International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Manual of Procedures

Version 5.0
31 May 2024

IMPAACT Manual of Procedures, Version 5.0, dated 31 May 2024
Overview of Section Contents and Summary of Changes

Section	Summary of Changes
Section 1 Overview of the IMPAACT Network	• Updated mission and moved to Section 1.1 • Clarified and updated IMPAACT scientific agenda and related research areas and priorities throughout Section 1.2 • Updated Figure 1-1 to remove the external scientific advisory group and clarified SLG at-large members • Updated sign-off requirements for the Network MOP to also include the SDMC and LC principal investigators and Operations Center Director in Section 1.4 • Updated Figure 1-2 • Added that Pharmacy Establishment Plans for NICHD-supported sites are managed through Westat in Section 1.5.1.3
Section 2 Network Groups	• Revised research area Scientific Committee names • Clarified clinical data safety monitoring responsibilities for DMC in Table 2-2 • Clarified technical assistance responsibilities for LC and Westat in Table 2-3
Section 3 Good Documentation Practice	• No changes; section version updated
Section 4 Protocol Teams	• Clarified that the protocol pharmacologist role may also be filled by a protocol pharmacometrician, and protocol statistician role may be filled by a protocol epidemiologist • Updated terminology for LDMS templates in Table 4-1 • Revised primary responsibility for LPC development from LT to LC representative in Table 4-1
Section 5 Community Participation and Engagement in the IMPAACT Network	• Added responsibilities for Community Engagement Program staff in Section 5 • Updated ICAB goals, roles and responsibilities, and participation requirements in Section 5.2 and its subsections • Updated ILG membership requirements, process for membership selection, roles and responsibilities, and SC representation in Section 5.3 and its subsections • Revised, clarified, and streamlined community input throughout the study lifecycle in Section 5.5 and its subsections
Section 6 Network Meetings and Communications	• Clarified conference call documentation in Section 6.1.3
Section 7 IMPAACT General Policies and Procedures: Funding, Conflict of Interest, Certificate of Confidentiality, and ClinicalTrials.gov	• Clarified timing for completion of the DAIDS ClinicalTrials.gov Protocol Checklist in Section 7.4.1 • Clarified sites to be included in Table 7-1 • Updated processes for requesting Letters of Support in Section 7.5
Section 8 Human Subjects Considerations	• No changes; section version updated

Section	Summary of Changes
Section 9 Protocol Development and Modifications	• Added cross-reference for SC voting members in Section 9.1.2 • Updated email alias for SDAC representatives in Section 9.1.3 • Clarified when sign-off is required, updated protocol section development prioritization, and added instructions for team members to inform CRMs when internal reviews are scheduled in Section 9.2.1 • Corrected expected timelines for protocol development in Table 9-1 • Clarified review members and conference call process for MPRG reviews in Section 9.2.4 • Added submission of completed RSR as part of CSRC review and clarified timelines in Section 9.2.5 • Clarified leadership review process for amendments in Section 9.3 • Added reference to new study enrollment systems, Stars, in Sections 9.3.2 and 9.3.3 • Revised general guidance for collaborative studies in Section 9.4
Section 10 Site Selection for IMPAACT Studies	• Clarified process for engaging sites beyond those affiliated with IMPAACT in Section 10.3
Section 11 Study-Specific Pre-Implementation Activities: Open to Accrual and Site-Specific Study Activation	• Revised primary author and required approvers for the Laboratory Processing Chart in newly added subsection 11.1.5.1 and in Table 11-1; clarified development and review process • Added subsection 11.1.5.2 to include processes related to specialty or focus laboratory readiness • Added reference to new study enrollment systems, Stars, in Sections 11.1.6, 11.2, and 11.2.7 • Updated versioning requirements for study-specific MOPs in Section 11.1.8 • Aligned SPDSMP finalization with DAIDS process requirements in Section 11.1.9 • Clarified requirements for primary SAPs in Section 11.1.10 • Added potential approvals of contracts/agreements in Section 11.1.11 • Added availability of ancillary supplies as part of pharmacy requirements in Section 11.2.6 • Added data management requirements in Section 11.2.7 • Clarified responsibilities for lab-related activation requirements in Section 11.2.8 • Added expectations for site-specific SOPs in Section 11.2.10 and added subsection for the age and identify verification SOP in Section 11.2.10.2

Section	Summary of Changes
Section 12 Study Implementation	• Updated roles/responsibilities related to study status change notifications (e.g., enrolling and closed to accrual) in Sections 12.1.2 and 12.2.4 • Added reference to Medidata Rave in Section 12.3.2 and clarified process for requests for eligibility corrections in Section 12.3.2.1 • In Table 12-1, created separate rows for all site email messages and Memoranda of Operational Instruction to clarify team sign-off requirements; shifted team sign-off requirements for SMC/DSMC to Section 13 • Revised standard Clinical Management Committee membership in Section 12.4.2 and clarified that designated clinicians on the CMC are responsible for responding to CMC queries
Section 13 Study Oversight	• Updated clinical site monitoring in Section 13.2 to align with similar text in new protocols • Clarified SMC chair and Operations Center representative roles in SMC summary review reports, added rows for Protocol and Laboratory Data Managers, and updated timelines for review of draft data reports in Table 13-1 • Clarified processes for closed review sessions in Section 13.5.2.2 • Clarified that draft documents, rather than near final drafts, are provided for initial SMC review and added processes related to team responses for initial reviews in Section 13.5.3.1 • Added guidance and process for team sign-off requirements in Section 13.5.3.2 and new Section 13.5.5 (with cross-reference in Section 13.8.2) • Clarified difference in processes for event-driven and interim analysis reviews compared to triggered or emergent safety reviews in Section 13.5.3.2
Section 14 Site Study-Specific Close-out	• Updated roles/responsibilities related to study status change notifications in Section 14.2 and in Table 14-2 • Clarified that the format and transmission method for sending test results to the DMC should follow the Data Transfer Agreement (DTA) in Section 14.3.5
Section 15 Ancillary Studies, Investigations, and Access to Study Data	• Clarified that information on available biological specimens can be accessed on the Specimen Repository website for approved studies in Section 15.1 • Added guidance around review of site-specific ICFs for NWCSs in Section 15.2 • Removed reference to required MOG/SLG review of ancillary proposals and noted proposal coordinator communicates with proposing investigators in Section 15.2.3 • Clarified communications around approvals or disapprovals and processes if MOG/SLG review is indicated in Section 15.2.4 • Clarified conditions under which an SDUA may not be required in Section 15.4.2 • Clarified responsibilities and procedures for NWCSs in Section 15.5

