



**Guidelines for Use of Back-Up Equipment  
and Back-Up Clinical Laboratories  
in DAIDS-Sponsored Clinical Trials Networks Outside of the US**

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## Introduction

This document was prepared by the Cross-Network Laboratory Focus Group (LFG) and represents a consensus from the Laboratory Centers of the HIV Vaccine Trials Network (HVTN), HIV Prevention Trials Network (HPTN), the Microbicide Trials Network (MTN), the AIDS Clinical Trials Group (ACTG), and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group.

In general, utilizing back-up equipment is preferable to using back-up clinical laboratories due to the costs and logistical difficulties associated with moving testing from one laboratory to another. However, in some cases, utilization of a back-up laboratory will be necessary.

In cases where testing clearly cannot be performed at the primary laboratory, a decision may be made by the primary laboratory management to move testing to a backup laboratory. Individual networks and DAIDS need to be consulted as soon as possible in this situation.

In less clear situations, whether or not to move protocol specific testing to a back-up laboratory will be the decision of the primary laboratory’s affiliated network(s) and will be based on a variety of factors including, but not limited to, protocol requirements, feasibility of back-up lab location, and back-up lab EQA status.

Guidelines for use of back-up equipment and back-up clinical laboratories in DAIDS-Sponsored Clinical Trials were developed first for safety testing laboratories. In most cases, the guidelines for non-safety laboratories will differ from those for safety laboratories in only limited ways, so for ease of communication and understanding, only the differences are described.

The term Primary Network Laboratory (PNL) refers to the primary Laboratory Center (previously referred to as Network Laboratory) responsible for coordinating oversight of cross network laboratory operations at a Clinical Research Site (CRS) participating on one of the DAIDS-sponsored clinical trials networks listed above. PNL assignments can be found on the HANC public website (<http://www.hanc.info/labs/Pages/PNL.aspx>).

These guidelines apply only to primary testing laboratories that are not in the United States (US).

Please direct any questions related to back-up lab guidelines to the appropriate DAIDS-sponsored quality assurance (QA) group:

Testing	QA Group
Safety	Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) <ul style="list-style-type: none"> <li>• <a href="https://psmile.org/contact.cfm">https://psmile.org/contact.cfm</a></li> </ul>
CD3, CD4 and CD8 flow cytometry	Immunology Quality Assurance (IQA) <ul style="list-style-type: none"> <li>• <a href="https://iqa.center.duke.edu/contact-us">https://iqa.center.duke.edu/contact-us</a></li> </ul>
PBMC cryopreservation	ACTG, IMPAACT, HPTN, MTN sites: IQA <ul style="list-style-type: none"> <li>• <a href="https://iqa.center.duke.edu/contact-us">https://iqa.center.duke.edu/contact-us</a></li> </ul> HVTN sites: HVTN Lab Center <ul style="list-style-type: none"> <li>• <a href="https://www.hvtn.org/en.html">https://www.hvtn.org/en.html</a></li> </ul>
Virology assays	Virology Quality Assurance (VQA) <ul style="list-style-type: none"> <li>• <a href="https://vqa.center.duke.edu">https://vqa.center.duke.edu</a></li> </ul>

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## Back-Up Lab Guidelines for Safety Testing Laboratories

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 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 or internal QC issues), 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, comparison checks, 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 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 study specific back-up plan, consultation with other network 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. Each network is ultimately responsible for ensuring that backup plans are in place and adequate for their protocol specific testing.

### **Development and review of the back-up plan**

Good Clinical Laboratory Practice (GCLP) (Section 4, Equipment) 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. Backup testing is referenced on the Protocol Analyte Lists (PALs) required by pSMILE for EQA considerations. Individual networks need to evaluate backup plans as part of study activation.

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 if available), 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 GCLP 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.

Prior to the use of back-up equipment or a back-up laboratory, the primary laboratory must contact all affected networks and the respective QA group. Each network should have a mechanism in place to advise their relevant data management center(s) and their DCLOT representative. Once this initial notification is completed, the primary laboratory should work with affected networks and/or their PNL as the primary contact to address the issue.

Individual networks and DAIDS may decide whether a primary laboratory should switch to a back-up laboratory for specific protocols. The PNL may facilitate back-up laboratory arrangements but the individual networks must review these arrangements to make sure they are satisfactory for relevant protocols. The primary laboratory is responsible for ensuring that back-up lab(s) are accurately listed on the study-specific Protocol Analyte List (PAL).

