using validated laboratory developed tests (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) (<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:NIAIDDCLOT CORs@mail.nih.gov).

1.4. Other tests

Different providers of EQA surveys send samples at different frequencies (e.g. most CAP surveys are sent three times a year). The laboratory should successfully pass at least one round of EQA for each clinical trial analyte and satisfy all other Network/ non-Network specific requirements before starting the trial. EQA results from safety, eligibility, and diagnostic tests will be reviewed by the DAIDS contractors and/or Network/non-Network laboratory managers. The laboratory will also receive assistance and instructions for corrective actions from DAIDS contractors and/or Network/

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

non-Network lab managers.

The cost of participation in EQA programs (buying, shipping and testing EQA panels) may be borne by DAIDS or may have to be included in the grant application. Please email [NIAID DCLOT CORs \(NIAIDDCLOT CORs@mail.nih.gov\)](mailto:NIAIDDCLOT CORs@mail.nih.gov).

2. End Point Tests not approved by FDA

Endpoint tests are performed for investigational or research purposes only and are not used for the diagnosis, treatment or management of trial participants. For pivotal 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 GCLP. See Appendix III DCLOT Algorithm for Determining Level of Validation Required for Endpoints Assays.

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, 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 email [NIAID DCLOT CORs](mailto:NIAID DCLOT CORs@mail.nih.gov) NIAIDDCLOT CORs@mail.nih.gov for more information on EQAPOL.

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

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.

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, processing, 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 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 data 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

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

(LIMS) or a laboratory data management system, computerized laboratory systems should be validated and compliant with [21 CFR Part 11](#).

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 operations.

All laboratories performing testing that supports a clinical trial sponsored by 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,

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

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

After a DAIDS audit, performed by DAIDS and/or its contractor, an audit report will be distributed to the laboratory. The laboratory is responsible for working with DAIDS and/or its contractor, 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 [DAIDS Clinical Laboratory Oversight Team](#) (NIAIDCLOT@niaid.nih.gov) for enquiries about the DAIDS-sponsored GCLP audit and report resolution processes.

7. 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 routine 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 an FDA- approved method if available. DAIDS and/or contractors can provide assistance in designing and reviewing validation studies.

For information on guidelines for conducting a validation study refer to the [GCLP standards/guidelines document](#) (<https://www.niaid.nih.gov/sites/default/files/gclp.pdf>).

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

8. 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.

9. 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.

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

Effective Date: 09/10/19

Document No.: **APP-A-OD-002.01**

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)- sponsored clinical research sites. Information on [GCLP eLearning modules \(https://daidslearningportal.niaid.nih.gov/\)](https://daidslearningportal.niaid.nih.gov/).

All clinical laboratory staff involved in specimen processing and testing must 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.

III. REFERENCES

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

IV. REVISION HISTORY

APP-A15-OPC-002.00 is the initial version of Appendix II 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 addition of 1.3. 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 8. PBMC EQA Section and requirement for GCLP training for all clinical laboratory staff involved in specimen processing and testing in 9. GCLP Training Section.

APP-A15-OPC-002.01 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.