Section	Summary of Changes
Section 16 Training for Site Key Personnel and Other Site and Laboratory Staff	• Added reference to DMC Introductory Training and eLearnings in Table 16-1 • Clarified processes and guidance for LDMS training in Section 16.2.1
Section 17 Laboratory Considerations	• Removed reference to regionally qualified laboratories • Clarified IMPAACT Laboratory Center responsibilities • Added additional and clarified current lab activation requirements to align with current lab activation template • Added that all clinical lab personnel involved in specimen processing/testing must take GCLP training • Clarified review of Action Plans and that critical findings to be reviewed by DCLOT • Clarified process and documents reviewed by DCLOT through activation approval process • Added reference to cross-network PBMC processes • Added considerations for specimen shipping and clarified QC process for specimen labels • Updated process for reviewing studies and specimens to be added to repository website • Clarified MTAs/STAs development and review process
Section 18 Network Evaluation	• Updated timing for external Network reviews to approximately mid-funding cycle, or as needed • Added Westat as a source for outstanding laboratory critical action items and revised the standard for protocol deviations to indicate they are informational only in Table 18-1 • Removed NEG as entity providing Network productivity numbers in Section 18.3 • Clarified response requirements for sites in Section 18.4
Section 19 Data Analysis and Publications Procedures	• Clarified that publications timelines may be adjusted to account for regulatory submissions, if applicable, in Sections 19.3.1 and 19.3.3 • Added that study monitoring must be complete prior to database lock in Section 19.3.5 • Clarified processes for internal organizational reviews of publications in Section 19.6 • Clarified that co-authors must review draft conference presentation materials and updated templates link in Section 19.8 • Updated guidelines for authorship consistent with minor changes made in the ICMJE criteria, updated January 2024, in Section 19.9.1 • Clarified lead author responsibilities in co-author determination in Section 19.9.2 • Clarified that community or external stakeholder materials may be posted publicly in Section 19.12.2
Appendix I Unblinding Procedures	• No changes; section version updated

TABLE OF CONTENTS

1 OVERVIEW OF THE IMPAACT NETWORK

1.1 Mission and Background of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network is a global collaboration of investigators, institutions, community representatives, and other partners with a mission to improve health outcomes for infants, children, adolescents, and pregnant and postpartum people who are impacted by or living with human immunodeficiency virus (HIV) by evaluating novel treatments and interventions for HIV and its complications and for tuberculosis (TB) and other HIV-related conditions through the conduct of high quality clinical trials. IMPAACT's vision and overall goal is to end the worldwide HIV epidemic among these populations. To achieve this goal, the IMPAACT Network evaluates novel and durable treatments for both HIV, TB, and related diseases and conditions, strategies for antiretroviral treatment (ART)-free remission, and strategies to prevent and manage neuropsychological and mental health complications of HIV and its treatment.

IMPAACT was formed in 2006 through a merger of investigators from the Pediatric AIDS Clinical Trials Group (PACTG) and the Perinatal Scientific Working Group of the HIV Prevention Trials Network (HPTN). Following recompetition of leadership grants in 2013–2014, a new seven-year funding cycle began in December 2014. The Network was successfully recompeted in 2020, with a new seven-year funding cycle beginning in December 2020.

Overall support and funding for IMPAACT is provided by the National Institute of Allergy and Infectious Diseases (NIAID), with support and co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the United States National Institutes of Health (NIH). See Section 1.5 for additional details related to NIH support of IMPAACT.

In this Manual of Procedures (MOP), "HIV" refers to HIV-1 unless otherwise stated, as HIV-1 is the most widespread type of HIV worldwide and is the most common circulating type of HIV in locations where IMPAACT studies are conducted.

See the IMPAACT Network website for additional details: https://www.impaactnetwork.org.

1.2 IMPAACT Scientific Agenda

IMPAACT's scientific research agenda aims to:

- Advance treatment during pregnancy and postpartum, aiming to optimize maternal and child health outcomes and accelerate the evaluation (pharmacokinetics [PK], safety, antiviral efficacy), licensure, and optimal use of potent and durable antiretrovirals (ARVs) and other therapeutics for pregnant people and infants, children, and adolescents with HIV and related diseases and conditions.
- Evaluate the potential for ART-free remission through therapeutic interventions aimed at prevention, clearance, and post-treatment control of HIV reservoirs in infants, children, and adolescents with HIV and leverage expertise for evaluation of vaccines for HIV and related/co-occurring conditions in these populations.
- Evaluate novel approaches for TB prevention, diagnosis, and treatment in infants, children, and adolescents, and pregnant and postpartum people with and without HIV that will lead to optimal dosing and regimens, licensing, and improved treatment outcomes.
- Determine optimal and feasible biological and behavioral methods for the prevention and management of neuropsychological and mental health complications of HIV and its treatment in infants, children, adolescents and pregnant and postpartum people.

IMPAACT's research agenda is organized into four research areas as described in detail below.

