17 LABORATORY CONSIDERATIONS

17.1 Network Laboratory Activities

Network laboratory activities are overseen by the IMPAACT Laboratory Center (ILC) and Westat. The ILC provides oversight of site laboratories and IMPAACT specialty laboratories sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Westat manages the oversight of laboratories supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

Note: As of April 2026, NICHD site-affiliated laboratories in Brazil, Kenya and Thailand are under ILC oversight. This includes all laboratory approvals/activations for IMPAACT studies as well as monitoring of external quality assurance (EQA) investigation reports (IRs) and audit action plans (APs).

- ***For the sites in these countries, Westat will oversee and obtain fully executed material transfer agreements (MTAs) as needed. The NICHD sites will continue shipping study specimens to the NICHD repository at Fisher BioServices.***
- ***For the remainder of this section, the reference to Westat laboratory oversight applies to those NICHD-supported US and non-US laboratories other than the three countries noted above.***
- ***For the remainder of this section, the reference to ILC oversight applies to all NIAID-sponsored US and non-US site-affiliated laboratories as well as the NICHD-sponsored laboratories in the three countries noted above.***

17.1.1 IMPAACT Laboratory Center

The ILC is affiliated with the University of California Los Angeles (UCLA), in Los Angeles, California, USA. The ILC is responsible for the oversight of laboratory activities associated with the conduct of IMPAACT studies at both United States (US) and non-US sites. The ILC is comprised of the IMPAACT Laboratory Center Principal Investigator (PI) and other personnel responsible for developing and overseeing the laboratory aspects of the protocols, ensuring that participating laboratories meet Division of AIDS (DAIDS) and applicable regulatory requirements for specimen handling, and maintaining good standing in all proficiency testing.

The ILC oversees and coordinates three types of laboratories that are distinguished by the types of assays they perform, their regulatory requirements, and their funding mechanisms. These include Site, Specialty, and Focus Laboratories. There are also multiple partners affiliated with IMPAACT and the ILC. These types of laboratories and affiliated groups are described in Table 17-1.

Table 17-1. Types of Laboratories and Groups Affiliated with IMPAACT

Laboratory Types	Description
Specialty Laboratories*	• Focus on supporting and advancing IMPAACT's research agenda through the development and validation of novel and unique assays and/or the application of standard assays to probe pathogenic mechanisms • IMPAACT currently supports Specialty Laboratories in the areas of HIV pathogenesis and pharmacology
Focus Laboratories (FLs)	• Funded on a contractual basis to support specific, unique assays that are not available at a funded Site or Specialty Laboratory, but are necessary to support IMPAACT activities
Site Laboratories*	• Perform routine study assays, such as hematology, chemistry, HIV RNA and DNA, ARV resistance testing, CD4 cell enumeration, etc. • Perform specimen processing, storage, and shipping activities for the site *(note: the ILC does not have oversight of processing facilities within sites)*

Table 17-1. Types of Laboratories and Groups Affiliated with IMPAACT

Laboratory Types	Description
Network Laboratory Centers (NLCs)	• All DAIDS-sponsored clinical trials Network Laboratory Centers are led by PIs whose personnel oversee the quality assurance (QA) of the non-US laboratories participating in DAIDS-sponsored clinical research • The ILC provides oversight to site laboratories sponsored by NIAID and IMPAACT specialty laboratories. Westat manages the oversight of laboratories supported by NICHD.
Primary Network Laboratory (PNL)	• DAIDS NLC assigned to specific non-US laboratories has primary responsibility for communications with that laboratory • Each PNL may have an assigned contact person and/or a PNL email address (e.g., impaact.labcenter@frontierscience.org for NIAID and NICHDLabSpecialist@westat.com for NICHD) to facilitate communication • Non-US laboratories have been instructed to direct all queries and requests for assistance to their PNL contact. Multiple networks may rely on the services of a particular non-US laboratory. It is the responsibility of the assigned PNL for communicating all laboratory-relevant information to the other NLCs, which may utilize these shared services. It is also the responsibility of the individual laboratory to notify the respective NLCs of any issues that may arise, inclusive of reagent or supply outages, and which ongoing studies may be affected so the NLC(s) may take appropriate action. • A list of the PNL assignments can be found on the Office of HIV/AIDS Network Coordination (HANC) website at: https://www.hanc.info/resources/sops-guidelines-resources/laboratory/primary-network-laboratory-assignments.html
Cross-Network Laboratory Focus Group (LFG)	• Comprised of members from DAIDS-funded networks: ACTG, HPTN, HVTN and IMPAACT • Individuals from Westat, who represent NICHD-sponsored IMPAACT sites, also participate in this group • Receives support from HANC for cross-network laboratory activities • Activities include communication processes for critical information across NLCs; standardized QA practices across networks; and harmonization of laboratory processes and procedures to increase efficiency, especially at the shared laboratory sites
DAIDS Clinical Laboratory Oversight Team (DCLOT)	• Comprised of DAIDS staff members who serve as laboratory points-of-contact to the DAIDS-funded networks • Mission is to harmonize laboratory-related guidelines and requirements for establishing new laboratories; ensure that studies are conducted in accordance with Good Clinical Laboratory Practice (GCLP); provide central guidance in clinical laboratory matters to various DAIDS entities; and optimize the contribution of DAIDS laboratory-related support contracts to network laboratories
Laboratory Directors Group (LDG)	• Comprised of IMPAACT Specialty Laboratory Directors • Primary objective of the LDG is to exchange ideas and identify scientific opportunities • Meets periodically via conference calls and during the IMPAACT annual meeting

*ILC oversees these laboratories.

Scientific progress by the Specialty Laboratories is periodically reviewed in conjunction with the ILC PI, representatives from the IMPAACT Scientific Leadership Group (SLG), and external advisors, as needed.

The ILC works closely with the Advancing Clinical Therapeutics Globally (ACTG)/IMPAACT Laboratory Technologists Committee (LTC), the ACTG Laboratory Center PI, and the Cross-Network Laboratory Focus Group (LFG) via HANC to harmonize IMPAACT laboratory policies and procedures with those of the ACTG, other NIAID networks, and NICHD, as applicable. Site laboratory training and support are coordinated with the Patient Safety Monitoring in International Laboratories (pSMILE), other EQA providers, and DCLOT. In addition, collaborations with and participation by Specialty Laboratory Directors and other IMPAACT Scientific Committees are sought as appropriate.

The ILC is responsible for the following activities for IMPAACT studies:

- Identifying and facilitating the implementation of state-of-the-art assays and technologies to advance IMPAACT's scientific agenda through leveraging the capabilities of specialty, focus, and contract laboratories.
- Working with protocol teams to ensure appropriate regulatory compliance for all laboratory tests.

The ILC is responsible for the following activities for site laboratories sponsored by NIAID and select NICHD sites:

- Confirming that all laboratory testing in support of IMPAACT studies meets DAIDS requirements. This includes generating and overseeing study-specific Domestic Analyte Lists (DALs) for US laboratories, Protocol Analyte Lists (PALs) for non-US laboratories, Laboratory Activation Checklists (LACs) and ushering these documents through the DCLOT laboratory approval process.
- Providing guidance to and oversight of Network laboratories responsible for the collection, testing, and reporting of results from biological specimens.
- Maintaining specific clinical laboratory documents using an electronic document management system and database.
- Assisting in the development and QA assessment of local laboratory capacity at the Clinical Trials Units (CTUs) participating in IMPAACT studies.
- Ensuring sites have submitted validation reports to EQA providers for new assays or laboratory equipment used in trials.
- Tracking regulatory and QA documentation (e.g., Laboratory Director curriculum vitae [CV], Clinical Laboratory Improvement Amendments [CLIA]/College of American Pathologists [CAP]) or equivalent accreditation certificates, and Laboratory Activation Checklist inclusive of the Attestation of Lab Documents and Study Requirements, to be signed by the Investigator of Record [IoR] and/or designee).
  - Note: The Attestation is considered part of the Laboratory Activation Checklist (LAC) as a stand-alone document
  - The LAC + Attestation are submitted to DCLOT for laboratory activation
- Working with protocol team members to develop, coordinate, and implement laboratory training(s).
- Conducting laboratory visits and assessing laboratory capabilities, if needed, to conduct IMPAACT studies.
- Liaising with EQA providers, vendors, and DAIDS contractors (e.g., pSMILE, Virology Quality Assurance [VQA], Immunology Quality Assessment [IQA], Tuberculosis Quality Assessment Program [TBQA], and Clinical Pharmacology Quality Assurance [CPQA]).
- Overseeing all NIAID-sponsored laboratories by performing ongoing review of Quality Assurance/Quality Control (QA/QC) and proficiency testing. Deficiencies, deviations, and poor

performance on proficiency testing that cannot be resolved, or serious breaches of GCLP, are brought to IMPAACT Network Leadership, if applicable, as they are identified.
- Providing continuous monitoring of laboratory performance throughout the duration of IMPAACT studies.

17.1.2 Westat

In collaboration with DCLOT, Westat provides support to select NICHD laboratories. Westat conducts the following tasks associated with their responsibility:

- Providing oversight of NICHD-supported laboratories responsible for the collection, testing, and reporting of results from biological specimens.
- Tracking of regulatory and QA documentation for select laboratories affiliated with NICHD sites sponsored by IMPAACT.
- Preparing select NICHD laboratories to implement specific IMPAACT studies.
- Confirming that all laboratory testing in support of IMPAACT studies meets DAIDS and ILC laboratory requirements, including study-specific PALs and DCLOT laboratory approval.
- Assessing laboratory capabilities to conduct IMPAACT studies.
- Liaising with EQA providers, vendors, and DAIDS contractors. This includes performing ongoing review of QA/QC and proficiency testing. Deficiencies, deviations, and poor performance on proficiency testing that cannot be resolved, or serious breaches of GCLP, are brought to NICHD by the Westat Laboratory Specialists as they are identified.
- Providing continuous monitoring of laboratory performance throughout the duration of IMPAACT studies.

