17 LABORATORY CONSIDERATIONS

17.1 IMPAACT Laboratory Center

The IMPAACT Laboratory Center (ILC) is affiliated with the University of California Los Angeles (UCLA), in Los Angeles, California. The ILC is responsible for the oversight of laboratory activities associated with the conduct of IMPAACT protocols at both United States (US) and non-US sites. The ILC is comprised of the IMPAACT Laboratory Center Principal Investigator (PI) and other personnel involved in the quality assurance oversight of IMPAACT laboratories participating in Division of AIDS (DAIDS)-sponsored clinical trials within the IMPAACT Network.

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, below.

The ILC provides oversight to site laboratories and IMPAACT specialty laboratories sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Clinical research sites (CRSs) sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) may also participate in IMPAACT studies and within the IMPAACT Network. Westat manages the oversight of laboratories supported by NICHD.

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 site laboratories sponsored by NIAID. Westat is responsible for site laboratory activities sponsored by NICHD. These respective duties include the following:

- Providing oversight of Network laboratories responsible for the collection, testing, and reporting of clinical trial results from biological specimens.
- Maintaining clinical laboratory documents using an electronic document management system and database.
- Assisting in the development and quality assurance assessment of local laboratory capacity at the Clinical Trials Units (CTUs) participating in IMPAACT studies.
- Reviewing and providing guidance on validation reports for new assays.
- Tracking regulatory and quality assurance documentation for all laboratories affiliated with NIAID and NICHD CTUs sponsored by IMPAACT.
- Preparing international (non-US) NIAID- and NICHD-supported laboratories to implement specific IMPAACT studies.
- Confirming that all laboratory testing in support of IMPAACT clinical trials meets the DAIDS requirements, including generating and overseeing study-specific Protocol Analyte Lists (PALs) and DAIDS Clinical Laboratory Oversight Team (DCLOT) laboratory approval.
- Working with protocol team members to develop, coordinate, or identify laboratory training(s) and materials.
- Conducting laboratory visits and assessing laboratory capabilities, if needed, to conduct IMPAACT studies.
- Liaising with External Quality Assurance (EQA) providers, vendors, and DAIDS contractors.
- Providing continuous monitoring of laboratory performance throughout the duration of IMPAACT studies.
- Overseeing all NIAID- or NICHD-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 Good Clinical Laboratory Practice (GCLP), will be brought to the IMPAACT Network Leadership, and NICHD if applicable, as they are identified.

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

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

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 several Specialty Laboratories in the areas of HIV Pathogenesis, Pharmacology, and Tuberculosis (TB) Diagnostics
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 the activities of IMPAACT trials
Site Laboratories*	• Perform routine study assays, such as hematology, chemistry, HIV RNA and DNA, ARV resistance testing, CD4 cell enumeration, etc.
Network Laboratories (NLs)	• Comprised of the network laboratory principal investigators and other network laboratory personnel involved in the quality assurance of the non-US laboratories participating in DAIDS-sponsored clinical trials • The NL for IMPAACT is the ILC (Westat laboratory representative is the primary contact for the NICHD-supported laboratories)
Primary Network Laboratory (PNL)	• DAIDS NL assigned to specific non-US laboratories and is responsible for all non-US laboratory-related communications • Each PNL may have an assigned contact person and/or a PNL email address (e.g., impaact.qaqc@fstrf.org) 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 NLs, which may utilize these shared services. • A list of the PNL assignments can be found on the HANC website at: www.hanc.info/labs/labresources/qualitymanagement/Lists/PNL%20Assignments/AllItems.aspx
Cross-Network Laboratory Focus Group (LFG)	• Comprised of members from DAIDS-funded networks: ACTG, HPTN, MTN, 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 NLs; standardized quality assurance practices across networks; and harmonization of laboratory processes and procedures to increase efficiency, especially at the shared laboratory sites

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

Laboratory Types	Description
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 lab-related guidelines and requirements for establishing new laboratories; ensure that protocols are conducted in accordance with GCLP; provide central guidance in clinical laboratory matters to various DAIDS entities; and optimize the contribution of DAIDS laboratory-related support contracts to network labs
Regionally Qualified Labs (RQLs)	• Laboratories that may be used to centrally perform testing (e.g., genotyping resistance testing) to reduce resource burden on clinical laboratories within the IMPAACT Network • Assays can include routine or specialty assays as needed to support IMPAACT studies
Laboratory Directors Group (LDG)	• Comprised of IMPAACT Specialty Lab 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.

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 trials 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 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, equipment, etc.), assay validations, and aspects of quality assessment and quality control.

The Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy outlines specific requirements for laboratory quality assessment procedures and QC activities. These policies cover required quality assessment activities for the laboratory and laboratory QC, including handling of reagents and conducting of assays. References for applicable US federal and international regulations are also included.

In accordance with DAIDS policy, all laboratory tests used for: 1) safety monitoring (e.g., hematology, chemistry); 2) patient management decisions (e.g., CD4, drug levels); 3) protocol eligibility (e.g., pregnancy tests); 4) primary study endpoints (e.g., HIV RNA); or 5) diagnosis (e.g., HIV, CMV, Syphilis, Hepatitis B), must:

- Be performed in a GCLP-compliant laboratory:

  - If in the US, must be College of American Pathologists (CAP) and/or Clinical Laboratory Improvement Amendments (CLIA) equivalent certified
  - For non-US laboratories, International Standardization Organization (ISO) 15189 compliance is suggested
- Meet DAIDS requirements, including age- and sex-appropriate reference ranges for study populations, verification studies for the US Food and Drug Association (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
- Successfully pass at least one round of EQA for each clinical analyte to be tested as part of an IMPAACT clinical trial and satisfy all other Network-specific requirements **prior** to testing in the conduct of an IMPAACT clinical trial. Demonstrate ongoing successful performance in EQA programs for all study analytes (e.g., passing two of the most recent three EQA panels through CAP/One World Accuracy [OWA], Virology Quality Assessment [VQA], Immunology Quality Assessment [IQA], etc.)

The compilation of these criteria, which include **S**afety, **P**atient management, **E**ligibility, **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 the DAIDS regulatory requirements as outlined below. Inclusion in the early stage of protocol development provides the ILC with lead time to ensure that proposed testing methods are available, meet regulatory requirements and, if not, work with DAIDS and others to develop appropriate plans to ensure compliance. The protocol team determines which laboratory assays are required including those pertaining to primary, secondary, and/or exploratory endpoints. 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 lab and assist in exploring options to ensure protocol-specific testing can be performed.

Protocol teams have an LTC member assigned to prepare a Laboratory Processing Chart (LPC) that outlines the specimen collection, processing, and shipping requirements for the study. The analytes required by the protocol and LPC are reflected in the study-specific PAL. Some IMPAACT studies have an accompanying manual of procedures (MOP) that is developed for a specific study, which may contain supplemental information and instructions related to laboratory procedures that need greater detail than what is included in the LPC.