### **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 (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 (e.g., from CAP, JCI, etc.)
- Participation and historic performance of the back-up laboratory on EQA surveys (e.g., from DAIDS sponsored EQA programs)
- Type of testing to be provided by the back-up laboratory (e.g., safety, primary endpoint, testing for patient management, etc.)
- Laboratory under DAIDS review

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, with appropriate comparison checks
- 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 must 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), or from other appropriate EQA providers. 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. 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. 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 and what documentation, if any, needs to be submitted to SMILE. 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, the laboratory director should confirm that (1) the instrument to be used has been appropriately calibrated as needed, 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 as well as confirming that (1) the instrument to be used has been appropriately calibrated as needed, and (2) that appropriate internal quality control (QC) samples have been analyzed, and that the results are within established 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 CRS 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 timeframe that is appropriate for the relevant analyte(s) (i.e., consistent with the site's specimen handling SOPs). If two 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, 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 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. For quantitative tests, correlation testing should be performed on a semi-annual basis at minimum, where applicable. For qualitative tests, verifying the successful EQA performance or use of participant specimens for the backup lab/instruments should be sufficient. 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 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 comparison 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 Laboratory Centers for other networks operating at the site. The PNL may coordinate communications to obtain approvals. In addition, the back-up laboratory will be required to undergo a DAIDS audit.

#### **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 coordinate discussions on 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 will coordinate informing pSMILE and the other networks about the alternate back-up plan and seek 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 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)).



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## **Back-Up Lab Guidelines for CD3, CD4 and CD8 Flow Cytometry Laboratories**

The Back-Up Guidelines for Safety Testing Laboratories also apply to CD3, CD4 and CD8 flow cytometry laboratories with the exceptions described below. 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.

### **Immunology Quality Assurance (IQA)**

IQA is the QA group responsible for monitoring CD3, CD4 and CD8 flow cytometry laboratories participating in DAIDS-sponsored clinical trials and assisting in the development of back-up plans. Whenever pSMILE would be contacted, copied or consulted during the process of developing back-up plans for safety labs, IQA should be involved similarly for flow cytometry laboratories.

### **Use of a back-up instrument at the same primary laboratory**

Many flow cytometry laboratories performing network trials have more than one analyzer at the primary laboratory. Laboratories can and should enroll all of their instruments in the UK NEQAS Immune Monitoring Program. Typically, one EQA panel can be shared by up to three instruments. Labs with more than three instruments can purchase additional panels or simply run comparison studies. Comparison studies are needed between instruments even if they are all enrolled in the UK NEQAS Immune Monitoring Program. Please contact the IQA for more information about performing comparison studies. The director of the primary laboratory should submit the comparability data to the IQA for review at least once.

### **Use of a back-up laboratory**

Use of a network affiliated back-up laboratory (rather than a back-up instrument at the primary laboratory) will be more challenging for flow cytometry laboratories due to the 48-hour processing time limit. If samples cannot be transported to a back-up laboratory and tested within 48 hours, the primary laboratory should contact the affected networks to discuss other options.

## **Back-Up Guidelines for Virology Laboratories**

The Back-Up Guidelines for Safety Testing Laboratories also apply to virology laboratories with the exceptions described below. 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.

### **Virology Quality Assurance (VQA)**

The VQA is the QA group responsible for monitoring the assay performance of virology laboratories participating in DAIDS-sponsored clinical trials. The VQA provides summaries of laboratory performance to the network leadership which includes individual panel scores and approval ratings. The networks use this information to determine if a laboratory may continue to do virological testing for clinical trials. If a primary testing laboratory's approval rating changes, then the PNL must facilitate communications with other affiliated networks and the primary testing laboratory to determine whether testing may continue or if specimens should be sent to a back-up laboratory. The designated back-up laboratory must be approved by the VQA for testing at the time their services are being used. A primary testing laboratory can only resume testing when indicated by the network.

### **Use of a back-up instrument at the same primary testing laboratory**

The VQA can provide guidance to virology laboratories for instrument validation, but individual pieces of equipment are not evaluated for proficiency testing. Laboratories may use VQA panels to evaluate instrument performance internally, but only one set of data will be analyzed formally for proficiency testing. If a manual method is used as a back-up for an automated system, then the manual method may be monitored by the VQA for informational purposes only. In this situation, the official proficiency testing scoring would be done using data generated by the automated processor, and a separate report would be created for informational purposes only by substituting the data from the manual method.

Some primary testing laboratories have more than one platform or method available for use. In these cases, the sites must have designated which platforms and methods are used for specific studies. Switching platforms or methods will require approval from the respective PNL and VQA.

### **Use of a back-up laboratory**

If a problem arises with the laboratory instrumentation used for virology testing, and a back-up instrument at the primary laboratory is unavailable, the primary laboratory should freeze the samples and contact their affiliated networks to discuss how to proceed with the testing of protocol related samples.