17.2 IMPAACT Laboratories

The following section applies to all laboratories affiliated with the IMPAACT Network or any study being performed under the guidance of the ILC. Information on policies and standard procedures related to requirements for DAIDS-supported laboratories and specimens derived from DAIDS-supported and/or -sponsored clinical research are available at:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

All laboratories affiliated with the IMPAACT Network are required to adhere to standards of DAIDS GCLP and local Standard Operating Procedures (SOPs) for proper collection, processing, labeling, transportation, and storage of laboratory specimens. The clinical research site (CRS) and CTU laboratories should also have in place a well-defined Quality Management Plan (QMP) that comprehensively covers specimen management issues, including specimen acquisition, tracking, processing, storage, backup plans (e.g., instrumentation, staffing, and equipment), assay validations, and aspects of quality assessment and QC.

The Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy cover required quality assessment activities for the laboratory and laboratory QC, including handling of reagents and conducting of assays. References for applicable US and non-US regulations are also included.

In accordance with DAIDS policy, all laboratory tests used for: 1) safety monitoring (e.g., hematology and chemistry); 2) patient management decisions (e.g., drug levels); 3) eligibility (e.g., pregnancy tests); 4) primary study endpoints or outcome measures (e.g., HIV RNA); or 5) diagnosis (e.g., HIV, CMV, syphilis, and hepatitis B), must:

- Be performed in a GCLP-compliant laboratory:
  - If in the US, must be accredited by CLIA or state equivalent, and certified by CAP or equivalent organization
  - For non-US laboratories, International Standardization Organization (ISO) 15189 compliance is recommended
- Meet DAIDS requirements, including age- and sex-appropriate reference ranges for study populations, verification studies for the US Food and Drug Administration (FDA)-approved tests, and validation studies for non-FDA-approved tests
- Be quality assured using DAIDS-approved EQA programs, or if not available, alternate proficiency assessments must be approved by DAIDS and the ILC

When introducing a new testing platform or method, laboratories typically have a validation reviewed by the respective DAIDS EQA provider (i.e., pSMILE, VQA, IQA, TBQA, and CPQA. In addition, the laboratory typically should successfully pass at least one round of EQA for the new clinical analyte(s) to be tested as part of an IMPAACT study. In some cases (e.g., novel bNAb testing), validation may not be available; appropriate requirements are determined on a study-specific basis.

Laboratories must satisfy all Network-specific requirements **prior** to testing in the conduct of an IMPAACT study. This includes demonstration of ongoing successful performance in EQA programs for all study analytes using metrics as determined by the DAIDS EQA providers.

The compilation of these criteria, which include **S**afety, **P**atient management, **E**ligibility, Primary **E**ndpoints and **D**iagnosis, are referred to as **SPEED** criteria.

17.3 Protocol-Specified Testing

Each protocol team determines the laboratory procedures, assays, and analytic approaches in accordance with the protocol-specified aims of the study. All protocol teams have an ILC representative assigned to ensure that proposed analytes and procedures are feasible and meet DAIDS regulatory requirements as outlined below. Inclusion in the early stage of protocol development provides the ILC with sufficient lead time to confirm that proposed testing methods are available and meet regulatory requirements. If gaps are identified, it allows the ILC to collaborate with DAIDS and other stakeholders to develop appropriate plans to ensure compliance. The protocol team determines which laboratory assays are required, including those pertaining to primary, secondary, and/or other/exploratory endpoints or outcome measures. Studies may also be conducted in research-relevant geographic regions, which may be reflected in specific sites being selected for participation. The ILC may be asked to determine the study-specific testing capabilities of a site laboratory and assist in exploring options to ensure that protocol-specific testing can be performed.

Protocol teams may have an LTC member assigned to assist with providing technical expertise in the development of the laboratory components of protocols as well as standardizing the handling, processing, labeling, and storage of clinical specimens. They assist the ILC representative in the development of the Laboratory Processing Chart (LPC)/MiLPC and study-specific lab training materials including, at minimum, a review of the lab training slides. The LPC outlines the specimen collection, processing, ~~s~~hipping, and storage requirements for the study, as described in Section 11. The analytes required per the

protocol are reflected in the study-specific LPC, PAL, and DAL. IMPAACT studies have an accompanying study-specific Manual of Procedures (MOP), which may contain supplemental information and instructions related to laboratory procedures that need greater detail than what is included in the LPC.

17.4 IMPAACT Laboratory Network Requirements: US Laboratories Affiliated with Sites

All laboratories located within the US) are required to provide the ILC or Westat with documentation that verifies their current abilities to conduct study-specific testing prior to the site/laboratory being activated, as shown in Figure 17-1.

17.4.1 Study-Specific Laboratory Activation: US (NIAID)

The site-affiliated laboratories are responsible for:

- Completion of the DAL
- Current documentation for each testing laboratory, for the duration of the study:
  - CAP accreditation (or equivalent)
  - CLIA certification (or equivalent)
  - Current Laboratory Director's CV

  Note: All documentation is submitted via the MiLab Central Database (www.milabcentral.org).

- Completion of the Laboratory Activation Checklist (LAC). This includes an Attestation, which is signed via DocuSign by the IoR or designee. Laboratory requirements covered by attestation include:
  - Appropriate numbers of staff have current International Air Transport Association (IATA) or Department of Transportation (DOT) training
  - Laboratory staff have participated in the requisite study-specific laboratory training
  - Appropriate numbers of staff have current CPQA certification for completion of the CPQA Tutorial, if required for the study. The tutorial is found on the DAIDS Learning Portal: https://daidslearningportal.niaid.nih.gov/.
  - Site/laboratory personnel are responsible for updating the respective parties and distribution lists with the appropriate and current site and laboratory contacts. Contacts for each testing laboratory as listed on the DAL are updated if any relevant lab staff changes occur during the duration of the study
  - Contractual and other regulatory arrangements (e.g., MTA, export permits) are in place for testing at all primary and backup laboratories that are not clearly designated as a Network-approved central laboratory outlined within the protocol and/or LPC
  - Sites intending to use a Network-approved central laboratory for an analyte not already designated for central laboratory testing need to inform that central laboratory of their intention to send additional specimens for testing

Once all LAC items have been completed, the LC representative signs the checklist and submits to DCLOT for their approval and signature.

The LC representative notifies the site/laboratory of the laboratory activation, via email, which includes the finalized DAL, DCLOT-signed LAC with attestation, and laboratory approval letter.

Note: It is the IoR/Laboratory Director's responsibility to ensure that the documentation confirming their attestation is readily available for inspection (e.g., IATA certifications for at least two staff members throughout the study duration).

17.4.2 Domestic Analyte List (MiDAL)

Prior to site laboratory activation, each US NIAID site laboratory must submit a DAL for review. Briefly, this is a list of the site-selected US laboratories that will be used to perform all the study-required testing.

Note: DALs are a requirement of US NIAID-funded laboratories only.

The ILC is responsible for developing a protocol-specific DAL template for each study based on the corresponding PAL for the non-US site laboratories. The DAL template is distributed by the ILC through the MiPAL system to sites that have been selected to participate in a given study. The site submits the completed DAL to the ILC representative for initial review and subsequent approval (see Figure 17-1).

- The DAL does NOT include testing that is completed at a centralized and/or specialized laboratory. Therefore, some study analytes listed in the Laboratory Processing Chart (LPC) will not be found on the DAL.
- CAP/CLIA certificates or the equivalent must be on file in MiLab for each testing laboratory for the analytes listed and this is documented on the DAL.
- The DAL includes the name of the processing laboratory for viable peripheral blood mononuclear cells (PBMCs) if relevant to the specific study.

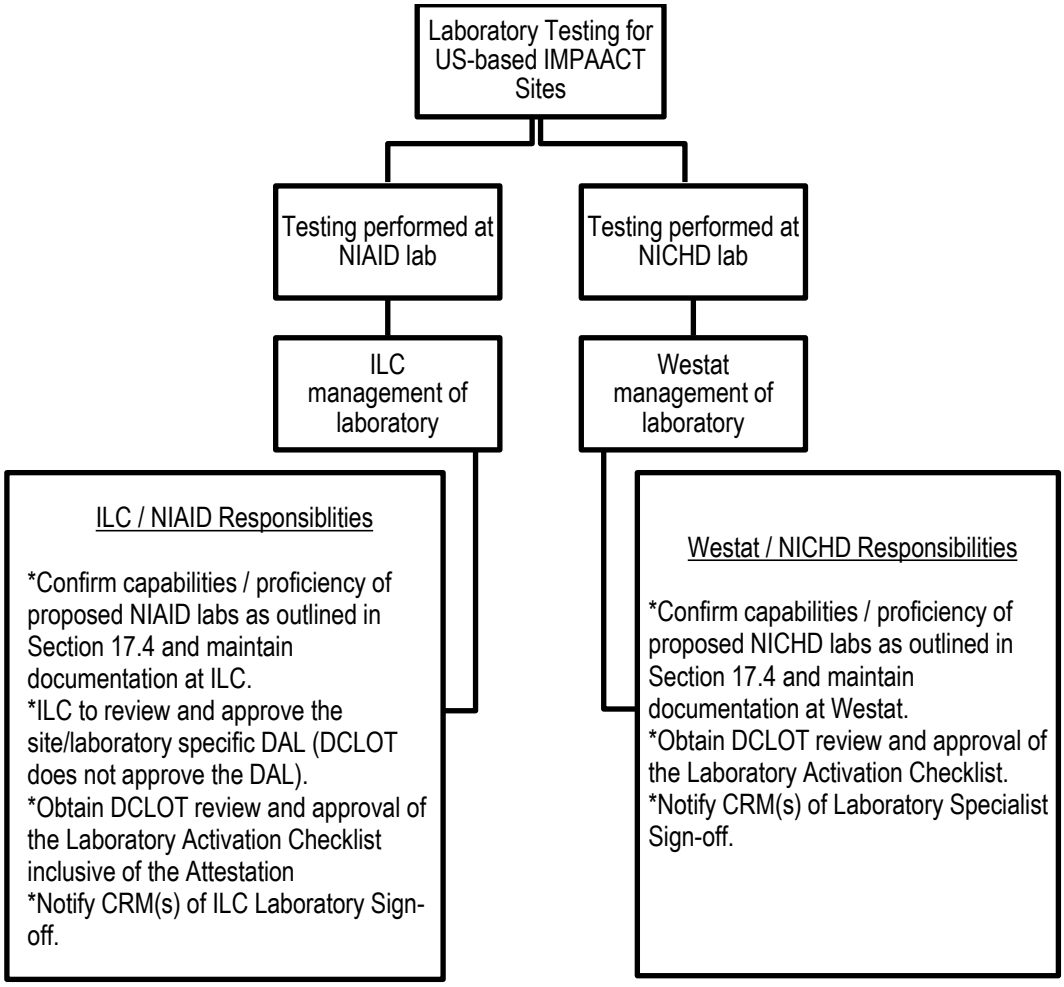
One purpose of the MiPAL system is to facilitate and expedite the completion, review, and approval process for the DAL in a web-based format. Through the use of the MiPAL and MiLab systems, the site-associated laboratories can submit their DAL data along with supporting assay and laboratory documents. ILC-approved DALs are maintained within the MiLab system.