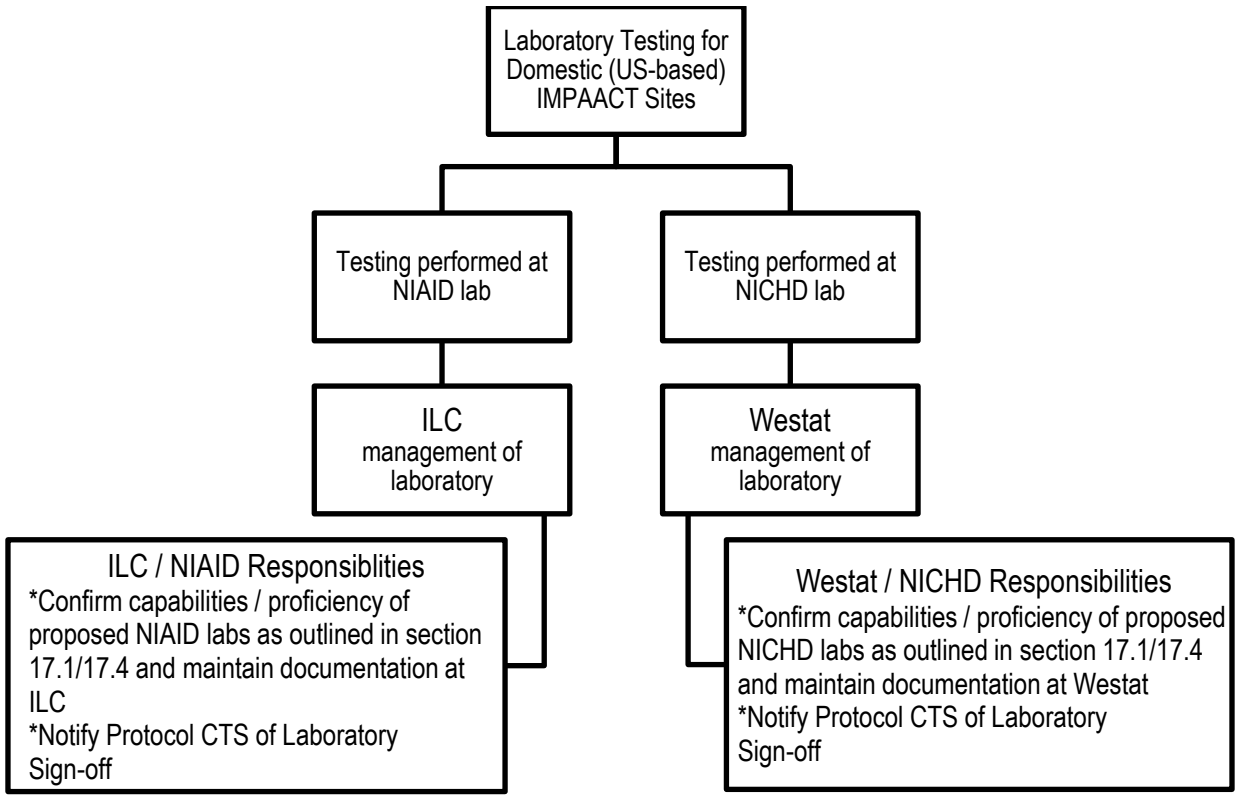
17.4 IMPAACT Laboratory Network Requirements: US Laboratories

All laboratories located within the United States (i.e., domestic laboratories) are required to provide the ILC with documentation that verifies their current abilities to conduct trial-specific testing prior to the site/lab being activated, as shown in Figure 17-1. This documentation should include current copies of:

- CAP and/or CLIA certifications as well as any state-required certification
- Laboratory Director's CV
- International Air Transport Association (IATA) training

- Local reference ranges for all assays being conducted for IMPAACT protocols (adult and/or pediatric) and
- Any IMPAACT study-specific training requirements (e.g., Dried Blood Spot [DBS] collection, clinical pharmacology, etc.).

Figure 17-1. Domestic (US-based) Laboratory Approval



17.5 IMPAACT Laboratory Network Requirements: Non-US Laboratories

17.5.1 Good Clinical Laboratory Practices (GCLP)

IMPAACT requires that each laboratory perform IMPAACT protocol testing in a manner that meets protocol sponsors' requirements as well as that of the Network. All laboratories should perform testing and conduct 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 recommended GCLP training), refer to the DAIDS Clinical Research Policies and Standard Procedures Documents website:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

DAIDS and/or its contracted Laboratory Monitoring Group (LMG; currently PPD) will conduct regular laboratory audit visits to determine laboratory adherence to GCLP standards. Each laboratory will be

notified of a pending audit and will confirm the dates of the audits with the LMG. The length and duration of these audits are determined by the scope of testing conducted at the laboratory. After the audit, the laboratory will receive an audit report and Action Plan (AP). The AP is reviewed by each affiliated Network Laboratory (NL) – for IMPAACT, this is the ILC for NIAID-supported sites and Westat for NICHD-supported sites – to determine which items, if any, are deemed critical to the respective network. In the event that an item is determined to be critical, the laboratory cannot begin new protocols until the relevant issue has been resolved. If an item is determined to be major and has the potential to affect study conduct, the ILC (NIAID) or Westat (NICHD) may hold study activation as well.

Laboratories are expected to resolve audit report findings deemed critical within 90 days following receipt of the DAIDS audit report and associated AP. The laboratory will work with DAIDS, pSMILE, and applicable NL, as needed, to resolve the audit report findings. Outstanding issues, even if within the 90-day completion window, that have been deemed critical may prevent laboratories from being activated to participate in new studies if they have the potential to inhibit the laboratory's ability to conduct the study according to GCLP and sponsor standards. Action items not denoted as critical are to be completed within 180 days.

17.5.2 Protocol-Specific Challenges

DAIDS requires that laboratories address all protocol-specific challenges prior to beginning testing in support of IMPAACT protocols. These challenges include (but are not limited to): specialized or non-standard EQA testing, validation and/or verification of new equipment/assays (for non-US laboratories), and specialized training. The laboratory will work with ILC (NIAID) or Westat (NICHD) to make sure these challenges have been adequately addressed.

