

Notes

An earlier version of this document was drafted by Paul Richardson, Estelle Piwowar-Manning, Erin Gover, and Kurt Michael. The document was finalized by the Cross-Network Laboratory Focus Group (LFG), representing the ACTG, MTN, HPTN, IMPAACT, and HVTN. The term “Primary Network Laboratory (PNL)” refers to the primary Network Laboratory responsible for overseeing laboratory operations at a Clinical Trials Unit (CTU) participating in one of the DAIDS-sponsored clinical trials networks listed above. The term “network” refers to one of these five network organizations.

These guidelines are for assays used for safety monitoring only. Laboratories should consult the DAIDS-sponsored Immunology Quality Assurance (IQA) group for back-up plans relevant to CD4 cell count testing and other testing performed under the guidance of the IQA, and should contact the DAIDS-sponsored Virology Quality Assurance (VQA) group for back-up plans relevant to viral load testing and other virology assays.

Introduction

Laboratories that participate in network trials funded by the National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), are required to participate in DAIDS-sponsored External Quality Assurance (EQA) testing programs for all protocol-related laboratory testing. Proficiency testing programs used by the laboratories must be approved by DAIDS, and the laboratory must be able to demonstrate continued successful participation in these programs to perform protocol testing.

In certain circumstances (e.g., analyzer repair or breakdown, lack of available consumables, lack of required reagents or control material, continued failure in an EQA program), a laboratory may need to use back-up equipment or a back-up laboratory for testing and reporting study specimen results. To ensure the safety of research subjects and the quality of data produced using back-up equipment, the primary testing laboratory must be able to demonstrate acceptable testing proficiency and equivalency between the primary and back-up instruments and/or laboratories for the relevant analyte(s) using tools such as laboratory audit reports, EQA history, instrument validations and reference ranges. It should also be noted that if the back-up plan involves the use of a non-FDA-approved kit or instrument, it may need to be validated depending on protocol requirements.

The development and approval of a back-up plan that demonstrates equivalency between back-up instruments and/or laboratories is the responsibility of the Director of the primary testing laboratory.

These guidelines are intended to provide information for the directors of DAIDS-sponsored clinical laboratories that perform testing for DAIDS-sponsored clinical trials. They outline the most thorough and ideal approach to developing and approving a back-up plan. However, the director of the primary laboratory may need to deviate from these guidelines depending on the analyte and the testing options available.

The role of the PNL will vary by network and/or analyte and may include guidance during the development of the back-up plan, consultation with other networks regarding their particular protocol and analyte needs, review and approval of relevant data and documents, and final review and approval of the back-up plan.

Development and review of the back-up plan

Good Clinical Laboratory Practice (GCLP) requires laboratories to demonstrate that back-up instruments and facilities are able to produce reliable results that are comparable to those obtained using the primary instruments and facilities. The primary laboratory should prepare a formal back-up plan for each analyte tested in network trials. This plan should include a detailed description of evaluation of the back-up instrumentation and/or facilities, including formal comparison studies, instrument validations, and reference ranges. The plan should also include pre-determined limits for comparability testing for each analyte. The back-up plan should be approved by the Primary Network Laboratory (PNL) before comparison studies are performed; if needed, the PNL will consult with other networks that have protocols planned or in progress at sites that uses the primary laboratory. The primary laboratory is encouraged to consult the PNL for guidance in the design of comparison studies. If needed, the PNL may contact SMILE or other groups for assistance.

Regardless of the arrangement used for back-up testing (see below), all documents relevant to use of the back-up equipment and/or back-up laboratories must be reviewed and approved by the Director of the primary laboratory; the PNL may also be consulted. This includes: the back-up plan, results from testing that support use of back-up equipment and/or facilities (including comparability testing and proficiency testing), approval of the back-up plan, and approval of use of the back-up equipment and/or a back-up laboratory. Other factors that may be considered in the approval to use back-up equipment and/or a back-up laboratory include: confirmation that appropriate Standard Operating Procedures (SOPs) are in place, review of previous PPD and/or DAIDS laboratory audits, appropriate data management systems are in place, etc. All documents related to approval of a back-up plan must be retained indefinitely at the primary laboratory.

Furthermore, the Director of the primary laboratory is responsible for ensuring that the results reported are reliable regardless of the arrangement used for back-up testing. The Director of the primary laboratory should carefully review the units of measurement and reference ranges used by a back-up laboratory, since these may differ from those used in the primary laboratory. Detailed knowledge of each network protocol will help the Director determine which back-up option is most appropriate for each protocol. Whenever use of back-up equipment or a back-up laboratory is considered, the primary laboratory should contact their PNL, who will contact the relevant data management center(s), the other networks operating at the site, DAIDS, and SMILE. Once this initial notification is completed, the primary laboratory should work with their PNL as the primary contact to address the issue. Inquiries from other groups (e.g., the relevant data management center(s), the relevant protocol teams, DAIDS, or SMILE) should be forwarded to the primary laboratory's PNL.