Training for the MiLab and MiPAL systems is available on the ACTG-IMPAACT Laboratory Center website in the form of videos: https://actg-impaact-lc.org/resources/videos/.

These include how to request a new MiLab user and an introduction to a MiLab user account.

Sites must submit updated DALs for review whenever laboratories or testing plans change. Laboratories must receive approval from the ILC prior to adding a new laboratory.

Figure 17-1. US-based Laboratory Approval



17.4.3 Study-Specific Laboratory Activation: US (NICHD)

For NICHD-sponsored laboratories, documentation consists of current copies of the following:

- Appropriate accreditations and certifications (e.g., CLIA and/or CAP) or equivalent for all laboratories performing study assays
- Approval by the IQA and satisfactory performance in the EQA program prior to laboratory activation should viable PBMCs be required
- HIV testing algorithm (if applicable to the study)
- All import/export permits required to complete the study (if applicable)
- Contractual and other regulatory arrangements (e.g., MTA and export permits) in place for testing at all primary and backup laboratories that are not clearly designated as a Network-approved central laboratory outlined within the protocol and/or LPC

- Attestation from the Laboratory Director and/or IoR or designee that:
  - Appropriate numbers of staff have current IATA or DOT training
  - Site staff have participated in the requisite study-specific training
  - Appropriate numbers of staff have received CPQA certification (if required for the study)
  - Normal reference ranges (pediatric) are available
- Any other DAIDS requirement(s)

Note: It is the IoR/Laboratory Director's responsibility to ensure that the documentation confirming their attestation is readily available for inspection (e.g., IATA certifications for at least two staff members throughout the study duration).

Site/Lab personnel are responsible for updating the respective parties and distribution lists with the appropriate and current site and laboratory contacts.

The above requirements are captured on a LAC that is approved by DCLOT. When a laboratory has met all requirements, the completed LAC is submitted to DCLOT for approval (i.e., signature) and then signed by the Westat Laboratory Specialist for final approval. When all signatures are obtained, the site and laboratory staff are notified via email of satisfactory laboratory activation with the completed LAC attached. The clinical research manager (CRM) is copied.

17.5 IMPAACT Laboratory Network Requirements: Non-US Laboratories Affiliated with Sites

17.5.1 Good Clinical Laboratory Practices (GCLP)

IMPAACT requires that each laboratory perform study-specific testing in a manner that meets the study sponsors' requirements as well as that of the Network. All laboratories conduct testing and operations to meet GCLP standards at a minimum. Adherence to GCLP standards ensures consistent, reproducible, reliable, and auditable laboratory results.

For additional information on GCLP (including GCLP training), refer to the DAIDS Clinical Research Policies and Standard Procedures Documents website:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

All clinical laboratory personnel involved in specimen processing and testing must take GCLP training, available on the DAIDS learning portal: https://daidslearningportal.niaid.nih.gov.

The GCLP training requirement does not apply to study nurses, physicians, or non-laboratory personnel who only collect and/or transport specimens. Fulfillment of GCLP training by study nurses, physicians, or other non-laboratory personnel who perform specimen processing and/or testing can be accomplished using one of the options listed here:

https://www.niaid.nih.gov/sites/default/files/daids-gclp-training-faq-may2023.pdf

DAIDS and/or its contracted Laboratory Auditing Group (currently PPD) conduct regular laboratory audit visits to determine laboratory adherence to GCLP standards. Each laboratory is notified of a pending audit and confirms the dates of the audits with the Laboratory Auditing Group. The length and duration of these audits are determined by the scope of testing conducted at the laboratory. After the audit, the laboratory receives an audit report and AP. The AP is reviewed by each affiliated NLC – for IMPAACT, this is the ILC for NIAID-supported sites, and Westat for NICHD-supported sites. Each network for

which the laboratory does study testing is responsible for reviewing the AP and grading the findings – 'critical', 'major', 'minor' and 'recommendation' – based on DAIDS GCLP Guidelines and any previous AP occurrences. Any items considered to be 'critical' are brought to the attention of the DCLOT coordinator during the reporting phase and before the release of the AP to the laboratory and affiliated Networks.

Laboratories are expected to resolve audit report findings within 30 days following receipt of the DAIDS audit report and associated AP. If a response for some or all of the findings is not received within 30 days, the laboratory works with DAIDS, pSMILE, and the applicable NLC, as needed, to resolve the audit report findings. All findings on the AP must be satisfactorily addressed prior to laboratory activation unless DCLOT provides an exemption (e.g., the AP includes an item related to TB testing and the study for which the laboratory is seeking activation is not a TB study).

17.5.2 Study-Specific Laboratory Activation

Prior to site implementation of a protocol, the ILC (NIAID) or Westat (NICHD) works with each site laboratory to confirm laboratory readiness for non-US laboratories. IMPAACT laboratory-specific study activation requirements include the following as appropriate:

- Completion and DCLOT approval of a study-specific PAL
- Receipt of an appropriate study-specific HIV testing algorithm for pediatric and/or adult participants
- Receipt of a study-specific Specimen Handling Query Sheet (NIAID) or Specimen Flow Chart (NICHD)
- Confirmation of successful proficiency testing performance for all study analytes, as monitored by pSMILE, IQA (CD4), and VQA
- Approval by the IQA and satisfactory performance in the EQA program prior to laboratory activation should viable PBMCs be required
- Confirmation of appropriate validation and/or verification for study-specified assays and instruments
- Normal references ranges/acceptable results are available for the study population, including age and sex matched norms as applicable. This requirement is included as part of the Attestation.
- Confirmation of compliant local laboratory backup arrangements
- Laboratory Director's CV (one time only, unless the Director has changed)
- Successful completion of all relevant outstanding Investigation Reports (IRs) for all study analytes
- Completion of all findings listed on the AP from the most recent DAIDS-contracted laboratory audit (unless exempted by DCLOT)
- Confirmation of documentation to allow export of specimens to the testing laboratories and/or repositories as required per the protocol (i.e., MTAs, Specimen Transfer Agreements [STAs], regulatory permit, etc.)
- Site/laboratory personnel are responsible for updating the respective parties and distribution lists with the appropriate and current site and laboratory contacts.
- Signed attestation by the IoR/Laboratory Director or their designee confirming:
  - At least two staff have current IATA specimen shipping certifications
  - Staff have participated in all required study-specific trainings including CPQA certification, if required
  - Contractual and other regulatory arrangements are in place for testing at all primary and backup laboratories that are not clearly designated as a Network-approved central laboratory outlined in the protocol and/or LPC
  - All required staff have completed GCLP training

  Attestations are to be redone when a new LAC is required; the attestation template includes the protocol version number.

All site-laboratory testing must be conducted using FDA-approved methods and kits, as appropriate and available. The use of non-FDA-approved test methods may be reviewed by the ILC on a case-by-case basis in consultation with DCLOT, the Network, and EQA providers to determine if additional assay validation requirements may be needed.

As described in Section 11, site-specific, laboratory-related activation requirements for each study are outlined by the ILC and Westat on template laboratory activation checklists for both US and non-US laboratories. The completed site-specific laboratory activation checklists are approved by DCLOT for laboratory activation for each study. Upon completion of all site-specific study laboratory activation requirements, the ILC (NIAID) or Westat (NICHD) notifies the laboratory, relevant site staff, and the Operations Center contact.

17.5.3 Protocol Analyte List (PAL/MiPAL)

Prior to site laboratory activation, each non-US site laboratory must submit a PAL for review, which includes the names of the processing (viable PBMC only) and testing laboratories, the methodology, EQA procedures used for each analyte, and any backup instruments/methods/laboratories. Serial numbers as well as the FDA and Conformité Européenne (CE; French for European Conformity) status of each instrument and/or assay must be included in the PAL so that validations and proficiency testing can be tracked. The ILC (for NIAID sites/laboratories), Westat (for NICHD sites/laboratories), and representatives from DCLOT (for both NIAID and NICHD sites/laboratories) carefully review each PAL to ensure it accurately reflects the study-specific testing requirements. The PAL also captures information provided by the site laboratory in the associated Specimen Handling Query Sheet/Specimen Flow Chart document (NIAID/NICHD) about the study-specific specimen management, processing (PK and viable PBMCs) and testing workflow.