1.2.1 Therapeutics

Priorities within the therapeutics research area include:

- Characterizing the PK properties and dosing of ARVs and other medications and relevant drug-drug interactions during pregnancy and lactation
- Evaluating novel prophylaxis regimens for infants born to people with HIV and other related diseases and conditions
- Identifying and rapidly evaluating the PK, safety, and antiviral efficacy of the most promising ARVs and other medications for treatment, accelerating licensure for pediatric populations living with HIV and other related diseases and conditions
- Optimizing the use of currently available ARVs in achieving virologic suppression among pediatric populations with ARV experience
- Evaluating ARVs and other medications and regimens that address the specific needs of adolescents with HIV

1.2.2 Tuberculosis

Priorities within the tuberculosis research area include:

- Evaluating the efficacy, PK, and safety of new and shorter drug regimens to prevent drug-susceptible and drug-resistant TB in infants, children, adolescents, and pregnant and postpartum people living with and without HIV
- Evaluating the efficacy, PK, safety, and acceptability of new drug regimens, optimizing existing drug dosing, and evaluating novel drugs for the treatment of prevent drug-susceptible and drug-resistant TB in infants, children, adolescents, and pregnant and postpartum people living with and without HIV
- Evaluating novel tools for the diagnosis of active TB, correlates of TB treatment response, and markers of disease progression in infants, children, and adolescents living with and without HIV
- Evaluating novel TB vaccines for prevention of TB disease

1.2.3 Cure and Immunotherapy

Priorities within the cure and immunotherapy research area include:

- Evaluating whether very early therapy with more potent ART that blocks virus entry and/or integration, in combination with broadly neutralizing antibodies (bNAbs), sufficiently limits HIV reservoir establishment in infants and leads to ART-free remission
- Evaluating immune-based therapies, including therapeutic HIV vaccines and bNAbs, in children and adolescents with HIV who have displayed long-term suppression on ART and therefore have small, low-diversity HIV reservoirs, with the goal of achieving ART-free remission
- Examining the potential for ART-free remission following combined initial therapy with ARVs plus immunotherapies, with and without latency reversal agents, in adolescents and young adults with horizontally acquired HIV to rapidly induce virologic control and potentiate elicitation of a "vaccinal effect" mediated through antigen-antibody immune complexes
- Examining the role of the central nervous system and T follicular helper CD4+ T cells as sanctuary sites following perinatal HIV infection and developing studies to explore the elimination of HIV reservoirs within these anatomic locations
- Identifying, within the context of IMPAACT ART-free remission and other clinical trials, optimal virologic and immunological biomarkers to detect and quantify HIV reservoirs, and predictors of reservoir size and time to viremic rebound

1.2.4 Brain and Mental Health

Priorities within the brain and mental health research area include:

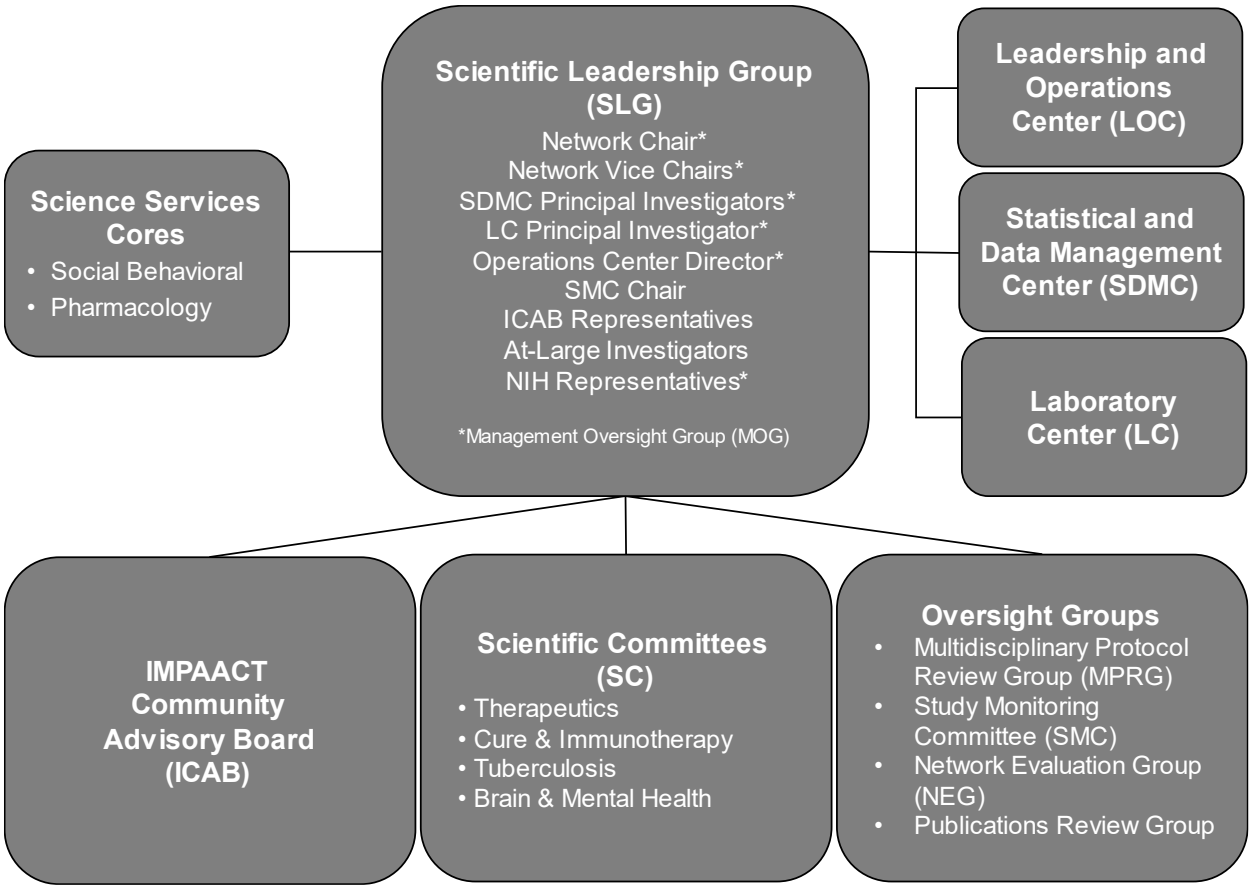
- Investigating potential neuroprotective and neurotoxic effects of ART to preserve neurocognitive development and mental health in infants, children, and adolescents
- Refining and optimizing the evaluation and treatment of neurocognitive and mental health disorders, particularly executive dysfunction, depression, and PTSD
- Evaluating novel preventive and/or therapeutic approaches to high-priority diseases of importance related to brain and mental health within pediatric, adolescent, and pregnant/postpartum populations with or affected by HIV, working with other partners and NIH Institutes