Laboratories must perform testing in accordance with the version of the protocol and any Letters of Amendment (LoAs) that are currently Institutional Review Board (IRB)-approved at their CRS. Minor LPC updates not related to a protocol version change or LoA should be implemented immediately. Protocols and related study documents, such as LPCs and LoAs, are posted on the IMPAACT website:

http://impaactnetwork.org/studies/index.asp

17.5.3 Non-US Laboratory-Related Protocol Activation Requirements

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

- Completion and DCLOT approval of a study-specific PAL
- Confirmation of successful proficiency testing performance for all study analytes
- Receipt of an appropriate study-specific HIV testing algorithm for infant and/or adult participants
- Successful completion of all relevant outstanding Investigation Reports for all study analytes
- Completion of all relevant Action Items from the most recent DAIDS-contracted Laboratory Audit
- Current age- and sex-appropriate normal reference ranges
- Confirmation of appropriate validation and/or verification for protocol-specified tests
- Local laboratory backup arrangements
- Confirmation of IATA specimen shipping certifications for at least two members of the site laboratory staff

- Confirmation of documentation (i.e., Material Transfer Agreements [MTAs], Specimen Transfer Agreements [STAs], regulatory permit, etc.) to allow export of specimens to the testing laboratories or repositories as required by the protocol
- Current Laboratory Director CV (signed and dated)
- Successful completion of the appropriate proficiency testing (EQA Program) for all assays required to conduct the study
- Study-specific training documentation (to be determined on a study-by-study basis)

For studies conducted under an Investigational New Drug (IND) application, laboratory testing is expected to be conducted using FDA-approved methods and kits, as appropriate and available. The use of non-FDA approved test methods will 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 11.2.8, laboratory-related activation requirements for each study are outlined on template laboratory activation checklists for US and international laboratories and must be approved by the protocol chair and DAIDS medical officer (MO) as part of the approval for the overall activation requirements for each study. Upon completion of all study-specific laboratory activation requirements, the ILC (NIAID) or Westat (NICHD) notifies the laboratory, relevant site staff, and the IMPAACT Operations Center contact.

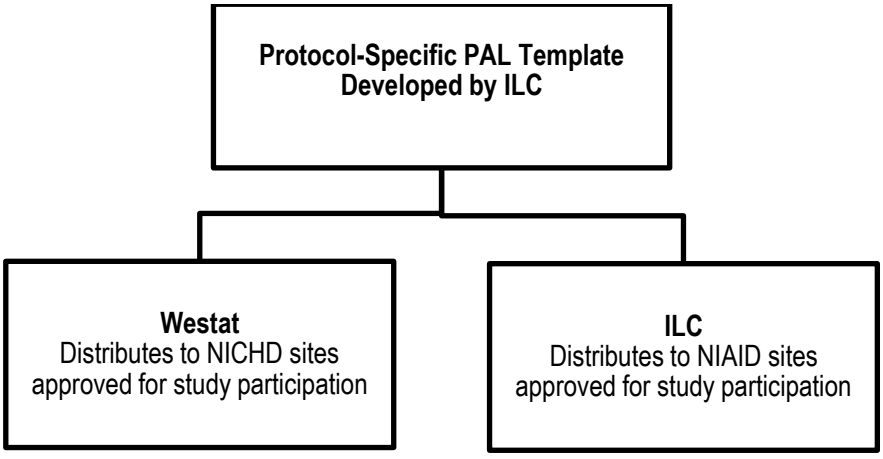
17.5.4 Protocol Analyte List (PAL)

Prior to site laboratory activation, each non-US site laboratory must submit a PAL for review, which includes the names of the processing and testing laboratories, the methodology, FDA approval status and EQA procedures used for each analyte, and any backup laboratories. The ILC (for NIAID sites/labs), Westat (for NICHD sites/labs), and representatives from DCLOT (for both NIAID and NICHD sites/labs) carefully review each PAL to ensure it accurately reflects the protocol-specific testing requirements. The PAL also captures information provided by the site laboratory about the protocol-specific specimen management and testing workflow.

The ILC is responsible for developing a protocol-specific PAL template for each protocol based on the current master PAL template provided by DCLOT and posted on https://psmile.org/index.cfm. The PAL template may be distributed by the ILC/Westat as a spreadsheet (IMPAACT 2009 and prior studies) or entered into the MiPAL system. 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. Sites and designated laboratories can complete their assigned MiPALs online at MiLabCentral.

Depending on the site affiliation, the ILC (NIAID sites) or Westat (NICHD sites) will be responsible for distributing the protocol-specific MiPALs/PALs for completion to laboratories/sites that have been approved to participate in a given study (see Figure 17-2: PAL Distribution). The site will submit the completed MiPAL/PAL to either the ILC or the Westat representative for initial review and subsequent review and finalization by DCLOT (see Figure 17-3: PAL Review and Study-Specific Laboratory Approval Process). Following finalization of the PAL, the completed PAL, along with any remaining associated documentation (e.g., normal reference ranges, updates on outstanding action plan items, etc.), will be sent to DCLOT for additional review and final laboratory approval. DAIDS-reviewed PALs are returned to the submitting laboratories; all finalized PALs are posted to the pSMILE website and copies are maintained by the ILC and Westat and within the MiPAL system.

Figure 17-2. PAL Distribution



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 17-4).

IMPAACT studies that are conducted under an IND application are subject to additional regulatory requirements. All testing for IND studies should be conducted utilizing FDA-approved assays and kits. Exceptions to this will be considered on a case-by-case basis in consultation with DAIDS.