The ILC and Westat are responsible for developing a study-specific PAL template for each protocol. The PAL template is distributed by the ILC (through the MiPAL system) or Westat (as a spreadsheet).

The purpose of the MiPAL system is to facilitate and expedite the completion, review, and approval process for the PAL in a web-based format. Through the use of the MiPAL system, the site-associated laboratories can submit their PAL data along with supporting assay and laboratory documents. NIAID sites and designated laboratories can complete their assigned MiPALs online in the overarching MiLab system. Training for the MiLab and MiPAL systems is available on the IMPAACT-ACTG Laboratory Center website in the form of videos: https://actg-impaact-lc.org/resources/videos/. These include how to request a new MiLab user and an introduction to a MiLab user account.

Select NICHD sites and designated laboratories can complete their assigned PALs using the Westat-provided spreadsheet.

Depending on the site affiliation, the ILC (NIAID sites) or Westat (NICHD sites) are responsible for distributing the study-specific MiPALs/PALs for completion to sites/laboratories that have been approved to participate in a given study. The site submits the completed MiPAL/PAL to either the ILC or the Westat representative for initial review and approval by DCLOT (see Figure 17-2).

Once approved, the completed PAL along with the required documentation is sent to DCLOT for additional review and final laboratory approval:

- Specimen Handling Query Sheet/Specimen Flow Chart (NIAID/NICHD)
- HIV Algorithm(s)
- Current pSMILE EQA Summary and Schedule for safety analytes tested in the PAL-designated primary laboratory(ies)
- Closed audit APs for the primary laboratory(ies)
- Completed and LC representative/NICHD Laboratory Specialist-signed LAC with Attestation

DAIDS-approved PALs and associated documents (Specimen Handling Query Sheet/Specimen Flow Chart, HIV Algorithm(s)) are posted to the pSMILE website and copies are maintained by the ILC within the MiPAL system and by Westat.

Laboratories must submit updated PALs for review whenever testing methods, instrumentation, or backup testing plans change. Laboratories must receive approval from the ILC (NIAID sites) or Westat (NICHD sites) and DCLOT prior to implementing the new testing methods or instrumentation or adding a new laboratory (see Figure 17-3).

Figure 17-2. PAL Review and Study-Specific Non-US Laboratory Approval Process

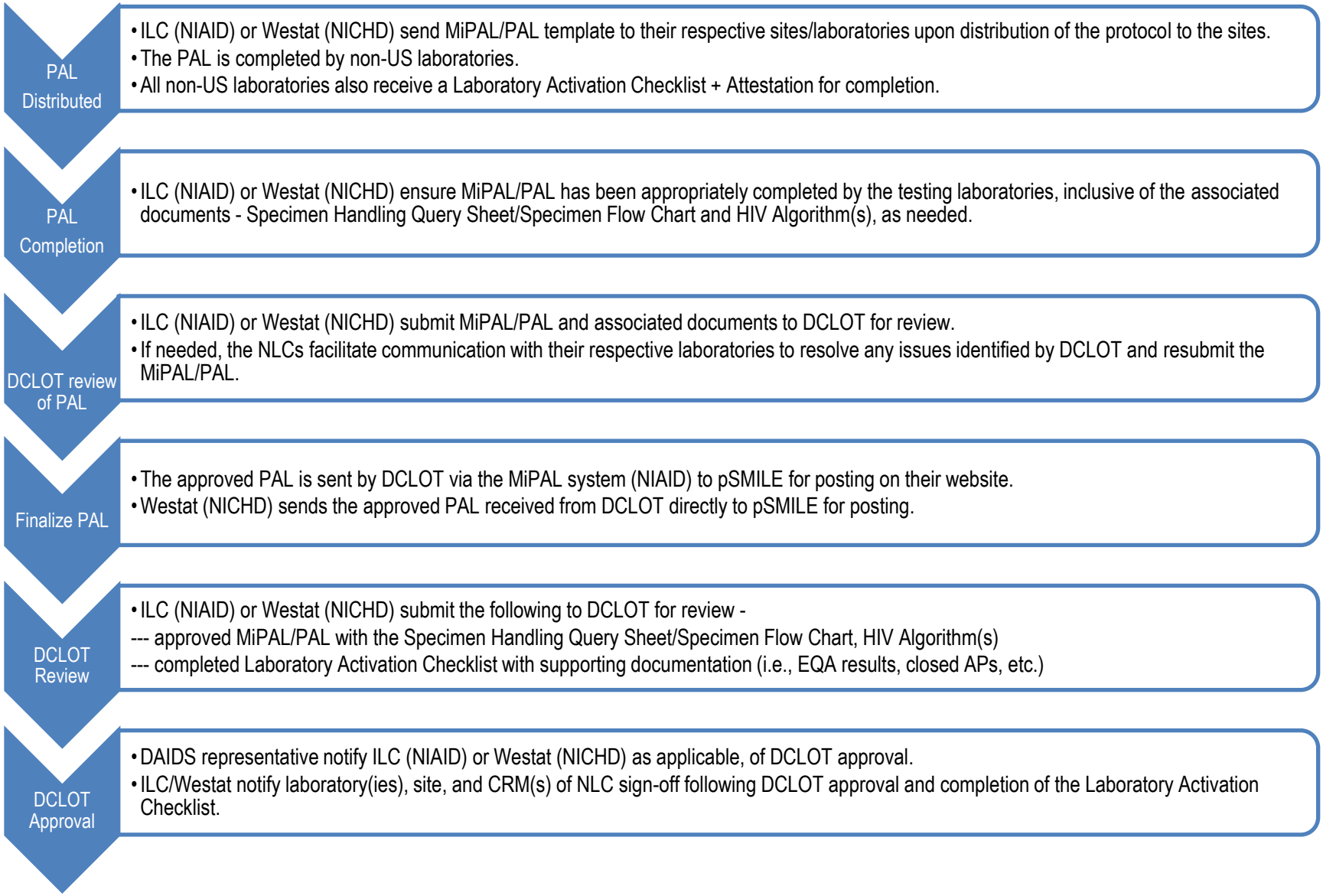
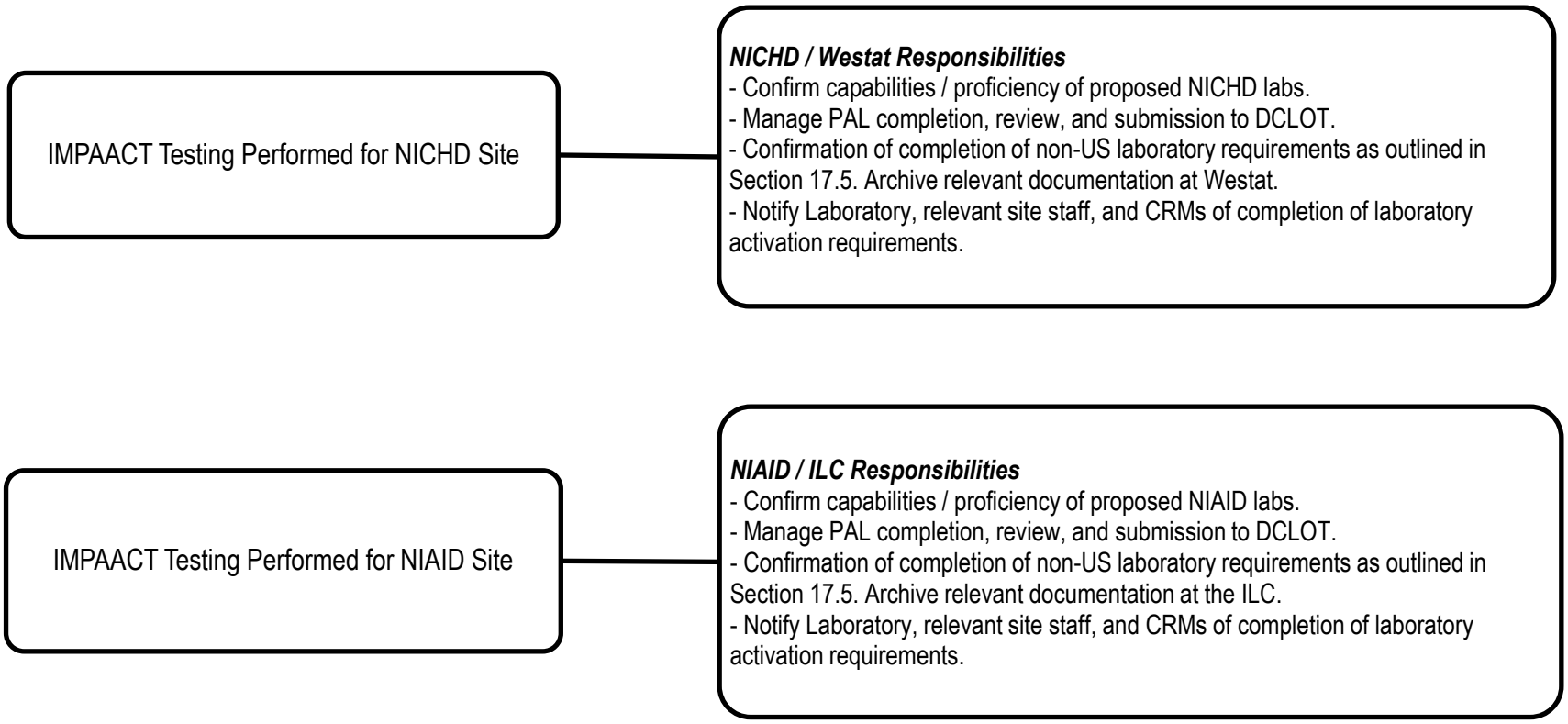


Figure 17-3. Non-US Laboratory Approval



17.6 Laboratory Data Management System (LDMS)

IMPAACT uses the LDMS for IMPAACT studies to assist with specimen data collection, generating specimen labels, specimen storage, and entry of results for certain assays. For each study, the LPC indicates which specimens are to be stored locally and which are to be shipped for testing or for storage at the central repositories. IMPAACT laboratories are required to use the LDMS Storage and Shipment modules for all Network clinical specimens that are stored or used for research laboratory assays.