1.3 IMPAACT Network Organization

The IMPAACT Network is led by the Network chair and vice chairs. The Network chair serves as the chair of the Scientific Leadership Group (SLG), which sets the overall research priorities of the Network, in close consultation with four scientific committees (SCs) aligned with the four research areas described above. With input from the IMPAACT Community Advisory Board (ICAB), the SLG along with the SCs drives the scientific research agenda in alignment with the Network's mission and scientific agenda. To enable the SLG to focus on scientific priorities and leadership, most of the Network management functions are the responsibility of the Management Oversight Group (MOG), whose membership is a subset of the SLG. Through this structure, protocol teams are formed, and studies are implemented at clinical research sites (CRSs), which furthers the IMPAACT Network's mission. Additional details on the roles and responsibilities of each component included in Figure 1-1 are provided in Section 2.

In addition to the groups included in Figure 1-1, CRSs and protocol teams support the overall development and implementation of IMPAACT studies. IMPAACT research is conducted through the NIAID- and NICHD-supported sites worldwide. Investigators and other representatives of these sites, including community representatives, participate in all levels of the IMPAACT Network structure. Further details on CRSs are included in Section 2. Protocol teams are created for each IMPAACT research study so that studies are designed and implemented with the highest scientific and ethical standards. Protocol teams assume primary responsibility for scientific leadership in the development, implementation, and day-to-day oversight of IMPAACT studies and the dissemination of their results. Further details on the composition and functions of protocol teams are included in Section 4.

Figure 1-1. Network Leadership Organizational Structure



1.4 IMPAACT Operational Policies

The organizations and individuals that comprise the IMPAACT Network adhere to relevant US Federal regulations, along with the NIH/NIAID/Division of AIDS (DAIDS) policies, as a condition of receipt of Federal funding. Each organization within the IMPAACT Network must adhere to their institutional policies and guidelines on issue escalation and quality management. Each CRS also adheres to relevant local regulations and policies. The work of the IMPAACT Network is performed in accordance with the standards of good documentation practices, as described further in Section 3. Communications from the IMPAACT Network, including images and documents, will adhere to the NIAID HIV Language Guide, which includes language suggestions for communicating about HIV and related topics.

IMPAACT-specific policies and procedures guide Network investigators, site staff, and other members in meeting relevant requirements and standardizing site operations for each IMPAACT study. These policies and procedures are contained in the following:

- ***IMPAACT Network MOP:*** This manual provides general guidelines for Network members and describes IMPAACT policies and procedures for all sites, protocol teams, and staff. The IMPAACT Operations Center coordinates the development and maintenance of the Network MOP in collaboration with representatives of the Statistical and Data Management Center (SDMC), Laboratory Center (LC), and Network leadership; representatives of the MOG are responsible for reviewing sections prior to their release. Sign-off of all sections is required from the Network chair, DAIDS Program Officer, SDMC principal investigators, LC principal investigator, and the Operations Center Director, or their designees.

- ***Study-specific Implementation Materials:*** In addition to study protocols, the conduct of each IMPAACT study may be guided by study-specific implementation materials, including a study-specific MOP, Laboratory Processing Chart (LPC), monitoring and analysis plans, and participant enrollment and data collection materials. The materials provide instructional and reference resources and are generally developed for each individual study. Note that study requirements and procedures (including those described in site and study-specific standard operating procedures [SOPs]) must be conducted in accordance with the study protocol. If study-specific implementation materials or tools are inconsistent with the protocol, the specifications of the protocol take precedence. See Section 11 for further details regarding study-specific implementation materials.

- ***Site and Study-specific SOPs:*** SOPs for site operations and study operations ensure standard, uniform performance of site and study-related tasks and compliance with IMPAACT procedures, International Council for Harmonisation Good Clinical Practices (ICH GCP) guidelines, and US Food and Drug Administration (FDA) regulations, where applicable.

1.5 Governmental Organizations Involved in IMPAACT Research

As described above, financial support for IMPAACT is provided by NIAID with co-funding from NICHD and NIMH. The Network works with governmental regulatory agencies including the US FDA, the US Office of Human Research Protection (OHRP), and similar agencies in other countries where IMPAACT research is conducted.

1.5.1 National Institute of Allergy and Infectious Diseases/Division of AIDS

NIAID and its co-funding Institutes have substantial scientific and programmatic involvement in the IMPAACT Network through technical assistance, advice, and coordination. The role of the NIH staff within IMPAACT is to assist and facilitate, not to direct, the research activities.

Within NIAID, DAIDS develops and implements the research agenda to address the HIV/AIDS epidemic, supporting a global research portfolio to advance biological knowledge of HIV/AIDS and its related co-infections and co-morbidities. DAIDS staff participate on IMPAACT protocol teams, as described in Section 4, and governing committees, as described throughout the Network MOP. They also facilitate communication among other partners, such as other funding agencies, pharmaceutical companies, the US FDA, and IMPAACT leadership. DAIDS also supports and funds clinical research sites that participate in the IMPAACT Network.

As shown in Figure 1-2, DAIDS is comprised of the Office of the Director and four scientific programs. The Prevention Sciences Program, which includes the Maternal, Adolescent, and Pediatric Research Branch, is the scientific program responsible for IMPAACT. In addition, several groups within the Office of the Director collaborate to support IMPAACT Network functions, including the Office of Clinical Site Oversight (OCSO), which includes the Pharmaceutical Affairs Branch (PAB) and Monitoring Operations Branch (MOB), and the Office for Policy in Clinical Research Operations (OPCRO), which includes the Regulatory Affairs Branch (RAB).