Individual networks and DAIDS will decide whether a primary laboratory should switch to a back-up laboratory for specific protocols. The PNL will facilitate back-up laboratory arrangements but the individual networks should review these arrangements to make sure they are satisfactory for relevant protocols.

External Quality Assurance

One approach to assuring acceptable performance for back-up equipment and laboratories would be to provide the testing laboratories with EQA surveys for all back-up instruments and back-up laboratories. In selected cases, DAIDS may approve the purchase of EQA surveys for a back-up laboratory (either network-affiliated or non-network-affiliated), particularly in cases where the primary laboratory is unable to share EQA materials. DAIDS will assess each situation on a case-by-case basis, taking several factors into consideration, including:

- Accreditation of the back-up laboratory by a non-U.S. organization
- Participation and historic performance of the back-up laboratory on EQA surveys (e.g., from international or in-country EQA programs)
- Type of testing to be provided by the back-up laboratory (e.g., safety, primary endpoint, testing for patient management, etc.).

Due to cost and other factors, DAIDS may not always be able to support the purchase of EQA surveys for a back-up laboratory. Therefore, another approach to the development of reliable and efficient back-up plans for laboratory testing may be needed. These approaches generally fall into one of three categories:

- 1) Use of a second instrument at the same facility,
- 2) Use of a local back-up laboratory that is actively participating in DAIDS-sponsored clinical trials,
- 3) Use of a local back-up laboratory that is not actively participating in DAIDS-sponsored clinical trials.

Each of these approaches is discussed below.

Alternative arrangements for back-up testing

1) Use of a back-up instrument at the same primary laboratory

Many laboratories performing network trials have more than one analyzer at the primary laboratory. Sites with multiple analyzers should have documentation in place that indicates whether EQA and comparability testing are performed routinely for both instruments, or whether EQA is performed for only one instrument (the primary instrument), and comparability testing is performed for the second instrument (back-up instrument). Guidelines for developing comparison criteria can be found in the Participant Summary booklet produced by the College of American Pathologists (CAP). As an example, the laboratory could compare results from 20 clinical samples obtained using both instruments, at least twice a year. An attempt should be made to include samples that span the accepted reportable range, and criteria for acceptability should be established prior to testing. In either case, the plan for performing EQA and/or comparability testing for the second instrument should be approved in advance by the PNL, and the EQA data and/or comparability data should be reviewed and approved by the PNL either on an on-going basis, or before the back-up instrument is used for protocol testing (see above).

If EQA is routinely performed for both instruments on an on-going basis, and the instruments are the same, it may be possible to perform EQA studies on both instruments using a single EQA panel. In this case, results from one analyzer should be submitted for grading by the EQA provider (e.g., CAP). If it is not possible to have the results of the second instrument submitted for grading by the EQA provider, the laboratory should manually grade the results from the second instrument. The laboratory should contact SMILE if needed for guidance on how to perform manual grading. Results from both instruments should be interpreted in comparison to results from EQA peers (e.g., CAP results from other laboratories using the same equipment and assay type). The Director of the primary laboratory must determine acceptable comparability limits for the relevant analyte(s).

Before protocol testing is switched to the back-up analyzer, and before the laboratory switches back to the primary analyzer (e.g. after equipment repair), the laboratory Director should confirm that (1) the instrument to be used has been recently calibrated, and (2) that appropriate internal quality control (QC) samples have been analyzed, and that the results are within established limits. Before switching to the back-up instrument, the site should identify samples that were recently analyzed using the primary

instrument, and should attempt to duplicate those results using the back-up instrument before running protocol samples. Before switching back to the primary instrument (e.g., after equipment repair), the laboratory should test a subset of clinical samples (e.g., 20 samples) on both the primary and back-up instrument, and confirm that the results are within the pre-determined comparability limits.

2) Use of network-affiliated laboratory for back-up testing

Some laboratories performing network trials may have another laboratory nearby (e.g. in country) that is also performing network trials (e.g. a neighboring CTU laboratory). For a second laboratory to be designated as a back-up laboratory, the primary laboratory should document that samples can be transported to the back-up laboratory within a time-frame that is appropriate for the relevant analyte(s) (i.e. consistent with the site's specimen handling SOPs). If two CTU laboratories are serving as back-up laboratories for one another, each laboratory should communicate with its partner laboratory to ensure that both laboratories are actively participating in an appropriate EQA program for each of the relevant analytes. A plan for using the back-up laboratory should be in place and approved by the laboratory Director and the PNL, ideally before a protocol starts. This plan should document the relationship between the two laboratories, the plan for EQA and comparability testing, and the procedures for switching testing from one laboratory to another. During the development of the back-up plan, the laboratory Director and PNL should review and approve (1) the historical and current EQA performance of the back-up laboratory, and (2) results from a recent comparability study (e.g. the laboratory could compare results from 20 clinical samples obtained using both instruments, at least twice a year.); as described above, an attempt should be made to include samples that span the accepted reportable range, and criteria for acceptability should be established prior to testing. All documents related to use of a back-up laboratory (e.g. EQA data, comparability data, approval) must be documented, signed, and retained indefinitely at the primary laboratory.