LDMS is managed by the IMPAACT Data Management Center (DMC) at Frontier Science Foundation. Information on LDMS is available at https://www.ldms.org.

Laboratories are expected to use LDMS quick add templates for logging IMPAACT study specimens. The use of LDMS quick add templates makes it easier for laboratory staff to enter specimens into LDMS by pre-populating the specimen entry screen with expected specimens. Laboratories are required to log all expected specimens for a visit into LDMS, use the appropriate condition codes and comments to document when expected specimens are not available, and update any specimens logged using quick add templates with the observed data (e.g., the actual volumes collected & processed).

IMPAACT laboratories are required to use the LDMS Specimen Management and Storage modules to provide information on specimen processing and storage conditions for all logged specimens. Use of the Shipping module is required for tracking all shipments.

Additional LDMS fields required when logging viable PBMCs are described in the IMPAACT Network PBMC Processing SOP found on the ACTG/IMPAACT LC website: https://actg-impaact-lc.org/wp-content/uploads/2024/09/IMPAACT-Network-PBMC-Processing-SOP.pdf.

Specimens must be uniformly labeled according to an LDMS-specified format, which requires a computer-generated label that contains IMPAACT-specified identifiers and a barcode. All processing sites/ laboratories must use LDMS to generate labels. However, under emergency conditions, legible hand-labeled specimens are accepted, provided that the specimens are accompanied by the LDMS-generated electronic shipping file.

All specimen labels must include:

- Participant Identification Number (PID)
- Global Specimen ID (for specimen dates after 1 September 2005; not required for handwritten specimen labels)
- Protocol Number
- Specimen Date
- Primary/Additive/Derivative/Sub-Add-Der
- Specimen Time (24 hour)
- Two-dimensional LDMS-generated Barcode (for specimen dates after 1 October 2008)

Additional information about using LDMS is available via the LDMS website at https://www.ldms.org.

17.7 Data Corrections

The DMC sends queries to processing and testing laboratories to inquire about data discrepancies or missing data. IMPAACT laboratories are required to resolve and respond to DMC queries within two weeks. Site laboratories make specimen inventory corrections within LDMS, adding aliquot comments in LDMS to document the date, responsible staff, and reason for correction. Testing laboratories submit corrected data to the DMC through the same mechanism used for the initial data submission.

It is very important that LDMS laboratories communicate data corrections made on shipped specimens with shipment recipients such as repositories and testing laboratories. If PID errors are identified on shipped specimens, site laboratories are asked to notify the laboratory data manager (LDM) for approval before making corrections.

The repositories will not relabel specimens; when necessary, site laboratories should relabel before shipping. When labels do not scan at the CRS/laboratory, a new LDMS-generated label should be printed to replace the faulty one. The condition code in the LDMS should be changed from satisfactory (SAT) to relabeled (RLB), or RLB should be added as the second condition code. Viable PBMCs should never be relabeled.

17.8 External Quality Assurance (EQA) Participation and Proficiency Testing (PT) Providers

Proficiency testing programs, also referred to as EQA programs, are used as an external check on the QC and QA of a test system.

Laboratories are required to participate in proficiency testing programs for each test performed in the laboratory. Non-US laboratories participating in IMPAACT studies must participate in the appropriate proficiency panels provided by DAIDS-approved proficiency testing providers. Panels are sent to the sites based on the assays performed for the specific IMPAACT study in which the site is participating.

- pSMILE evaluates and develops the capability of non-US laboratories to participate in National Institute of Health (NIH) - DAIDS - supported clinical research by monitoring their PT performance across various EQA programs, including safety lab testing (e.g., chemistry, hematology, serology), point of care testing (e.g., urinalysis, pregnancy testing, HIV rapid testing), multiple aspects of TB testing
- All non-US labs are required to participate in the IQA CD4 PT program as well as the VQA PT programs for quantitative HIV-1 RNA PCR, qualitative HIV-1 Total Nucleic Acid Testing (NAT) and Genotypic HIV-1 Drug Resistance (RT/PR and INT):

https://dhvi.duke.edu/programs-and-centers/immunology-virology-quality-assessment-center/research-programs/immunology-quality-assessment/programs/CD4

https://dhvi.duke.edu/programs-and-centers/immunology-virology-quality-assessment-center/research-programs/virology

- All laboratories – both US and non-US – are required to participate in the IQA PBMC Cryopreservation program:

https://dhvi.duke.edu/sites/default/files/2026-04/IQA%20Cryopreservation%20PT%20Program%20Description_V5.pdf

IMPAACT Network Pharmacology Specialty laboratories coordinate with the CPQA on review of their assay validation plans, SOPs, and associated EQA. All Pharmacology Specialty Laboratories, whether US or non-US, are required to participate in the CPQA program.

Laboratories work directly with each DAIDS EQA provider or pSMILE to ensure that the appropriate testing panels have been ordered and are being tested by the laboratory. The ILC or Westat works with the various EQA providers and/or pSMILE to assist laboratories with any issues or problems with proficiency testing results, and work in collaboration with other NLCs and the site laboratory to monitor the follow up and resolution of corrective actions, as needed.

Prior to study activation, a laboratory must have satisfactory performance as defined by each of the DAIDS EQA programs. Following the validation/verification of a new instrument/method, a laboratory must pass one round of proficiency testing prior to utilization for study testing. Proficiency testing is an ongoing process with a regular schedule and continuous monitoring. Once a site is participating in a study, they must maintain satisfactory performance for each of the DAIDS EQA programs.

For additional information on pSMILE and DAIDS-approved EQA providers, please refer to the pSMILE, IQA, VQA and DAIDS websites:

- https://psmile.org/index.cfm
- https://dhvi.duke.edu/programs-and-centers/immunology-virology-quality-assessment-center/research-programs/immunology-4
- https://dhvi.duke.edu/programs-and-centers/immunology-virology-quality-assessment-center/research-programs/virology-2
- https://www.niaid.nih.gov/research/daids-clinical-research-policies-non-us-labs

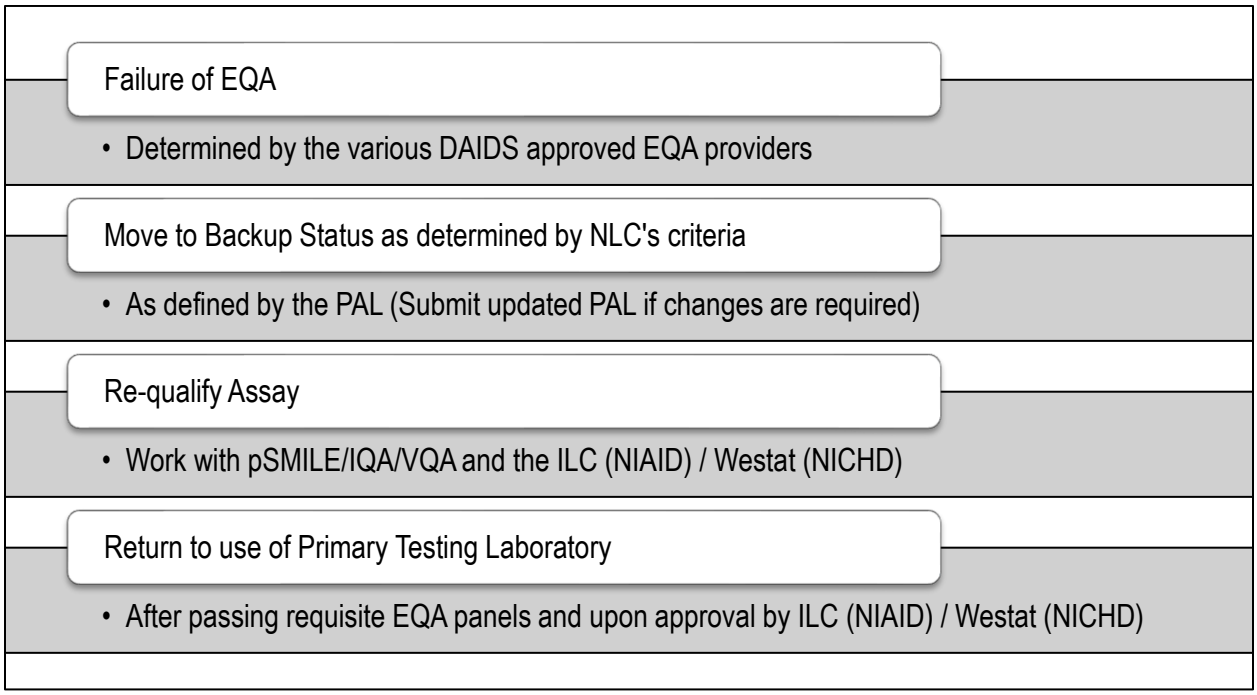
17.9 Testing Backup Plans

IMPAACT requires all non-US laboratories to establish/identify a backup testing plan (i.e., a second instrument, method or alternative laboratory) for all analytes used for study testing to ensure that study testing is not interrupted due to an instrument or laboratory issue. For non-US laboratories, this information is to be included on the PAL.