Figure 17-3. PAL Review and Study-Specific Laboratory Approval Process

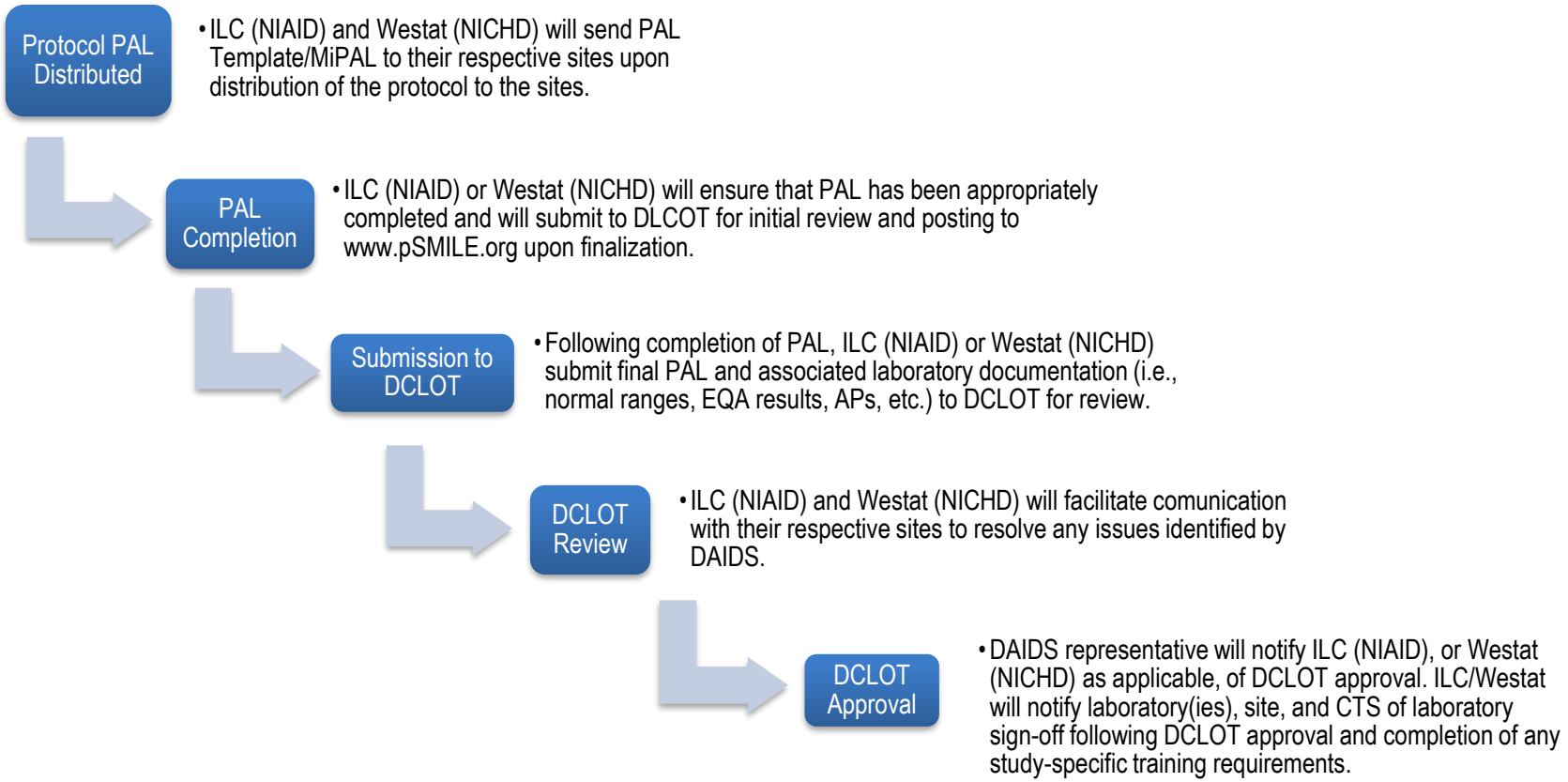
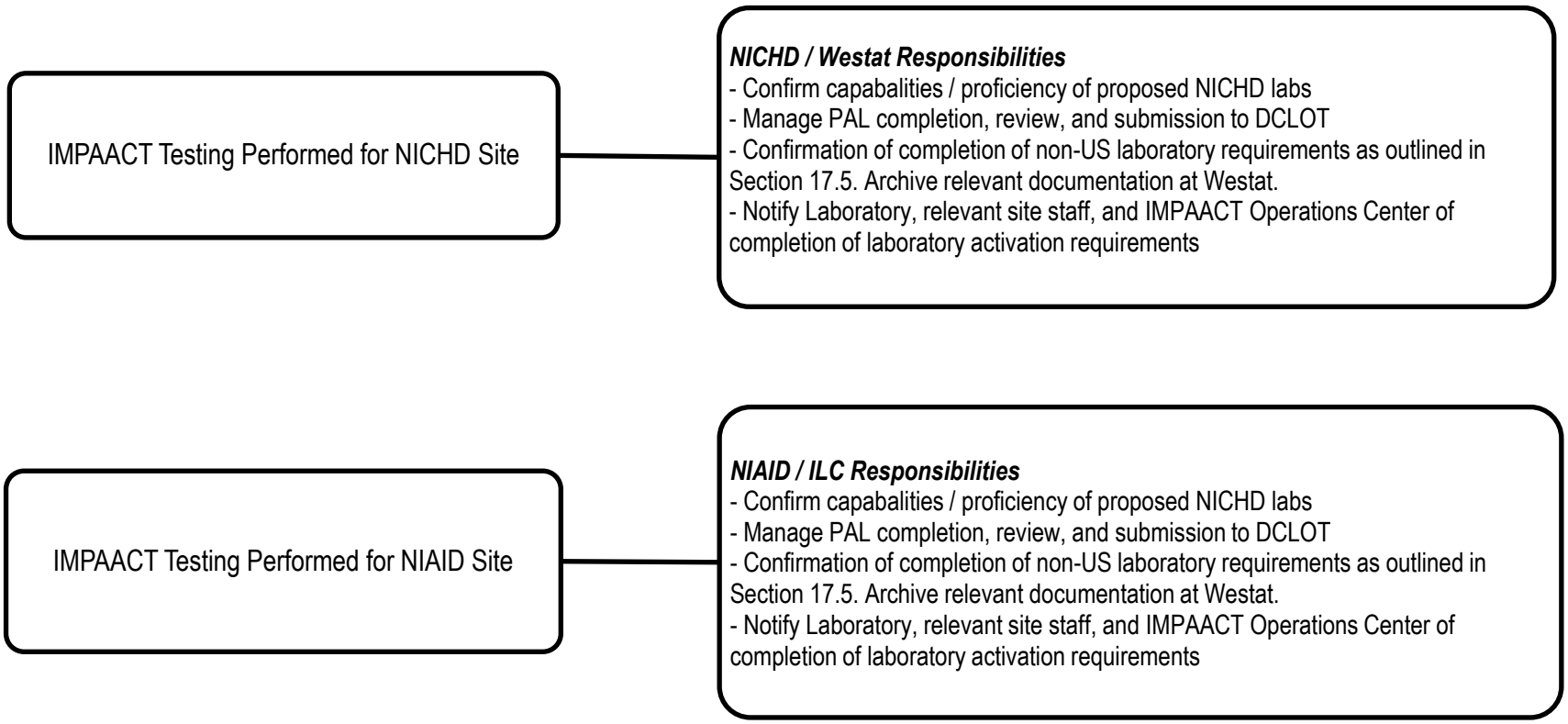


Figure 17-4. Non-US Laboratory Approval



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, Shipment, and Export modules for all Network clinical specimens that will be stored or used for research laboratory assays. Laboratories using LDMS for Windows are expected to export at least once per week.

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 have access to LDMS preloads (also called quick add templates) for most IMPAACT protocols. The use of LDMS preloads for available protocols makes it easier for laboratory staff to enter specimens into LDMS by pre-populating the specimen entry screen with expected specimens. Laboratories are expected to log all expected specimens for a visit into LDMS, and then use the appropriate condition codes and comments in order to document when expected specimens are not available and update any preloads with the observed data.

IMPAACT laboratories that process viable peripheral blood mononuclear cells (PBMCs) are required to use the LDMS Specimen Management and Storage modules to provide information on specimen processing and storage conditions for all logged PBMC specimens. The following additional fields are required for all viable PBMCs:

- Processing date
- Processing time
- Processed by tech initials
- Frozen time

Additional information about entering PBMC specimen information into LDMS is available via the following online tutorial as part of FSTRF Films at https://www.ldms.org/resources/videos/.

IMPAACT laboratories performing assays that are supported by LDMS are required to submit those assay results using LDMS.

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 site processing laboratories communicate data corrections made on shipped specimens with shipment recipients such as repositories and testing laboratories. If participant identification number (PID) errors are identified on shipped specimens, site labs are asked to notify the laboratory data manager (LDM) for approval before making corrections. Relabeling is generally not recommended except to correct PID errors on non-viable specimens.

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

Proficiency testing programs, also referred to as EQA programs, are used as an external check on the quality control and quality assessment 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 via the CAP, OWA, the IQA program, the United Kingdom National External Quality Assessment Service (UKNEQAS) – administered by the IQA, the DAIDS VQA programs, the Clinical Pharmacology Quality Assurance (CPQA) program for pharmacology testing, as well as other approved proficiency providers. Panels are sent to the sites based on the assays performed for the specific IMPAACT study in which the site is participating.

