DAIDS Requirements for Non-U.S. Laboratories Guidance to Investigators Applying for Funding to Conduct HIV/AIDS Clinical Trials

This document outlines the Division of Acquired Immunodeficiency Syndrome (DAIDS) laboratory-related requirements and deliverables to be included in a Comprehensive Laboratory Plan.

1.0 Diagnosis, safety tests, CD4 and Virological tests, and Primary endpoints

Tests that are used for diagnosis (e.g., HIV, TB, Syphilis, HSV), 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), or as primary study endpoints must be performed in laboratories that are conducting operations in a Good Clinical Laboratory Practice (GCLP) manner. Tests must be quality assured by external proficiency testing surveys provided by the College of American Pathologists (CAP) or equivalent, and the use of U.S. Food and Drug Administration (FDA) (or equivalent)-approved methodologies is strongly encouraged. If non-approved methods are considered, these must be validated in a study that compares a proposed methods to a FDA (or equivalent)-approved one. Guidelines for conducting a validation study are described in Section 5. Method Validation, courtesy of the HIV Prevention Trials Network (HPTN) and Microbicide Trials Network (MTN):

http://www.hptn.org/web%20documents/CentralLab/HPTN-MTNLABMANUALVersion1.0.pdf

Laboratories should be conducting operations in a Good Clinical Laboratory Practice (GCLP) manner. Guidelines for GCLP are described in the Good Clinical Laboratory Practices document and include the following topics:

Overview of Good Clinical Laboratory Practice (GCLP)
Organization and Personnel
Facilities and Personnel
Records and Reports
Testing Facility and Operation
Specimen Management and Tracking
Verification of Performance Specification
Laboratory Safety
Laboratory Information Systems
Quality Management Systems

The training of laboratory staff in the principles of GCLP is strongly encouraged. For information about DAIDS-sponsored GCLP training workshops, please contact Janice Darden at jdarden@niaid.nih.gov.

Accreditation by Clinical Laboratory Improvement Amendments (CLIA) (http://www.cms.hhs.gov/clia/) or an equivalent in-country organization, e.g., South African National Accreditation System (SANAS) (http://www.sanas.co.za/) is highly recommended.

A. CD4 testing

CD4 determinations must be done using standard flow cytometric measurements, and consideration should be given to Centers for Disease Control and Prevention (CDC) guidelines that describe dual-platform technology – Morbidity and Mortality Weekly Report (MMWR) 1997;46 (No. RR-2), http://www.cdc.gov/mmwr/preview/mmwrhtml/00045580.htm or single-platform technology - MMWR 2003;52(RR-02), http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5202a1.htm.

The CD4 laboratory must successfully participate in the CD4 proficiency testing (PT) program administered by the United Kingdom (UK) National External Quality Assessment Service (NEQAS) and must be responsive to the trouble-shooting and assistance efforts by the DAIDS Immunology Quality Assessment (IQA) contract. Information about the UK NEQAS CD4 PT program can be found at www.ukneqasli.org. Enrollment in this program will have to be requested from DAIDS. Please contact Daniella Livnat at 301 435 3775 or email to dlivnat@niaid.nih.gov. Proficiency testing samples are sent every two months, beginning with January. The CD4 laboratory will have to pass at least one round of PT before testing study subjects.

Annual cost of participation is approximately $400 (U.S.) when all forms and results are returned by the web, and approximately $450 (U.S.) if returned by mail or fax. There is an additional $130 (U.S.) annual cost for shipping the PT samples from the UK NEQAS to the laboratory by courier (TNT/DHL). These costs should be taken into account when preparing the budget for conducting the trial. 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 proficiency panels and these too should be taken into account when preparing the budget for conducting the trial.

B. HIV Virology

The use of FDA-approved methods is strongly encouraged. Consensus virological methods can be found at: http://aactg.s-3.com/labmanual.htm.

Laboratories performing HIV viral load tests, HIV DNA PCR and HIV genotypic drug resistance testing must participate in the DAIDS Virology Quality Assessment (VQA) program. More information about this program may be found at: http://aactg.s-3.com/vqa.htm.

To request enrollment in VQA PT program(s), please contact Joe Fitzgibbon at 301 451 2738 or email to jfitzgibbon@niaid.nih.gov. For HIV viral load certification, the

laboratory is required to successfully complete testing of an initial panel of 20 coded samples and two subsequent five-sample panels. The process of achieving certification takes at least five months.

There is no fee for participating in this 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.

C. Other tests

Tests must be monitored by external proficiency testing (PT) surveys provided by the College of American Pathologists (CAP) or equivalent. Non-CAP providers of PT panels must be reviewed and approved by DAIDS. To check on the suitability of non-CAP PT providers, please contact Daniella Livnat at 301 435 3775 or email to dlivnat@niaid.nih.gov.

Different providers of PT surveys send samples at different frequencies. Most CAP surveys are sent three times a year. The laboratory will have to successfully pass at least one round of PT for each test. PT results (raw data) will have to be sent to a DAIDS contractor – SMILE (patient Safety Monitoring in International Laboratories) - for review. The laboratory will receive assistance and instructions for corrective actions from SMILE. For instructions to submit PT results please contact Daniella Livnat at 301 435 3775 or email to dlivnat@niaid.nih.gov.

The laboratory will have to successfully complete two rounds of PT before testing study subjects.

The cost of participation in PT programs (buying, shipping and testing PT panels) should be taken into account when preparing the budget for conducting the trial.

DAIDS will verify participation and successful performance of the laboratory in the various PT programs.