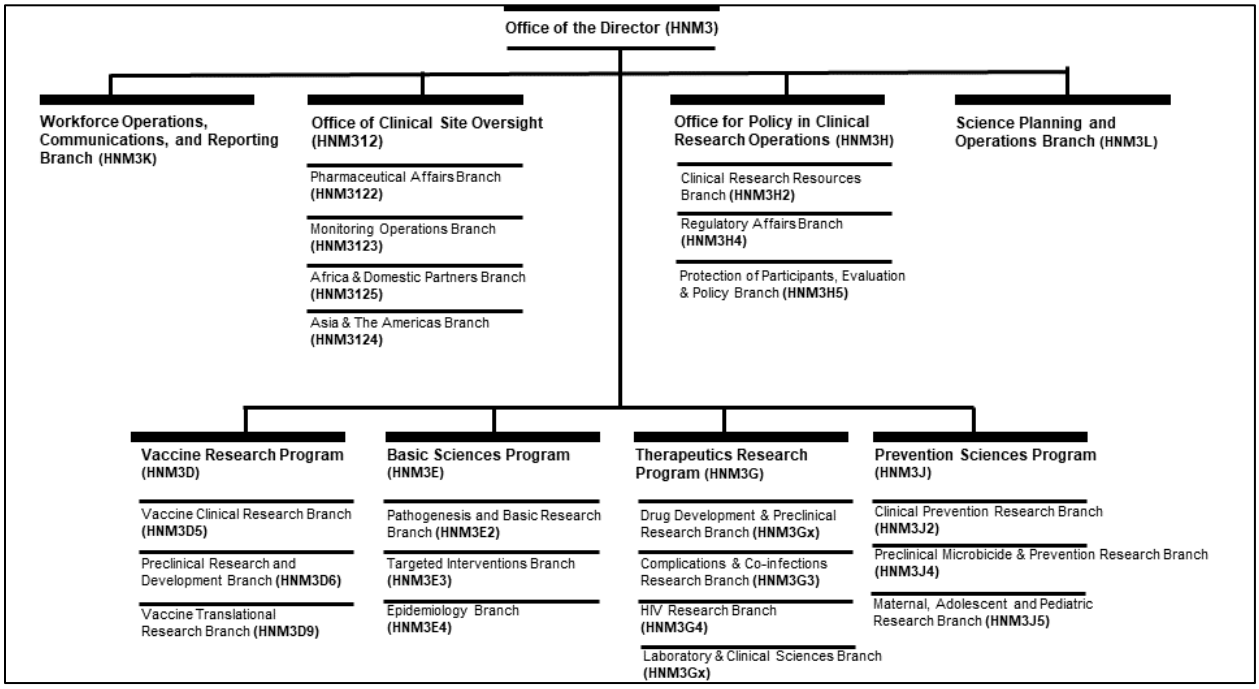
When an IMPAACT study is to be conducted under an Investigational New Drug (IND) application, DAIDS typically holds the IND and negotiates a clinical trial agreement (CTA) with the collaborating pharmaceutical company to document the responsibilities and rights of each party for the clinical trial. The agreement typically includes, but is not limited to, IND application sponsorship (if applicable), provision of study products, safety and data monitoring, confidentiality, and access to data. In general, terms in the CTA covering access to data conform to DAIDS and Network policies. See Section 11 for additional details related to the CTA process.

DAIDS typically has the option to file an IND application for investigational agents evaluated in IMPAACT studies. Appropriate DAIDS staff advise protocol teams on behalf of NIH on the specific regulatory requirements for IND sponsorship. In situations in which DAIDS is the IND sponsor, they also assemble, review, and submit the required regulatory documents to the US FDA, as described in Section 9.

Further details on DAIDS's roles and responsibilities within the IMPAACT protocol development and modification process are described in Section 9.

General information on DAIDS may be found on the DAIDS website.

Figure 1-2. DAIDS Organizational Structure



Note: Last accessed on 4 April 2024 from: https://www.niaid.nih.gov/about/division-aids-org-chart

1.5.1.1 Maternal, Adolescent, and Pediatric Research Branch of the Prevention Sciences Program

The Maternal, Adolescent, and Pediatric Research Branch of the Prevention Sciences Program within DAIDS is responsible for IMPAACT. As part of this responsibility, its representatives participate across all areas of the Network. DAIDS staff participate on IMPAACT protocol teams, as described in Section 4, and governing committees, as described through the Network MOP.

For all IMPAACT protocols, a DAIDS medical officer (MO) is assigned to the protocol team, as described in Section 4; of note, during study implementation, the DAIDS MO monitors the safety of the intervention(s) in ongoing studies and is provided with the interim and final analysis reports. When a protocol is sponsored or co-funded by a collaborating institution or research group (i.e., NICHD or NIMH), monitoring activities may also be conducted by their medical representative(s). As described further in Section 12, the NICHD MO may be designated by the DAIDS MO to serve as the DAIDS MO designee to meet quorum requirements.

1.5.1.2 Office for Policy in Clinical Research Operations

The Office for Policy in Clinical Research Operations (OPCRO) manages and supports DAIDS clinical research and helps ensure the following:

- Compliance with applicable regulations, standards, and good clinical practice guidelines
- Study participant safety and welfare
- Study quality and integrity

Regulatory Affairs Branch

The Regulatory Affairs Branch (RAB) is a branch within OPCRO. RAB is responsible for regulatory affairs across the DAIDS programs. RAB performs regulatory management and surveillance and is the liaison to the US FDA for clinical trials sponsored/funded by DAIDS. RAB members sign the Form FDA 1571 for DAIDS-sponsored INDs.

Protection of Participants, Evaluation, and Policy Branch

Protection of Participants, Evaluation, and Policy Branch (ProPEP) is a branch within OPCRO. ProPEP provides subject matter expertise on human subjects protection (HSP) matters (i.e., 45 CFR 46, 21 CFR 50, and 21 CFR 56), Institutional Review Board/Ethics Committee (IRB/EC) requirements, and HSP/GCP compliance issues. ProPEP also develops and maintains DAIDS policy documents to promote harmonization and to ensure compliance with applicable laws, regulations, guidelines, and policies, and serves as the liaison to OHRP.