3) Use of a non-network-affiliated laboratory for back-up testing

Some primary laboratories performing network trials do not have another network-affiliated laboratory in close enough proximity and/or testing the appropriate analyte(s) to serve as a back-up laboratory. In this case, the primary laboratory should identify an alternate, non-network-affiliated laboratory to serve as a back-up laboratory. A major consideration in selecting a non-network-affiliated laboratory to serve as a back-up laboratory is whether that laboratory participates in the relevant DAIDS-sponsored EQA program(s) (e.g. CAP), and if not, whether they participate in a DAIDS-approved alternate EQA program for the relevant analyte(s) (e.g. an in-country EQA program). Some options are described below:

- The back-up laboratory participates in the relevant DAIDS-sponsored EQA program(s); this is the preferred arrangement. In this case, if the back-up laboratory has a recent history of successful EQA performance and SMILE can access the relevant EQA data, evaluation and approval of the back-up laboratory could be handled as if it were a network-affiliated laboratory (see above).
- The back-up laboratory does not participate in the relevant DAIDS-sponsored EQA program(s), but does participate in an acceptable alternate EQA program for the relevant analyte(s). In this case, the primary laboratory should consider donating extra EQA material to the back-up laboratory, for testing on an on-going basis, or as needed (e.g. if use of the back-up laboratory is considered). Alternatively, the primary laboratory can seek permission from DAIDS to obtain EQA panels for the back-up laboratory (see below). Regardless of the source of the EQA material (primary laboratory, or purchased separately for the back-up laboratory), the primary laboratory should manually grade the results (see above). In this case, DAIDS also recommends that the primary laboratory attempt to obtain other indicators of laboratory performance from back-up

laboratory (e.g. EQA results from other local or international providers, internal laboratory quality control results, etc.).

In either case (i.e. the back-up laboratory does or does not participate in the relevant DAIDS-sponsored EQA program(s)), the primary and back-up laboratories should still perform correlation studies on the same samples (e.g. 20 clinical samples tested in both laboratories, at least twice a year), to document comparability of results obtained in the two laboratories. DAIDS recognizes that some back-up laboratories may not appreciate the need for performing proficiency testing and/or correlation studies. If the back-up laboratory is not willing to perform this testing on an on-going or as-needed basis, the primary laboratory should contact their PNL for further guidance. If an alternate strategy is used to assess the suitability of a back-up laboratory, the strategy selected must be pre-approved by the PNL and the Network Laboratories for other networks operating at the site.

In addition, the back-up laboratory will be required to undergo a DAIDS audit and to resolve critical audit findings.

Deviations from an approved back-up plan

In some instances, unforeseen situations may arise that make it impossible to follow an approved back-up plan (e.g. the back-up analyzer at the primary or back-up laboratory is not in service, there are delivery problems with reagents or QC materials at the back-up laboratory, transportation between the primary and back-up laboratory is not available, the back-up laboratory has had unacceptable performance on EQA surveys). In these situations, the primary laboratory should contact their PNL to discuss the following options:

- Halt protocol testing until the back-up analyzer and/or back-up laboratory is fully operational, or until the primary laboratory is able to resume testing. This may be acceptable if the delay in testing does not negatively impact protocols running at the site or participant safety.
- Send samples to another network-affiliated laboratory. Ideally, the alternate laboratory would have documented proficiency in testing the relevant analyte(s).
- Send samples to a non-network-affiliated laboratory. In this case, the Director of the primary laboratory must use his or her knowledge of the area to identify an appropriate local laboratory. Ideally, the alternate back-up laboratory would be actively participating in an EQA program (e.g., from a local or in-country provider). If possible, evidence of successful participation in such a program should be obtained by the primary laboratory.

In each case, if possible, comparison testing should be performed at the alternate laboratory, using clinical samples, to ensure good result correlation. The PNL must approve use of the alternate back-up laboratory before protocol samples are sent for testing. The PNL will be responsible for reviewing analysis of EQA and comparability test results, as well as validation studies for the back-up instrument, seeking assistance from SMILE if needed. The PNL is also responsible for informing SMILE and the other networks about the alternate back-up plan, and for seeking their input when needed. Individual networks will make final decisions for their respective protocols and each network will be responsible for contacting the relevant protocol teams and for contacting their DAIDS Program Officer. Whenever a primary laboratory deviates from the original, approved back-up plan, the primary laboratory should document the occurrence in Regulatory Notes to File, and should forward a sample Chain of Custody plan to their PNL and to the relevant protocol teams (i.e. teams for protocols using the relevant analyte(s)).