- All backup instruments or laboratories should either participate in EQA programs or have documented comparison testing performed between the primary and backup instruments to ensure integrity of testing.
- When a laboratory does not meet the minimum requirements for testing specimens based on their EQA results, it is necessary for them to use the backup laboratory as defined by their approved PAL (see Figure 17-4).
- More information regarding establishment of backup laboratories for DAIDS-sponsored sites can be found in the *Guidelines for the Development of Plans for Back-Up Labs* available at https://www.hanc.info/resources/sops-guidelines-resources/laboratory.html.

All laboratories must perform internal investigations for any EQA performance that is less than satisfactory. This process includes the timely submission of an Incident Report (IR) form. The IR process is facilitated by the DAIDS EQA providers and/or pSMILE. Unless otherwise stated on the IR form, the laboratory should complete an IR within 30 days. Laboratories with outstanding IRs are not allowed to participate in new studies. If the outstanding IRs are for analytes not relevant to the new study, a final decision on laboratory participation is made according to the ILC (NIAID) or Westat (NICHD) policy.

Figure 17-4. Moving to Backup Status



17.10 Instrument and Method Validation

DAIDS and IMPAACT require laboratories to perform validation: a) prior to implementing a new method or instrument into routine use; b) whenever the conditions change for which the method/instrument has been validated; or c) if the change is outside the original scope of the method/instrument. Validation should include diagnostic accuracy, precision, sensitivity, specificity, linearity, and reference range, as applicable.

Each laboratory prepares a validation plan for the new method/instrument to be established. Validation is submitted to the appropriate DAIDS EQA provider(s) (i.e., IQA, VQA, etc.) for review. Validations requiring pSMILE review are submitted through the MiLab system (for NIAID-sponsored sites) or NICHD Laboratory Specialist inbox (for NICHD-sponsored sites) for screening and then forwarded to pSMILE by the ILC or Westat. (Note: It is acceptable for an NICHD site laboratory to directly submit the validation to pSMILE and copy the NICHD Laboratory Specialist.) In some cases, the ILC, EQA provider or pSMILE may work with the laboratory in advance to establish a validation plan. Once the DAIDS EQA providers or pSMILE have deemed validation complete, the ILC (NIAID) or Westat (NICHD) approves use of that instrument/method for IMPAACT testing.

For non-US laboratories that are monitored by the ILC, any instrument and/or method that is to be added to a PAL is submitted to Laboratory Inventory Oversight in the MiLab system.

Resources on performing method/instrument validations are available in the NIH/NIAID/DAIDS GCLP guidelines at:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management.

Resources are also available on the pSMILE website at:

https://resources.psmile.org/resources/test-method-validation-and-verification
https://resources.psmile.org/resources/daids-gclp-standards

17.10.1 Change of Test Method/Kit/Instrument Mid-Study

Any change of test method, kit, or instrument after a trial has begun enrolling (aka mid-study) is not encouraged for IMPAACT laboratories. If a change in method/kit/instrument amidst study testing cannot be avoided, IMPAACT laboratories should notify the ILC (NIAID) or Westat (NICHD) representatives of a planned change in testing method/kit/instrument mid-study **before** implementing the change. This notification includes the following documentation to support the change:

- A summary of any completed validation performed for the method/kit/instrument as outlined above.
- A written summary of the comparison between methods/kits/instruments which addresses the reason for the change, information on methods/kits/instruments compared, summary of study results, and conclusion of the study.
- The corresponding package insert for any new method
- Demonstration of successful EQA performance using the new method/kit/instrument.

Any change in testing method/kit/instrument must be recorded as an update to the PAL. The respective laboratory requests the current, previously approved PAL to be reopened. For laboratories under ILC oversight, such a request is formally made via the MiPAL system. This request should only be submitted once the updated/modified validation has been reviewed and approved. The updated PAL must then be sent to the ILC or Westat and approved by DCLOT *prior* to the change(s) being implemented.

17.11 Management and Testing Plans

In accordance with IMPAACT requirements, all laboratories performing testing for IMPAACT studies should have a Specimen Management Plan, a laboratory Data Management Plan, and a laboratory Quality Management Plan (QMP).

- The Specimen Management Plan describes specimen acquisition, recording, testing, storing, and shipping, including specimen flow charts for specific studies, QA oversight, and corrective action procedures.
- The Data Management Plan describes the systems and processes for acquisition, data entry, recording, exporting, reporting, modification, security, and archiving of laboratory test results. The plan describes the QA oversight and corrective actions as well as how all laboratory test results are integrated into the general study database. Testing laboratories sending external data transfers to the DMC outside of electronic case report forms or LDMS (e.g., sending an Excel spreadsheet through the Data Submission System (DSS) on the DMC portal website) establish Data Transfer Agreements (DTAs) with the DMC that define the data format, content, and submission timeline.

- The laboratory QMP describes the overall QA/QC systems in place for study testing within the laboratory. For additional information on QMPs, please refer to the DAIDS requirements for non-US laboratories and resources available on the pSMILE website; these can be found at the following links:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-non-us-labs
https://resources.psmile.org/resources/quality-management

17.12 Shipping Capabilities

IMPAACT requires that laboratories maintain shipping capabilities outside of the US in accordance with IATA regulations and local country requirements. This includes adherence to International Civil Aviation Organization (ICAO)/IATA and DOT regulations on Category A/B shipments and shipping supplies.

Laboratories need to be capable of shipping required study specimens to facilities as outlined in each study-specific LPC, which are available on the IMPAACT website. Laboratories must also have the capacity to use LDMS to create the required shipping documents and files.

17.13 Specimen Shipping

IMPAACT requires laboratories adhere to the shipping guidelines established in the ACTG/IMPAACT Laboratory Manual when shipping IMPAACT specimens. Details on shipping requirements for IMPAACT, including a template specimen shipment notice and specimen checklist, are available in the ACTG/IMPAACT Laboratory Manual at:

https://www.hanc.info/labs/labresources/procedures/Pages/actgImpaactLabManual.aspx

Additional resources for shipping to BRI may be found here:

https://actg-impaact-lc.org/wp-content/uploads/2026/01/BRI_LTC_Call_16Jan26_HB_Final_PDF.pdf

17.13.1 Shipping Frequency and Monitoring

Shipments to the NIAID (BRI) and NICHD (Fisher BioServices) repositories must be prepared and shipped according to the shipping instructions posted on the ILC, HANC and/or IMPAACT websites, including the study-specific LPC.

The Network policy for quarterly frequency of specimen shipments and semi-annual for viable PBMCs to the respective repositories was detailed in memos distributed by:

- ILC (NIAID) on 24 APR 2024; available here: https://actg-impaact-lc.org/wp-content/uploads/2026/04/FINAL-IMPAACT-Shipping-Plan-Memo_24Apr2024.pdf
- Westat (NICHD) 09 DEC 2024; available on the NICHD/Westat website (access required): https://www.nichdclinicalstudies.org/Pages/Home.aspx

Individual studies may have established study-specific shipping frequencies; therefore, laboratories should always refer to the LPC for the most applicable information.

- NIAID/BRI: Shipments to BRI are evaluated according to the procedures described in the Shipment Evaluation SOP (LTC SOP 073) found here: https://www.hanc.info/resources/sops-guidelines-resources/laboratory/actg-impaact-laboratory-resources.html
- NICHD/Fisher BioServices: Shipments to Fisher BioServices are evaluated according to the procedures described in the NICHD Repository Shipping SOP found here: https://www.hanc.info/resources/sops-guidelines-resources/laboratory/actg-impaact-laboratory-resources.html

Shipments to testing laboratories must be sent as instructed in the LPC or as requested by the LDM. When requesting specimen shipments, LDMs provide a letter of instructions and a detailed listing of specimens that need to be shipped, if applicable. Laboratories should notify the LDM if they are not able to ship according to the time frame defined in the LPC or in the specimen request letter.

17.13.2 Shipping Box Requirements

Both the LDMS-generated electronic shipping file and storage boxes must be labeled with the batch number(s), protocol number(s), laboratory LDMS number, and CRS number. Multiple boxes can be put into the same shipping batch and on a single electronic file.

Laboratories should send -70°C full boxes when possible to the designated repository to avoid unnecessary specimen manipulation associated with re-packaging and consolidating boxes at the repository. However, in the interest of specimen integrity and minimizing storage time in local laboratory freezers, there is no minimum number of specimens per shipment to BRI (NIAID) or Fisher (NICHD). Laboratories should ship at the frequency specified in the LPC.

Processing sites/laboratories should perform 100% QC of all specimen labels, whether computer generated or handwritten, to ensure they are legible, complete, and can be read at the NIAID (BRI) or NICHD (Fisher BioServices) repositories and testing laboratories. Each label is scanned into LDMS prior to packing the shipment, with the exception of PBMCs where the labels are scanned prior to labeling the specimen tube. Before shipping, laboratories perform QA/QC in LDMS to check that all barcodes on labels are scannable, confirm that the box positions of all specimens match the box positions assigned in LDMS, and check that box positions match on all the shipping documents.

Laboratories may ship specimens from multiple studies (designated for storage in -70°C freezers) together to the designated repository in the same freezer storage box.

Note: The prior requirement that specimens for a given study are separated by an empty slot from specimens for a second study no longer applies.

IMPAACT CRS laboratories that are conducting testing for both the ACTG and IMPAACT networks **may not** ship ACTG and IMPAACT specimens together in the same shipment to BRI for specimen storage.

17.14 Specimen Archive and Destruction

IMPAACT periodically evaluates completed studies to determine whether specimens should be listed on the Specimen Repository Website and whether specimens should be archived for long-term storage or destroyed.

Once a study reaches the status *Participants Off Study & Primary Analysis Completed (POS-PAC)*, per DAIDS Study Status definition, the Operations Center reviews the protocol sample informed consent form (ICF) and confirms with the DMC if specimens are available in centralized repositories. If specimens are available and the protocol ICF allows for future use of samples, the Operations Center submits a repository spreadsheet listing to the DMC, and the DMC adds the applicable studies to the Specimen Repository Website.