1.5.1.3 Office of Clinical Site Oversight

The Office of Clinical Site Oversight (OCSO) facilitates the clinical research of the DAIDS scientific programs by overseeing NIAID-supported CRSs associated with the NIAID-sponsored HIV/AIDS clinical trials networks. As such, it performs the following key functions:

- Manages the NIAID Clinical Trials Units and CRSs associated with the HIV/AIDS Clinical Trials Networks
- Coordinates a range of clinical site management activities for the networks
- Serves as a resource on operational and regulatory issues and ensures that appropriate clinical research standards, policies, and procedures are used by CRSs
- Provides oversight and management of a contract to ensure that clinical site monitoring is conducted in accordance with applicable regulatory requirements
- Provides pharmaceutical expertise for protocol development and implementation, as well as oversight of a study product storage and distribution contract
- Verifies that optimal safeguards are employed for participant safety and ensures that high quality research practices are used
- Monitors clinical sites' progress enrolling underserved populations and ensuring community representation

Pharmaceutical Affairs Branch

The Pharmaceutical Affairs Branch (PAB) in OCSO assigns a DAIDS pharmacist to participate on each IMPAACT protocol team, as described in Section 4; the DAIDS pharmacists' roles include:

- Coordination and oversight of the supply, packaging, and distribution of study products
- Advisement to protocol teams on all pharmaceutical aspects of protocol development, including consultation on available dosage forms and placebos, product packaging, and supply to sites
- Coordination with pharmaceutical companies, as applicable, to ensure adequate and timely supply of study products
- Oversight and monitoring of quality assurance standards and SOPs for all pharmacy- and product-related issues at research sites participating in IMPAACT trials

PAB is responsible for the review and approval of each CRS Pharmacy Establishment Plan (PEP), which must be in place at each CRS prior to protocol registration. For NICHD-funded CRSs, PEPs are reviewed and finalized by the Westat Pharmacist.

PAB assesses the pharmaceutical aspects of each protocol and communicates its assessment during Scientific Review Committee (SRC) reviews.

Monitoring Operations Branch

The Monitoring Operations Branch (MOB) in OCSO serves as a resource on operational and regulatory issues and ensures that appropriate clinical research standards, policies, and procedures are used by NIAID-funded clinical research sites and provides oversight and management of a contract to ensure that clinical site monitoring is conducted in accordance with applicable regulatory requirements. MOB staff coordinate with NICHD's clinical site monitoring contractor to ensure consistency in site monitoring plans and approaches across all sites (NIAID-funded and NICHD-funded) participating in IMPAACT studies.

1.5.1.4 DAIDS Contractors

Regulatory Support Center

The DAIDS Regulatory Support Center (RSC) is a contract-based organization that provides comprehensive clinical regulatory support for all IMPAACT studies. DAIDS RSC works closely with DAIDS OPCRO. This support consists of:

- Reviewing protocol documents for regulatory compliance
- Preparing and filing new IND Applications and amendments to existing INDs in compliance with the procedural and substantive requirements of 21 CFR 312 (examples of submissions to the FDA include original IND Applications, Annual Reports, Safety Reports, and Responses to FDA Requests for Information)
- Reviewing all informed consents (ICs) during review at the Clinical Sciences Review Committee (CSRC) and Prevention Sciences Review Committee (PSRC) and Regulatory Review stages
- Translating sample ICs into Spanish
- Reviewing and tracking all required clinical site regulatory documents for all protocol versions at each CRS to ensure that all documents needed to fulfill the study sponsor's regulatory obligations relating to protocol registration are reviewed for completeness and accuracy within the specified timeline set up by the sponsor
- Planning and conducting trainings on protocol registration procedures as requested by DAIDS
- Collecting adverse events reported by sites participating in IMPAACT studies, processing the events for review by the DAIDS MO, and preparing the reports for transmittal to the FDA, if required
- Establishing internal procedures and developing safety training for the CRSs
- Supporting the DAIDS CSRC and PSRC by providing technical and administrative support to the SRC reviews of concept proposals and protocols
- Preparing CTAs
- Distributing and managing Investigator Brochures (IBs) and safety information

Clinical Research Products Management Center

The Clinical Research Products Management Center (CRPMC) is a contract-based organization that provides centralized ordering, storage, and distribution of study products evaluated in IMPAACT trials. The CRPMC works closely with PAB. CRPMC responsibilities include:

- Receiving shipments of study products from the manufacturer
- Storing products under appropriate and secure conditions
- Communicating with and distributing study products to authorized IMPAACT site pharmacists
- Monitoring study product inventories
- Monitoring study product expiry dates
- Recalling and processing study product returns
- Executing final dispositions of study products
- Maintaining records of study product management
- Repackaging or relabeling study products under Good Manufacturing Practices (GMP), as needed
- Preparing participant kits, if needed, for specific protocols

The CRPMC also provides the Clinical Site Monitor with reports of product shipments to the CRSs for protocol monitoring and study assessment visits.

Clinical Site Monitoring Contractor

The Clinical Site Monitoring Contractor (CSM) is a contract-based organization that evaluates the NIAID-funded CRSs for adherence to Good Clinical Practice (GCP), regulatory compliance, accurate protocol implementation, internal quality assurance, HIV testing and counseling, and test agent accountability. The CSM works closely with the MOB.

CSM staff visit CRSs periodically to review study documentation for selected protocols and participants, review regulatory documents, audit pharmacies, and document error resolution per assignments received from DAIDS. Further details on monitoring by the CSM are included in Section 13.

NICHD-funded CRSs are monitored by a separate contractor, which collaborates with the MOB to ensure a consistent monitoring approach for IMPAACT studies.

1.5.2 *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NICHD is a co-funding Institute and has substantial scientific and programmatic involvement in the IMPAACT Network through technical assistance, advice, and coordination. NICHD staff participate on IMPAACT protocol teams, as described in Section 4, and governing committees, as described throughout the Network MOP. For all IMPAACT protocols, an NICHD MO is assigned to the protocol team, as described in Section 4.

NICHD also supports and funds CRSs that participate in the IMPAACT Network; these sites are overseen by a separate coordinating center that works collaboratively with DAIDS.