Laboratories work directly with each EQA provider to ensure that the appropriate testing panels have been ordered and are being tested by the laboratory. The ILC (NIAID) or Westat (NICHD) will follow all correspondence between the laboratory sites, pSMILE (for CAP or OWA issues), IQA (for UK NEQAS/PBMC Cryopreservation issues), and the VQA regarding any issues or problems with proficiency testing results, and work in collaboration with other Network laboratories and the site laboratory to monitor the follow up and resolution of corrective actions, as needed. IMPAACT Network Pharmacology Specialty laboratories coordinate with the CPQA on review of their assay validation plans and SOPs and associated EQA.

Laboratories must test all proficiency specimens in the same manner as patient specimens with no specified technologist assigned to run these specimens. The laboratory manager or designee shall review the final result forms before they are submitted to the proficiency testing provider within the specified deadline for submission of results. All proficiency testing reports must be reviewed and signed off by the laboratory director or manager. Prior to study activation, the laboratory needs to pass one round of proficiency testing. Once a site is participating in a study, the process for monitoring proficiency testing performance for each of the EQA programs (e.g., CAP, VQA, and IQA) follows the processes listed in Section 17.8.1. The status of pharmacology testing and assay validation is provided to the ILC monthly via the Drug Assay Directory.

Laboratories should be using DAIDS-approved EQA providers (e.g., CAP, CPQA, UKNEQAS, OWA, IQA, and VQA).

For additional information on DAIDS-approved EQA providers, please refer to the DAIDS Requirements for Non-US Laboratories websites:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-non-us-labs
https://psmile.org/index.cfm

17.8.1 College of American Pathologists (CAP)

CAP or OWA – pSMILE is responsible for the enrollment and monitoring of site laboratories in the CAP or OWA programs for chemistry, hematology, microbiology, viral markers, urinalysis, etc. Most CAP and OWA panels are sent out three times per year, although some analytes only have two panels per year. A score of less than 80% for an analyte constitutes unsatisfactory performance in a panel event. If a site laboratory fails to report that a panel has not been received, this will be considered unsatisfactory.
For analytes monitored by pSMILE, IMPAACT considers successful EQA performance to be the passage of the previous 2-of-3 EQA panels. For those panels that receive a percent grade, this means passing with 80% or greater, unless otherwise specified.

Example: Laboratory X submitted three CAP Chemistry panels in 2015. Albumin, Lactate, and Total Bilirubin were tested in this panel. The following results were received:

Analyte	1/A-2015	2/B-2015	3/C-2015	Successful EQA Performance
Albumin	20%	100%	60%	No
Lactate	100%	100%	100%	Yes
Total Bilirubin	100%	60%	80%	Yes

In this example, Laboratory X **does not** demonstrate successful EQA performance for Albumin in 2015.

17.8.2 DAIDS Virology Quality Assessment (VQA)

Virology Testing

When specified in the protocol that a VQA-certified laboratory is to be used for a virologic assay, laboratories are required to demonstrate successful performance in the VQA program. VQA monitored assays include HIV viral load (HIV RNA quantification), HIV DNA assays (Whole Blood and DBS), and HIV-1 genotypic resistance assays (including Geno-integrase). The ILC (NIAID) or Westat (NICHD) will assist with enrollment in this EQA program for Network-affiliated laboratories, as deemed necessary, by protocol participation and testing requirements.

Laboratories must be in good standing with the VQA for each virology assay they plan to use for protocol testing, as required. Laboratories must complete Investigational Reports (IRs) from the VQA when performance issues are identified.

For additional information on the VQA program and virology testing requirements, refer to:

https://www.hanc.info/labs/labresources/vqaResources/Pages/default.aspx

17.8.3 Immunology Quality Assessment (IQA)

The IQA is responsible for the enrollment and monitoring of site laboratories in the UK NEQAS Immune Monitoring Program for lymphocyte subsets and cryopreservation of PBMCs.

Lymphocyte Subset Testing

When specified in the protocol that an IQA-certified laboratory is to be used for an immunologic assay, laboratories must demonstrate successful performance for CD4, CD8, and CD19 testing, if applicable, via flow cytometry by continued participation and proficiency in the IQA Flow Cytometry PT program or the UKNEQAS (for non-US laboratories). The ILC (NIAID) or Westat (NICHD) will assist with enrollment in this EQA program for Network-affiliated laboratories, as deemed necessary by protocol participation and testing requirements.

Laboratories are evaluated for their ability to perform the measurement and absolute count on blinded specimens. These specimens include replicates, allowing for inter- and intra-laboratory performance

evaluation. Laboratories must be in good standing with the IQA for the respective assay they plan to use for protocol testing, as required. Laboratories must complete IRs from the IQA when EQA performance issues are identified.

Flow cytometry must be performed using standard flow cytometric measurements and in accordance with Centers for Disease Control (CDC) guidelines for flow cytometry. The CDC guidelines are available at Morbidity and Mortality Weekly Report (MMWR) 1997; 46 (No. RR-2) and MMWR 2003; 52(RR-02).

17.9 Peripheral Blood Mononuclear Cell (PBMC) Separation and Cryopreservation

Laboratories performing cryopreservation for IMPAACT studies should demonstrate successful performance of PBMC separation and cryopreservation. The laboratory must be able to separate viable PBMC and to pellet cells in accordance with the Cross Network PBMC Processing SOP, available via the HANC website at https://www.hanc.info/labs/labresources/procedures/Pages/pbmcSop.aspx (if asked for a username and password, click "Cancel").

Successful performance for PBMC processing is demonstrated by continued participation and proficiency testing with the IQA Cryopreservation PT program for viability and viable recovery of cells. The ILC (NIAID) or Westat (NICHD) will assist with enrollment in this EQA program for Network-affiliated laboratories, as deemed necessary by protocol participation and testing requirements. Laboratories must complete IR from the IQA when performance issues are identified.

IMPAACT requires that all laboratories performing cryopreservation of PBMCs must use approved lots of Fetal Bovine Serum (FBS), per the Cross Network PBMC Processing SOP. Only validated lots of FBS may be used. Information on ordering FBS is available on the HANC website at https://www.hanc.info/labs/labresources/procedures/Pages/ActgImpaactFbsOrdering.aspx (if asked for a username and password, click "Cancel").

Laboratories are approved to conduct viable PBMC processing for IMPAACT clinical trials if they are in good standing with the IQA and as mandated by the protocol. The ILC (NIAID) or Westat (NICHD) reviews grading for viability and viable recovery. Information on the IQA PBMC Cryopreservation program is available at https://iqa.center.duke.edu/programs/cryopreservation.