Separately, the ILC and Repository Advisory Group (RAG) coordinator or designee initiate a review of studies to determine whether specimens should be archived for long-term storage or be destroyed once a study is Concluded, per the DAIDS Study Status definition, or approximately two years following the study status of POS/PAC, whichever happens first. The ILC/RAG generate a study status report of eligible studies meeting the timeline for evaluation and coordinates with the DMC Laboratory Data Division Chief (or designee), to confirm if specimens are currently available. Coordination with the Operations Center also occurs to identify whether any specimen storage and shipment restrictions exist within the applicable protocol.

Following this initial review, the DMC queries the protocol team to confirm if all protocol testing has been completed for POS/PAC studies. At a minimum, consensus should be obtained from at least one protocol chair, one LDM, and one statistician. Once completion of protocol testing is confirmed for POS/PAC studies, and for all Concluded studies, if the protocol does not allow for long-term storage, the DMC notifies the site laboratories and repositories, as applicable, that specimens must be destroyed. For protocols that specify long-term storage and future testing is permissible, the RAG coordinator generates a memorandum for IMPAACT Management Oversight Group (MOG) review. The MOG determines if specimens, or a subset of specimens, should be transitioned to a centralized repository, destroyed, or remain locally at site laboratories. The RAG coordinator distributes the MOG decision to the applicable protocol team members, including the DAIDS and NICHD medical officers, protocol chairs, statisticians, LDMs, and CRMs. The DMC notifies applicable laboratories and repositories as needed to facilitate destruction, shipment, or ongoing storage as per the MOG response. If MOG guidance is to destroy specimens at site laboratories, sites are advised that if they choose to retain samples, it is with no additional Network funding, tracking or management, and sites are responsible for ensuring compliance with all applicable regulatory and ethical requirements for any future use of these samples.

At this time, the DMC notifies laboratories to destroy specimens collected from participants who did not enroll (i.e., screen failures), did not consent, or withdrew consent, for future use of specimens (i.e., for non-protocol-specific testing). The DMC monitors that shipping and destruction are carried out.

In addition, the necessity to destroy specimens may be associated with any of the following:

- A CRS or laboratory is defunded or closing: For active studies, the CRS contacts each study team to determine their shipment or destruction instructions. For closed studies, the DMC provides the CRS and/or laboratory with an inventory listing and instructions about which specimens need to be destroyed or shipped to a repository.
- Local laws or regulations limit the storage and use of specimens: It is the CRS's responsibility to track their own local laws and regulations, and to contact the study team and ILC/Westat when specimen destructions are required. Upon team or ILC/Westat approval, the CRS may contact the laboratories and repositories to request specimen destruction. The DMC also reviews the information collected in the Material Transfer Agreement Tracker (MTAT) and contacts the CRS about the potential need to destroy specimens.
- A freezer failure or a thawed or otherwise compromised shipment: The CRS or laboratory shall communicate with the ILC/Westat and study team for approval to destroy compromised specimens.

- Specimens were collected outside the protocol requirements or without consent: The CRS shall contact the study team and ILC/Westat when specimen destruction is required due to a protocol deviation. Upon team or ILC/Westat approval, the CRS may contact the laboratories and repositories to request specimen destruction.
- Remnants remain after testing is complete: Unless otherwise stated in the study-specific LPC, remnant specimens that exist in storage after the required protocol-related testing is completed should be destroyed and not used for any other purposes or shipped to the biorepository.

The PI of the laboratory or repository is responsible for ensuring that IMPAACT specimens are stored and ultimately destroyed in accordance with all IMPAACT Network and institutional polices, institutional review board (IRB)/Ethics Committees (EC), any applicable local or country laws, and in a GCLP-compliant manner.

Laboratory/repository staff check specimen inventories to ensure that the specimens are stored in the facility and note and resolve any discrepancies such as specimen type, numbers, source protocol, etc., before destruction. Laboratory/repository staff update LDMS to accurately reflect that specimens were destroyed, including removing the specimens from the storage module, assigning the appropriate condition (e.g., DSR code for destroyed), and adding comments to document the date, responsible staff, and reason for specimen destruction. Lastly, laboratory/repository staff notify the DMC when the specimen destructions have been completed. The DMC reports the status of specimen destruction to the RAG.

For more guidance on destroying specimens, CRSs can reference *Discarding and Destroying Locally Stored Specimens* [LTC-SOP-77] available at:

https://actg-impaact-lc.org/wp-content/uploads/2026/04/LTC_SOP_77_Discarding_and_Destroying_Locally_Stored_Specimens_v1.0_20APR2026.pdf

17.15 National Approval Requirements and Material Transfer Agreements

IMPAACT requires laboratories to obtain any required national approvals necessary for testing in support of IMPAACT studies, including MTAs, STAs, and permits (when applicable to the site and study).

Note: if the testing which will utilize the specimens covered by the MTA is NOT for a protocol (e.g., NWCS), the ILC/Westat are not responsible for facilitating those agreements. Please see Section 11 for more information.
MTAs/STAs between the sites of specimen origin and testing/end user **laboratories and the Network repositories are the responsibility of the respective site**. These agreements are facilitated by the ILC or Westat. For select sites, these MTAs are submitted through the MiMTA portal in MiLab for easier tracking. The ILC or Westat review these documents to confirm that the specimen types and proposed testing for the respective protocol are accurate. Final copies of the executed MTAs/STAs are to be provided to the ILC or Westat for archiving. For select sites, the ILC files fully executed MTAs in MiLab. The documents are also maintained by the sites.

Use of BRI as a "pass through" to other laboratories is not allowed. The MTAs/STAs with BRI must allow for specimen transfer to a third party.

As part of site-specific study activation, non-US CRSs make an entry into the MTAT on the DMC Portal to provide the DMC and ILC with general information about the content of their MTAs for the study. See Section 11 for more details regarding site-specific study activation.

17.16 IMPAACT Quality Assessment Monitoring

Site laboratories performing testing are aligned with and chosen by the CTUs. The capabilities and performance of these laboratories are reviewed by the ILC (NIAID) or Westat (NICHD) to ensure regulatory compliance.

By law, all US laboratories performing clinical testing must be CLIA certified or equivalent and inspected every two years. Current certifications must be provided to the ILC (NIAID sites) or Westat (NICHD sites).

All non-US laboratories are assessed continuously to ensure that they meet minimum standards for GCLP compliance as described at:

https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

17.16.1 Laboratory Monitoring by DAIDS

DCLOT monitors and/or contractors (e.g., PPD) conduct routine audits of laboratories performing IMPAACT studies, usually on an annual basis.

17.16.2 Laboratory Monitoring by IMPAACT

ILC (NIAID)/Westat (NICHD) personnel conduct periodic laboratory visits to assess the implementation of IMPAACT protocols and laboratory QC procedures, including proper maintenance of laboratory testing equipment and appropriate use of reagents. The purpose and scope of the visit are discussed with site laboratory personnel prior to the visit. Whether on site or centrally located, ILC (NIAID)/Westat (NICHD) staff work directly with IMPAACT laboratory staff to address and resolve any QA/QC problems identified through proficiency testing, during laboratory visits or by the laboratory during study preparation or implementation.

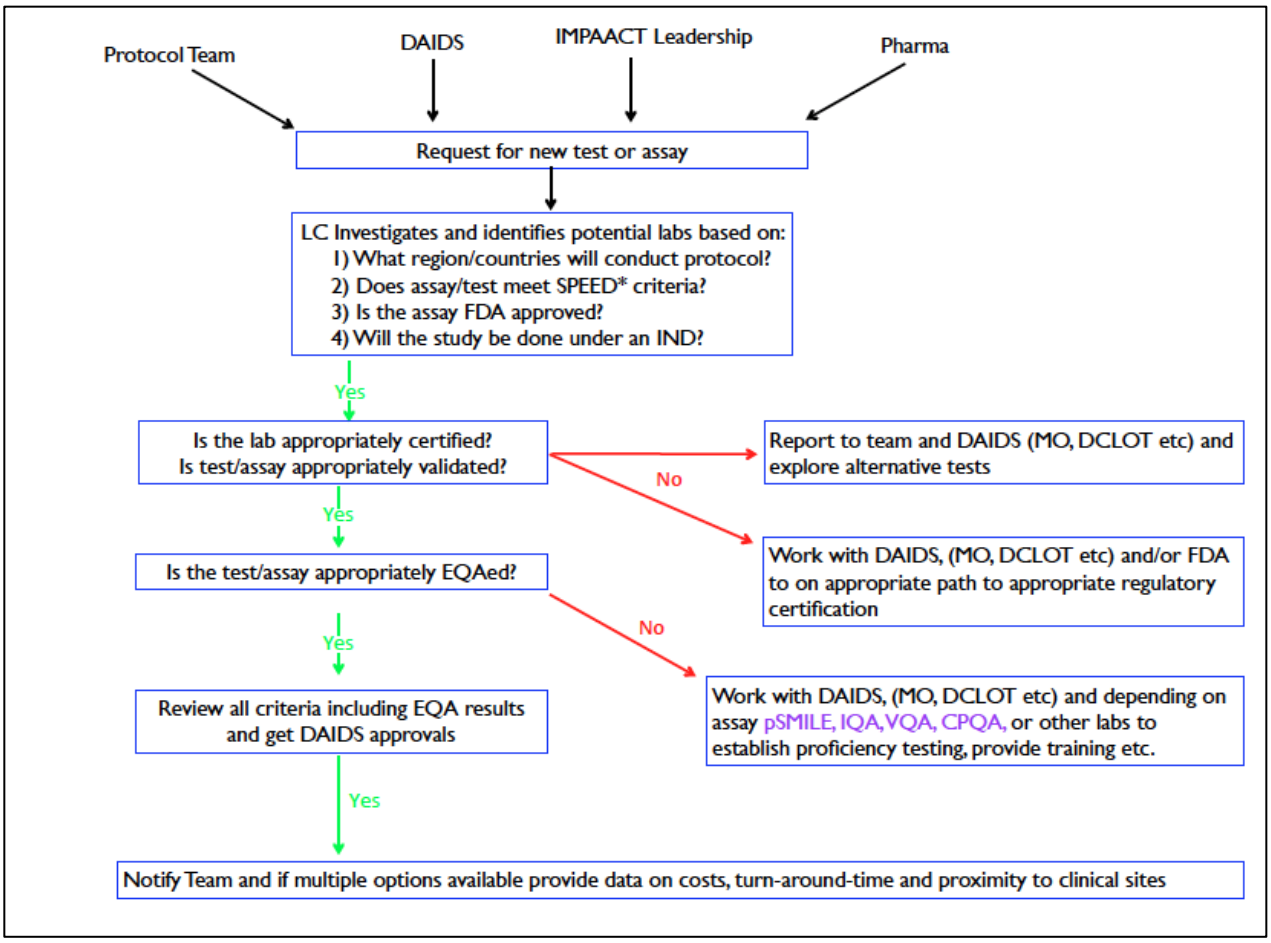
17.16.3 Laboratory Evaluation by the IMPAACT Network Evaluation Group (NEG)