Each participating laboratory must have the following Standard Operating Procedures (SOPs). (The attached documents provide the elements that should be included):

- Tests to be employed in the trial in a format that includes information about test principle, specimen requirements, reagents, supplies and equipment, procedure, calculations, quality control, procedural notes and references
- Bio-Safety (biohazard, occupational, chemical):

  http://www3.niaid.nih.gov/NR/rdonlyres/BD30CC5A-9FC7-4962-9AE0-48DC88D1E3EC/0/ChemBiohazardSOPElements.doc
- Instrument operation, calibration, maintenance and validation:

http://www3.niaid.nih.gov/NR/rdonlyres/6CF731F6-629A-460D-94FF-A3172D4DC778/0/EquipmentSOPElements.doc

- General specimen management (collection, receipt, processing, testing, shipping and tracking):

  http://www3.niaid.nih.gov/NR/rdonlyres/4696CACF-7A99-45D3-A436-B3A345D6FBCE/0/SpecimenMgmntSOPElements.doc

- General data management (description of computerized systems, data acquisition, recording/entry, modification, signatures, export, archiving, security, and integration into the study database):

  http://www3.niaid.nih.gov/NR/rdonlyres/8A5F0FBE-5FBE-49A1-B251-8E84B128F0FE/0/LabDataMgmntSOPElements.doc

- Laboratory quality assurance (QA) plan/manual to regularly review all components of laboratory activities, including intervention and corrective action plan, and plans for backup testing facilities. The elements of the laboratory QA plan are described in the attached document:

  http://www3.niaid.nih.gov/NR/rdonlyres/6AFF42D5-58BB-4A79-BF52-78AE156FEB2C/0/ElementsOfQMPlan.doc

For requirements described in Section I above, please include the following in the Comprehensive Laboratory Plan:

- Proof of laboratory accreditation/certification if available
- A spreadsheet that lists all the tests that will be done for the trial, all the laboratories in which these tests will be done, and the external QA providers and PT surveys that will be used to monitor each test. The template below is provided for your convenience as an example of how this information can be provided. You may modify this as appropriate.

  http://www3.niaid.nih.gov/NR/rdonlyres/C1076997-2029-42B5-AC25-39E53E8C4686/0/LabSpreadsheet.xls

- A completed Laboratory Self-Description Module for each proposed participating laboratory. The template below is provided for your convenience as example of how this information can be provided. You may modify this as appropriate.

  http://www3.niaid.nih.gov/NR/rdonlyres/474B75F3-D526-4C0E-BE8F-086A87C34B55/0/LabSelfDescModule.doc

- Normal ranges for tests or a plan to obtain normal ranges by testing specimens from the local population
- Master list of all the laboratory's SOPs
- A copy of the index of the laboratory's QA plan/manual

2.0 Research Use Only endpoint tests (research tests not yet validated and approved by an International Conference on Harmonisation (ICH) regulatory body such as the FDA)

RUO endpoint tests (e.g., ELISPOT, ICC, pharmacological, virological) should be performed in laboratories that conduct operations in a Good Clinical Laboratory Practice (GCLP) manner. External PT should be applied to such tests. If existing PT surveys are not available, a suitable form of alternative proficiency assessments needs to be devised and proposed to DAIDS for approval.

A description of the elements of GCLP and a comprehensive presentation about GCLP are found in section I above. The training of laboratory staff in the principles of GCLP is strongly encouraged. For information about DAIDS-sponsored GCLP training workshops, please contact Janice Darden at jdarden@niaid.nih.gov.

For requirements described in Section II above, please include the following in the Comprehensive Laboratory Plan:

- A list of the RUO tests
- Test SOPs in a format that includes information about test principle, specimen requirements, reagents, supplies and equipment, procedure, calculations, quality control, procedural notes and references
- Complete identifying information for the laboratories indicated above
- A description of the external PT measures undertaken for each test in each laboratory
- A documentation of the ability of staff to proficiently perform proposed tests
- A description of the GCLP operations in the laboratory
- A copy of the index of the laboratory's QA plan

3.0 Study-specific Specimen Management plan

Each study must have a specimen management plan that describes sample acquisition, recording, testing, storing and shipping, including specimen flow chart, QA oversight and corrective action (the latter two may be included in the Laboratory QA plan). If shipments of specimens are to occur, they must be done according to the most current International Air Transport Association (IATA) shipping regulations:

http://www.iata.org/ps/publications/9065.htm.

For requirements described in Section III above, please include the following in the Comprehensive Laboratory Plan:

- The specimen management plan
- Proof of training in IATA shipping regulations (certification) if specimen shipments are planned for the trial

4.0 Study-specific Laboratory Data Management plan

Each study must include a laboratory data management plan that describes the 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 (LDMS), the elements of 21 CFR Part 11 compliance (http://www.fda.gov/ora/compliance_ref/part11/) should be taken into consideration.

For requirements described in Section IV above, please include the following in the Comprehensive Laboratory Plan:

- The laboratory data management plan
- A description of the testing that was done to ensure that data flow smoothly and maintain integrity from the point of acquisition to the study database
- Proof of 21 CFR Part 11 compliance if available

5.0 Laboratory-specific auditing - provided by DAIDS

DAIDS and/or its contractors will conduct laboratory-specific audit visits to determine laboratory readiness to participate in trials, and, as indicated, during the conduct of a trial. The Laboratory Assessment document shows the scope of the audit:

http://www3.niaid.nih.gov/NR/rdonlyres/C012BE9C-88EC-476A-89D5-4338ED612748/0/DAIDSLabAudit.doc