17.10 Mycobacterium Tuberculosis Quality Assessment (TBQA) Program

The *Mycobacterium Tuberculosis* (*M.tb*) Quality Assessment (TBQA) program, operated by MRI Global, provides appropriate resources to assess the ability of laboratories located both inside and outside the US to accurately and reliably perform *M.tb* testing (organism-based and hot-based) to diagnose active and latent *M.tb* infection, monitor disease progression, and assess treatment response and vaccine efficacy in direct support of clinical trials sponsored by the IMPAACT Network. The TBQA program provides assistance and training to laboratories that are having performance difficulties. As new tests/methodologies are developed, the TBQA program will facilitate their adaptation, standardization, and quality assessment prior to inclusion in NIAID-sponsored clinical investigations.

Additional updates on the program will be included as the program evolves.

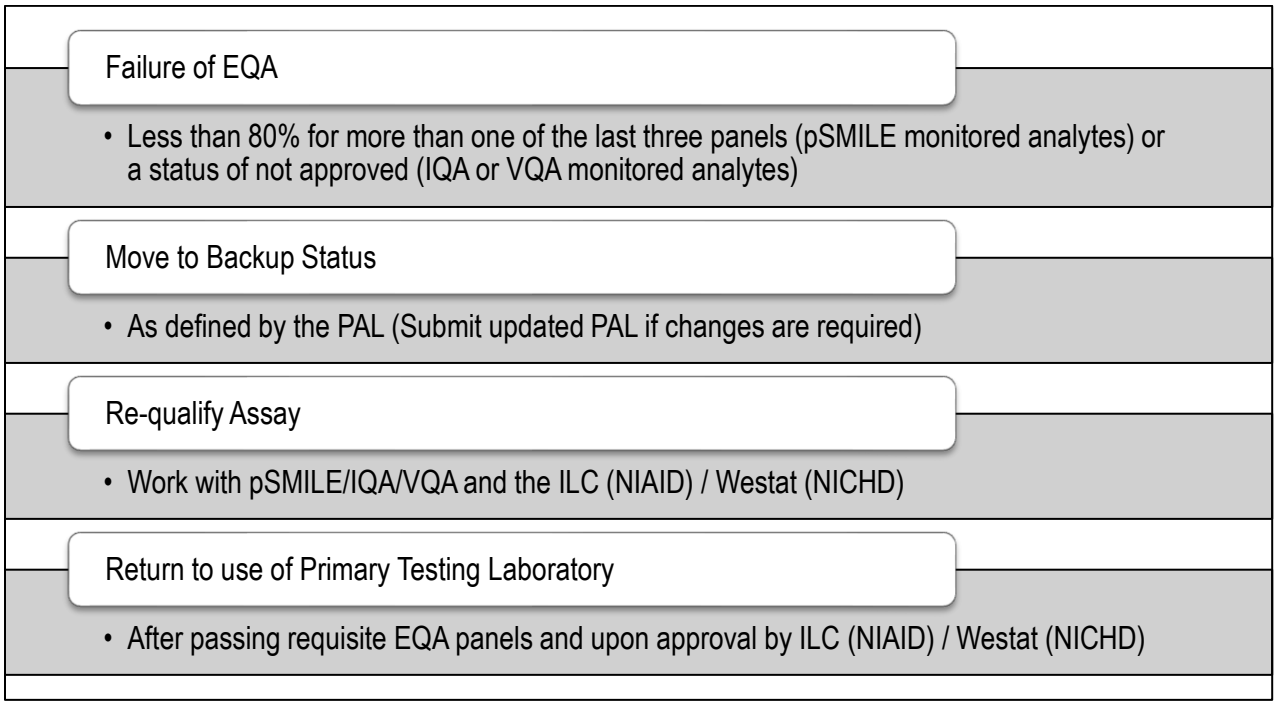
17.11 Testing Backup Plans

IMPAACT requires all laboratories to establish/identify a backup testing plan (e.g., a second instrument or alternative laboratory) for all routine protocol testing. Laboratories must identify a testing backup for

each analyte (or instrument) tested for a particular protocol to ensure that protocol testing is not interrupted due to an instrument or laboratory issue. For non-US laboratories, this information is to be included in 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 lab as defined by their approved PAL (see Figure 17-5).
- More information regarding establishment of backup laboratories for DAIDS sponsored sites is available at https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx.

Figure 17-5. Moving to Backup Status



All laboratories must perform internal investigations for any EQA performance that is less than satisfactory. This process includes the timely submission of an IR form. The IR process will be facilitated by the IQA, VQA, pSMILE, protocol teams, or either the ILC (NIAID) or Westat (NICHD). Unless otherwise stated on the IR form, the laboratory should complete an IR within 30 days.

17.12 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 testing should include diagnostic accuracy, precision, sensitivity, specificity, linearity, and reference range.

Each laboratory should prepare a validation plan for the new method/instrument that will be established. Validation plans should be submitted to the EQA provider coordinator (pSMILE, IQA, VQA, etc.) and the ILC (NIAID) or Westat (NICHD) for review. In some cases, the ILC or EQA provider may work with the laboratory in advance to establish a validation plan.

Once validation testing has been completed, the laboratory should submit a validation summary report that includes testing results and evaluation criteria used to the ILC (NIAID) or Westat (NICHD) for review and approval before the new method is used for IMPAACT clinical trial testing.

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 at the pSMILE website at http://resources.psmile.org/resources/equipment.

17.12.1 Change of Test Method/Kit/Instrument Mid-Protocol

Any change of test method, kit, or instrument after a protocol has begun (aka mid-protocol) is not encouraged for IMPAACT laboratories. If a change in method/kit/instrument amidst protocol testing cannot be avoided:

IMPAACT laboratories should notify the ILC, as well as NICHD/Westat representatives as applicable, of a planned change in testing method/kit/instrument mid-protocol **before** implementing the change. This notification should include documentation to support the change:

- A summary of any 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.
- Demonstration of successful EQA performance using new method/kit/instrument. Prior to implementing a new method/kit/instrument, IMPAACT laboratories should demonstrate successful EQA performance using the new method/kit/instrument. Please refer to the section above on EQA for additional information.
- A validation should be completed prior to implementing a new method or instrument.
- Any change in testing method/kit/instrument should be recorded as an update to the PAL. The updated PAL must be sent to the ILC and approved by DCLOT prior to the change(s) being implemented.

Please refer to the section above on instrument and method validation for additional information.

17.12.2 IND Studies

The use of FDA-approved testing kits in all IMPAACT IND studies is preferred by IMPAACT. The FDA approval status of testing kits should be documented on each protocol-specific testing plan (PAL) for IMPAACT IND studies. The ILC (NIAID) and/or Westat (NICHD) will work with DAIDS to determine how to proceed in the event that a laboratory is unable to complete testing with an FDA-approved kit.

17.13 Management and Testing Plans

In accordance with IMPAACT requirements, all laboratories performing IMPAACT protocols should have a Specimen Management Plan, a Laboratory Data Management Plan, and a Laboratory Quality Management Plan.