1.5.3 National Institute of Mental Health

NIMH is a co-funding Institute and has substantial scientific and programmatic involvement in the IMPAACT Network through technical assistance, advice, and coordination. NIMH staff participate on IMPAACT protocol teams, as described in Section 4, and governing committees, as described throughout

the Network MOP. For select IMPAACT protocols, an NIMH MO is assigned to the protocol team, as described in Section 4.

1.5.4 US Food and Drug Administration

In its capacity as a regulatory agency of the US Federal government, the US FDA has responsibility for reviewing and approving protocols for IMPAACT studies conducted under an IND, regardless of whether the studies are conducted at US or non-US sites. For many IMPAACT studies, DAIDS holds the IND and thus is responsible for working directly with the US FDA. The US FDA receives and reviews copies of serious adverse event reports that meet the criteria of Title 21, Code of Federal Regulations (CFR) 312.56. The US FDA is responsible for review of study data that are submitted in support of licensure applications and may conduct audits of IMPAACT studies, including but not limited to conducting regulatory inspections at US and non-US sites.

Additionally, in-country agencies may also provide regulatory oversight of IMPAACT trials performed in non-US settings.

1.5.5 Department of Health and Human Services

1.5.5.1 Office for Human Research Protections

The US Office for Human Research Protections (OHRP) fulfills responsibilities set forth in the Public Health Service Act, including monitoring compliance relative to Department of Health and Human Services (DHHS) regulations for the protection of human subjects in research supported by any component of the DHHS. OHRP is also responsible for establishing criteria for and negotiating Assurances of Compliance with institutions engaged in research involving human subjects supported by the DHHS. The IMPAACT Network operates in full compliance with the regulations and guidelines of OHRP.

For IMPAACT, DAIDS is responsible for protocol review, including review and approval of sample IC language. The approved language is subsequently distributed with the protocol for relevant IRB/EC review and approval.

1.5.5.2 US Office for Civil Rights

For studies conducted in US settings in institutions that are covered entities, compliance with the Health Insurance Portability and Accountability Act (HIPAA) must be assured. Each institution is responsible for ensuring its own compliance. For non-US institutions, each institution is responsible for determining whether it is a covered entity under HIPAA and, if so, whether each covered entity is responsible for ensuring compliance with this requirement, as set forth in Title 45 CFR 160 and 164.

2 NETWORK GROUPS

The IMPAACT Network comprises a global network of clinical research sites (CRSs), the Leadership and Operations Center (LOC), Laboratory Center (LC), Statistical and Data Management Center (SDMC), IMPAACT Community Advisory Board (ICAB), and other groups and committees charged with the scientific, management, and operational support of the Network. The Network is led by a chair and vice chair(s), who are accountable to the National Institute of Allergy and Infectious Diseases (NIAID) Program Officer. Additional information concerning these entities is provided in this section.

2.1 Network Leadership

The IMPAACT Network is led by the Network chair and vice chair(s) in collaboration with the Scientific Leadership Group (SLG), Scientific Committees (SCs), and Management Oversight Group (MOG). The leadership group is responsible for ensuring the efficient development and implementation of the IMPAACT research agenda as well as managing and coordinating activities across the Network.

2.1.1 Network Chair and Vice Chairs

The Network chair is an investigator with experience reflective of the Network's scientific agenda and operational scope. They serve as chair of the SLG and MOG. Responsibilities include serving as the LOC principal investigator (PI); overseeing and managing the Network's finances; directing the Network and executing its plans as determined by the SLG, MOG, and National Institutes of Health (NIH) partners; ensuring collaboration with other research networks and groups, including pharmaceutical companies; and serving as the Network's executive representative. Other responsibilities include but are not limited to

maintenance of Network policies and procedures, regulatory compliance and performance evaluation, review of publications, and collaboration with the community. The Network chair must commit a minimum level of effort of 50% for the term of service, which is the award period of the IMPAACT Network grant.

The SLG (described in Section 2.1.2) elects the Network chair and vice chair(s). The SLG reviews applicant submissions and SLG voting members elect the chair, after a broad solicitation for individuals with relevant expertise and experience. Applicants need not be associated with an IMPAACT site; however, site leadership experience is considered a strength. Election decisions are generally expected to be based on at least 75% concurrence among voting members. Any current SLG member who applies is recused from the entire review and election process.

As needed, a call for applicants and/or nominations for Network chair typically takes place at least 15 months before beginning a new Network grant funding cycle so that the elected chair can be named in the application for the new grant. The newly elected chair serves in a transitional capacity as Network chair-elect, participating as a non-voting member of the SLG and MOG, until the new grant is awarded, at which time they assume the duties of Network chair.

If it becomes necessary to replace the Network chair, a special election may be held. One of the vice chairs will serve as chair until the replacement is selected.

The Network vice chair(s) should meet the same requirements as the chair and is/are elected following the same procedures as the Network chair. The primary duties of a vice chair are to assist the Network chair, assume the powers and duties of the Network chair in their absence or, in case of a potential conflict of interest, lead meetings in the absence of the Network chair. The Network vice chair(s) also serve(s) as chair(s) of some Network committees and groups.

2.1.2 Scientific Leadership Group

The SLG sets the overall scientific agenda of the Network. The Network chair serves as the chair of the SLG; other members include the Network vice chairs, SDMC PIs, LC PI, Operations Center Director, Study Monitoring Committee (SMC) chair, ICAB chair, up to four at-large investigators, and NIAID, National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH) representatives. At-large members of the SLG are selected by the MOG to ensure appropriate breadth and depth of scientific expertise and diversity, reflective of the Network's research agenda and geographical scope. *Ex officio* members of the SLG may also serve as voting members.

The primary responsibilities of the SLG are to:

- Set, develop, and execute the overall scientific agenda of the Network, in close collaboration with the SCs and the ICAB
- Prioritize studies across research areas and the overall research portfolio
- Review evolving HIV/AIDS science and determine implications for the Network
- Review new study proposals
- Identify gaps in the Network's research agenda and commission studies to address these
- Liaise with other research networks and groups to foster collaboration

The SLG convenes regularly via conference call and in person, including periodically with the SC chairs and vice chairs and, as needed, with external advisors. When voting is required, SLG members with conflicts of interest (e.g., part of the team developing a proposal) abstain from voting, and decisions are

generally expected to be based on at least 75% concurrence among voting members. Voting members include all listed SLG members above, with one voting representative from each of the three NIH institutes. If decisions are mixed or split, the chair and vice chair(s) may determine next steps, based on the results, and generally include additional follow-up to reach consensus. To ensure coordination and communication, additional representatives of the Operations Center, SDMC, LC, and NIH sponsoring institutes may participate in SLG meetings as observers.