On behalf of the MOG, the NEG develops and carries out the network evaluation program. This program focuses on critical aspects of study implementation at the site level, such as participant accrual and retention, data quality, laboratory performance, and regulatory issues. Additional details can be found in Section 18, Network Evaluation.

17.17 Introduction of Novel/Non-Standard Analytes into IMPAACT Studies

When a “non-standard” analyte is incorporated into an IMPAACT study, the ILC identifies and investigates potential laboratories that can perform the test, establishes the certification status of potential laboratories, determines the regulatory status of the analyte or test that is needed (FDA-approved or cleared), verifies whether the study is under an IND or not, and assures appropriate EQA. The ILC then works with DAIDS, DCLOT, and the appropriate EQA provider and/or pSMILE to bring the new tests on board. This process is outlined in Figure 17-5.

Figure 17-5. Process for Introducing a New Test/Assay



*SPEED criteria: **S**afety, **P**articipant Management, **E**ligibility, Primary **E**ndpoint, **D**iagnosis

All new assays and methods implemented for use with clinical specimens from IMPAACT trials must be validated and/or verified before being put into service. Decisions regarding the use of a new assay are made by protocol teams, IMPAACT Leadership, and/or DAIDS. Once the need for a new assay has been identified and appropriate laboratories identified, the ILC oversees the process using standards set forth by DAIDS, CAP, CLIA, the Clinical and Laboratory Standards Institute (CLSI), and FDA.

The processes and procedures to bring on a new test depend on the type of "test system" being introduced. CLIA regulations recognize three types of test systems:

1) Test systems that are FDA-cleared or approved and run by the laboratory without modification,
2) Test systems that are FDA-cleared or approved and run after modification by the laboratory, and
3) Test systems that have not been subject to FDA clearance or approval. These tests are often referred to as Laboratory Developed Tests (LDTs).

Prior to testing clinical specimens, the testing laboratory using an unmodified FDA-approved or FDA-cleared test(s) must verify that test(s) perform(s) as expected by obtaining data on:

- Analytic accuracy
- Precision
- Reportable range (clinical reportable range and linearity)

DAIDS mandates the use of FDA-approved assays, and exceptions are evaluated on a case-by-case basis. Any tests that are not FDA-approved, or which have been modified, must be approved prior to use. CLIA does not define the term "modified," but modifications are generally considered to include changes in test components (extraction, amplification, and/or detection), procedural parameters, assay cutoff values, specimen types or collection devices, etc.

If the new assay or test meets regulatory criteria for modified FDA-approved tests or for non-FDA-cleared tests (e.g., LDT), the laboratory must perform a validation study. The validation study must establish the test's:

- Accuracy
- Precision
- Analytical sensitivity (lower limit of target detection, as appropriate)
- Analytical specificity (including interfering substances)
- Reportable range of test results
- Reference intervals (normal values) and
- Efficiency or call rate for genotyping assays (for assays in which a large number of specimens are available)

These performance specifications are established through the following experiments:

- A comparison of methods experiment to estimate inaccuracy/bias (may include a recovery experiment) [accuracy]
- A replication experiment to estimate imprecision [precision]
- A linearity experiment to determine reportable range and lower limit of quantification (LLOQ) (for quantitative assays) [analytic sensitivity]
- A limit of detection experiment to estimate the lowest concentration that can be detected [analytic sensitivity]
- An interference experiment to determine constant interferences [analytic specificity]
- A reference value study to determine reference range(s) [reference interval] that is compliant with *ILC SOP PRJSTR 002 Establishment of Reference Ranges (Adult and Pediatric)*

The method selected for determining performance specification depends on the particular test method, but must be scientifically defensible and based on methods employed by colleagues or as reported in the literature. The ILC proposes validation and verification study plans in consultation with DCLOT. Prior to initiating testing, the validation and/or verification reports must be approved by the ILC and DCLOT.

If no EQA program can be identified, a plan that meets study-specific regulatory requirements for proficiency testing is developed based on CLSI guidelines (GP29-A2 Vol. 28 No. 21) and submitted for approval (Clinical and Laboratory Standards Institute (CLSI) Assessment of Laboratory Tests When Proficiency Testing Is Not Available; Approved Guideline—Second Edition).

17.18 Changes in Laboratory Personnel

IMPAACT requires that laboratories notify the Network of changes in key laboratory personnel. Key personnel include the Laboratory Director (usually an MD or PhD scientist, who reviews and signs all operating procedures and reports, and who is ultimately responsible for a laboratory's performance and capabilities) and Laboratory Manager/Supervisor (one or more persons responsible for overseeing daily laboratory operations, review and release of testing results, proficiency testing results, and writing laboratory SOPs). Other personnel that are critical contacts for IMPAACT are also considered key personnel. If the Laboratory Director changes, the site should provide a signed and dated copy of the new Laboratory Director's CV.

In the event that key personnel are no longer associated with a laboratory, new key personnel are appointed, or key personnel roles change, an email needs to be sent to impaact.labcenter@frontierscience.org and to the NICHD/Westat representative (NICHDLabSpecialist@westat.com), if applicable, notifying them of this change. It is critical that the Network be aware at all times of the communication structure and appropriate contacts at each laboratory. The notification includes:

- The name of the key personnel who has either left or whose role has changed
- The effective date of the change and whether it is permanent or temporary
- Information about whom to contact during any transition period
- In the case of departure of key personnel, the name and contact information for their replacement

IMPAACT laboratories also notify the DMC about personnel changes using the Submit Contact Changes utility available on the DMC portal (https://www.frontierscience.org/IMPAACT/).

17.19 Laboratory Relocation

IMPAACT requires that laboratories notify the Network of any laboratory relocations affecting IMPAACT testing (including equipment moves within the laboratory/inter-laboratory). If a laboratory plans to relocate, notification must be sent to DAIDS and the ILC (NIAID) or Westat (NICHD) before the move occurs and again once the move is complete:

- Notification is sent to impaact.labcenter@frontierscience.org and to the NICHD/Westat representative (NICHDLabSpecialist@westat.com) if applicable.
- In addition, non-US laboratories are required to complete the Laboratory Relocation Planning Guide-Move Checklist available on the pSMILE website:

  https://resources.psmile.org/resources/physical-facilities/rdp-700-laboratory-relocation-planning-checklists.docx/view

A copy of the relocation checklist must be submitted to impaact.labcenter@frontierscience.org and the NICHD/Westat representative (NICHDLabSpecialist@westat.com), if applicable.

IMPAACT laboratories also notify the DMC about any address, phone, or email changes using the Submit Contact Changes utility available on the DMC portal (https://www.frontierscience.org/IMPAACT/).

17.20 Additional Resources

Websites for general information related to topics covered in this section, as well as those specifically cited in this section, are listed below.

General Information

DAIDS and the US NIH have established specific requirements for laboratory processing and testing specimens from research participants enrolled in studies that are funded by DAIDS. The policy referenced above has specific requirements for both US and non-US laboratories which are as follows:

- US Laboratory Requirements: https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs
- Non-US Laboratory Requirements: https://www.niaid.nih.gov/research/daids-clinical-research-policies-non-us-labs

Additional references and links are as follows:

- IMPAACT LC Resource Documents: https://actg-impaact-lc.org/
- ACTG/IMPAACT Laboratory Manual: https://www.hanc.info/labs/labresources/procedures/Pages/actgImpaactLabManual.aspx
- HIV/AIDS Network Collaboration: https://www.hanc.info/
- LDMS Website: https://www.ldms.org/

Specimen Shipping, Shipping Materials, and Information

- Saf-T-Pak; Dangerous Goods Safety Training: https://inmarkinc.com/training-solutions/
- International Air Transport Association: http://iata.org/index.htm
- FedEx Dangerous Goods Shipping Seminars: https://www.fedex.com/en-us/service-guide/dangerous-goods/resources.html
- US DOT: https://www.transportation.gov
- US DOT/Transporting Infectious Substances Safely: https://www.phmsa.dot.gov/transporting-infectious-substances/transporting-infectious-substances-overview

Risk Group Assessments

- ABSA International, The Association for Biosafety and Biosecurity: http://www.absa.org/
- CDC Select Agent Listings and Regulations: http://www.selectagents.gov/

Other Resources

- U.S. Department of Agriculture: Animal and Plant Health Inspection Service: http://www.aphis.usda.gov/