- The Specimen Management Plan should describe specimen acquisition, recording, testing, storing, and shipping, including specimen flow charts for specific protocols, QA oversight, and corrective action procedures.
- The Data Management Plan should describe the systems and processes for acquisition, data entry, recording, exporting, reporting, modification, security, and archiving of laboratory test results. The plan should describe the QA oversight and corrective actions, and how all laboratory test results will be integrated into the general protocol database. Testing laboratories sending external data transfers to the DMC outside of electronic case report forms/LDMS (e.g., sending an Excel spreadsheet through the Data Submission System (DSS) on the DMC portal website) shall establish Data Transfer Agreements (DTAs) with the DMC that define the data format, content, and submission timeline.
- The laboratory Quality Management Plan should describe the overall quality control and quality assurance systems in place for clinical trial testing within the laboratory.
- For additional information on quality management plans, please refer to the DAIDS Requirements for Non-US Laboratories websites:

https://www.niaid.nih.gov/research/daids-clinical-research-policies-non-us-labs
http://resources.psmile.org/resources/process-control

17.14 Shipping Capabilities

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

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

17.15 Specimen Shipping

IMPAACT requires laboratories to adhere to the shipping guidelines established in the ACTG/IMPAACT Laboratory Manual when shipping IMPAACT protocol specimens. Details on shipping requirements for IMPAACT are available in the ACTG/IMPAACT Laboratory Manual at:

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

17.15.1 Shipping Frequency and Monitoring

Shipments to the NIAID (BRI) and NICHD (Fisher) Repositories must be prepared and shipped per the shipping instructions posted on the HANC and/or IMPAACT websites, including the protocol-specific LPC.

- NIAID/BRI: https://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx Shipments to BRI will be evaluated according to the procedures described in the Shipment Evaluation SOP [LTC SOP 073].
- NICHD/Fisher: https://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx (NICHD Repository Shipping SOP)

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

17.15.2 Specimen Label Requirements

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 will be accepted, provided that the specimens are accompanied by the LDMS-generated electronic shipping file.

All specimen labels must include:

- 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)

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 clinic site number. Multiple boxes can be put into the same shipping batch and on a single electronic file.

Processing sites/laboratories will QC all specimen labels, whether computer generated or handwritten, to ensure they are legible, complete, and can be read at the NIAID (BRI) and NICHD (Fisher) repositories and protocol testing laboratories. Each label is to be scanned into LDMS prior to packing the shipment, with the exception of PBMCs, as the labels should be scanned prior to labeling the specimen tube.

17.15.3 Shipping Box Requirements

Laboratories should send -70°C full boxes when possible to the designated repository in order to avoid unnecessary specimen manipulation associated with re-packaging and consolidating boxes at the

repository. Before shipping, laboratories need to check and confirm that the box positions of all specimens match the box positions assigned in LDMS and shown on all the shipping documents.

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

IMPAACT CRS laboratories that are conducting protocol 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.

17.16 Specimen Destruction

In cases where laboratory specimens need to be destroyed following the completion of protocol required testing, destruction should occur as indicated by the IRB/Ethics Committee (EC) or as dictated by institutional policies or governmental agencies. The necessity to destroy specimens may be associated with any of the following:

- Individual participants do not consent, or withdraw consent, for future use of specimens (i.e., non-protocol specific testing).
- Protocol informed consent (IC) did not include consent for future use of specimens associated with non-protocol testing.
- Local laws or regulations limit the storage and use of specimens obtained during the course of an IMPAACT study.
- The CRS is defunded or closing.
- A freezer failure.
- A thawed or otherwise compromised shipment.

In the case of a freezer failure or compromised shipment, the CRS, laboratory, or repository will promptly notify the study team of the event and request their guidance for what should be done with the specimens.

For all other scenarios listed above, before initiating sample destruction, the IMPAACT LC will coordinate with the study team, including SDAC, to confirm that all protocol defined testing is complete, and then confirm specimen destruction approval from the following: protocol chair(s), DAIDS MO, and the NICHD MO. The Management Oversight Group (MOG) will be notified of the decision during the next scheduled meeting.

After protocol-defined testing is complete and all approvals are in place, the IMPAACT LC will notify the DMC which specimens need to be destroyed, and the DMC will then be responsible for notifying the laboratories and repositories that specimens may be destroyed. In some scenarios, such as for compromised freezers or shipments, the LC may communicate directly with the laboratory or repository about the approval for specimen destruction.

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, any applicable local or country laws, and in a GCLP compliant manner.

Laboratory/repository staff will check specimen inventories to ensure that the specimens are stored in the facility and will note and resolve any discrepancies such as specimen type, numbers, source protocol, etc., before destruction. Laboratory/repository staff will update LDMS to accurately reflect that specimens were destroyed, including removing the specimens from the storage module, assigning the appropriate

condition (e.g., DSR), and adding comments to document the date, responsible staff, and reason for specimen destruction. Lastly, laboratory/repository staff will notify the DMC when the specimen destructions have been completed.

17.17 National Approval Requirements and Material Transfer Agreements

IMPAACT requires laboratories to obtain any required national approvals necessary for testing in support of IMPAACT protocols, including Material Transfer Agreements (MTAs), Specimen Transfer Agreements (STAs), and permits (when applicable to site and protocol).

- MTAs between testing/end user laboratories are the responsibility of the laboratory organizations/institutions (e.g., Laboratory X in South Africa and Laboratory Y in Uganda). Final copies of the executed MTAs/STAs should be provided to the ILC (NIAID) or Westat (NICHD) for archiving.
- MTAs/STAs between site laboratories and the Network repositories, BRI (NIAID)/Fisher (NICHD), will be facilitated by the ILC (NIAID) and Westat (NICHD) for their respective laboratories. The ILC (NIAID) and Westat (NICHD) review these documents to confirm that the specimen types and proposed testing for the respective protocol are accurate. MTAs between repository/shipping laboratories are the responsibility of the laboratory repositories/organizations/institutions. Final copies of the executed MTAs/STAs should be provided to the ILC (NIAID-supported sites) or Westat (NICHD-supported sites) for archiving.
- NICHD/Westat may use the IMPAACT/BRI repository as a pass through to US-based end user labs when deemed appropriate or as outlined in the LPC.

17.18 IMPAACT Quality Assessment Monitoring

Site laboratories, including specimen processing laboratories, are aligned with and chosen by the CTUs. The capabilities and performance of these labs are reviewed by the ILC (NIAID)/Westat (NICHD) to ensure regulatory compliance.

By law, all US (i.e., domestic) laboratories performing clinical testing must be CLIA certified or equivalent (e.g., CAP, etc.) and are inspected every two years. HANC posts available, current CLIA/CAP certifications for US site laboratories on their website.

All laboratories outside of the US (i.e., non-US, international) 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.

17.18.1 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. The DMC may provide the monitoring contractor with site-specific laboratory information to enable them to conduct expected monitoring of specimen processing and storage of study-specific archived specimens.

17.18.2 Laboratory Monitoring by IMPAACT

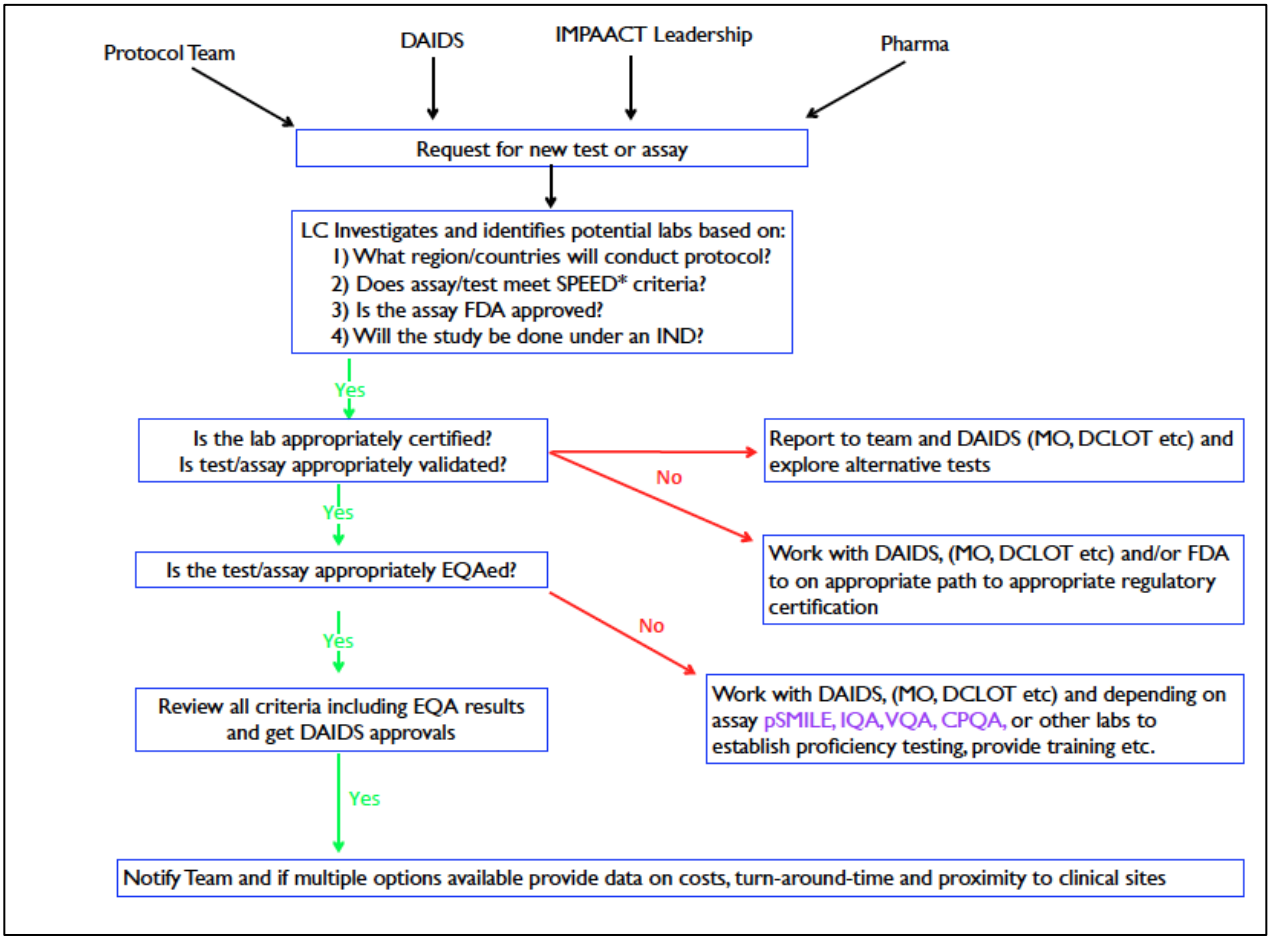
ILC (NIAID)/Westat (NICHD) personnel conduct periodic laboratory visits to assess the implementation of IMPAACT protocols, laboratory quality control procedures, including proper maintenance of laboratory testing equipment and appropriate use of reagents. The purpose and scope of the visit is

discussed with laboratory site personnel prior to the visit. Whether on site or centrally located, ILC (NIAID)/Westat (NICHD) staff work directly with IMPAACT site staff to address and resolve any quality control or quality assurance problems identified through proficiency testing or site visits or by the site during study preparation or implementation.

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

When a "non-standard" analyte is incorporated into an IMPAACT clinical trial, 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 to bring the new tests on board. This process is outlined in Figure 17-6.

Figure 17-6. Process for Introducing a New Test/Assay



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, Scientific Committees, 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, the CAP, CLIA, the Clinical and Laboratory Standards Institute (CLSI), and the 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 tests must verify that test(s) perform(s) as expected by obtaining data on:

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

For IND studies, FDA-approved tests are preferred. Any tests that are not FDA-approved, or which have been modified, must be approved prior to use in an IND study. 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 should be 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 LC 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.

17.20 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 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 should also be considered key personnel.

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.qaqc@fstrf.org and to the NICHD/Westat representative 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 should include:

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

17.21 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 should be sent to impaact.qaqc@fstrf.org and to the NICHD/Westat representative, if applicable.
- In addition, non-US laboratories are required to complete the Laboratory Relocation Planning Guide-Move Checklist, available on the pSMILE website:

http://resources.psmile.org/resources/equipment/validation/Equ3.0-28%20Lab%20Relocation%20Planning%20Guide-Move%20Checklist.doc

Please submit a copy of the relocation checklist to impaact.qaqc@fstrf.org and the NICHD/Westat representative, if applicable.

IMPAACT laboratories will 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/).

17.22 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 National Institutes of Health (NIH) have established specific requirements for laboratory processing and testing specimens from clinical trial 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://impaactnetwork.org/resources/lab-center/laboratory-guidance-documents
- ACTG/IMPAACT Laboratory Manual: https://www.hanc.info/labs/labresources/procedures/Pages/actgImpaactLabManual.aspx
- HIV/AIDS Network Collaboration: https://www.hanc.info/Pages/default.aspx
- LDMS Website: https://www.ldms.org/

Specimen Shipping, Shipping Materials, and Information

- CDC Shipping Regulations: http://www.cdc.gov/laboratory/specimen-submission/shipping-packing.html
- US Postal Service: http://www.usps.com
- Saf-T-Pak: https://inmarkinc.com/training-solutions/
- CDC Office of Health and Safety – Biosafety: https://www.cdc.gov/labs/BMBL.html
- International Air Transport Association: http://iata.org/index.htm
- FedEx Dangerous Goods Shipping Seminars: http://fedex.com/us/services/options/express/dangerousgoods/seminars.html?link=4
- Dangerous Goods: http://www.dangerousgoods.com
- DHL: http://www.dhl-usa.com/solutions/express.asp?nav=dhlExp
- US Department of Transportation: 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

- American Biological Safety Association: http://www.absa.org/
- CDC Select Agent Listings and Regulations: http://www.selectagents.gov/

Other Resources

USDA Plant and Animal Health Inspection Service: http://www.aphis.usda.gov/permits/index.shtml