Decisions made by the SLG are communicated in writing to the relevant parties, and updates on plans and activities are provided to SLG members during routine calls or otherwise as needed. Updates to other Network members are provided via email broadcasts, website postings, conference calls, and other means as appropriate. On an ongoing basis, the SLG reviews and prioritizes new study proposals; review is based on scientific merit, potential public health impact, and feasibility and research advantage of Network implementation, as described in Section 9. See Section 6 for details regarding Network meetings and communications.

2.1.3 Management Oversight Group

As described in Section 2.1.2, the SLG focuses on the scientific priorities for the Network, whereas the Network management and oversight functions are the responsibility of the MOG. The MOG is comprised of a subset of SLG members, and the Network chair serves as the chair of the MOG; other members include the Network vice chair(s), SDMC PIs, LC PI, Operations Center Director, and NIAID, NICHD, and NIMH representatives.

The primary responsibilities of the MOG are to:

- Oversee the Network's fiscal matters
- Evaluate and recommend the distribution of resources across Network components
- Review site selection and accrual plans
- Ensure regulatory compliance
- Develop collaboration agreements
- Monitor Network performance and productivity
- Review and approve the Network Manual of Procedures (MOP)
- Conduct other administrative and operational aspects of the Network's business

The MOG convenes regularly via conference calls and in person. When voting is required, MOG members with conflicts of interest (e.g., being part of the team developing a proposal) abstain from voting, and decisions are generally expected to be based on at least 75% concurrence among voting members. Voting members include all listed MOG members above, with one voting representative from each of the three NIH institutes. If decisions are mixed or split, the chair and vice chair(s) may determine next steps, based on the results, and generally include additional follow-up to reach consensus. To ensure coordination and communication, additional representatives of the LOC (including the Finance and Contracts Office at Johns Hopkins University [JHU]), SDMC, LC, and NIH sponsoring institutes may participate in MOG meetings as observers.

Decisions made by the MOG are communicated in writing to the relevant parties, and updates on plans and activities are provided to MOG members during routine calls or otherwise as needed. Updates to other Network members are provided via email broadcasts, website postings, conference calls, and other means as appropriate. See Section 6 for details regarding Network meetings and communications.

2.1.4 Scientific Committees

The IMPAACT Network is committed to conducting high quality clinical trials that advance the prevention and treatment of HIV and its complications for infants, children, adolescents, and pregnant and postpartum people globally. The Network's research agenda includes four scientific aims, reflecting the following key research areas:

- Therapeutics
- ART-Free Remission ("Cure")
- Tuberculosis
- Brain and Mental Health

For each research area, a SC continually reassesses research priorities considering emerging science as well as new ideas and opportunities, seeks collaboration with other research networks and entities, and oversees the development and review of study proposals based on scientific priorities.

The SCs are responsible for:

- Reviewing their respective portfolios of studies in the context of evolving science and standards of care
- Identifying gaps in the science and new interventions for priority populations
- Ensuring that new high priority study proposals are developed for consideration by the SLG

SCs convene regularly via conference call and in person. SC chairs and vice chairs periodically meet with the SLG via conference call or in person. SCs are expected to collaborate on areas of topical overlap and mutual interest, each drawing upon the expertise of others as needed. See Section 6 for details regarding Network meetings and communications.

2.1.4.1 SC Chairs and Vice Chairs

SC chairs and vice chairs are selected by the SLG to ensure appropriate breadth and depth of scientific expertise and diversity, reflective of the Network's research agenda and geographical scope. Chairs and vice chairs are accountable to the SLG. They are responsible for leading their respective SCs and participating in SLG conference calls and meetings as requested to discuss their SCs' research agendas and priorities. Each SC also has a designated SLG liaison who is available for Network leadership consultation on an ongoing basis.

2.1.4.2 SC Membership

Each SC is composed of experts in the relevant field and typically includes a chair and vice chair, at-large members, and representatives from the ICAB, SDMC, LC, Operations Center, NIAID, NICHD, and NIMH. At-large members are chosen by the chair and vice chair and confirmed by the SLG after a broad solicitation for individuals with relevant expertise and experience.

When voting is required, SC members with conflicts of interest (e.g., being part of the team developing a proposal) abstain from voting. Voting members include all listed members above, with one voting representative from the ICAB, each of the central resource groups, and each of the three NIH institutes. Voting may be considered completed once at least 60% of at-large members plus the chair and vice chair have voted; if decisions are mixed or split, the chair and vice chair may determine next steps, based on the results.

To ensure coordination and communication with Network leadership, a liaison from the SLG is also selected to participate in each SC; this person is not considered a voting member. To augment or expand existing expertise within a SC or to replace a departing member, the SC chair and vice chair may propose additional individuals for membership, with appointment to be confirmed by the SLG.

2.1.5 Removal of Any IMPAACT Leadership Member

In the unlikely event that any IMPAACT leadership (SLG or SC) member needs to be removed for cause, a written proposal to remove the member must be submitted with support from at least three voting members of the group (SLG or SC). Removal of the member is based on at least 75% concurrence among voting members of the group and requires concurrence from NIAID. Removal of an SC member also requires concurrence from the SLG.

Leadership members include the Network chair, Network vice chairs, at-large SLG members, SC chairs and vice chairs, and all other members of the SLG, except for NIH members.

2.2 Advisory Groups

2.2.1 IMPAACT Community Advisory Board

The IMPAACT Community Advisory Board (ICAB) is responsible for advising the Network leadership, SCs, protocol teams, and other Network groups on issues related to the planning and implementation of the IMPAACT research agenda and for supporting local (site) community programs through training and information exchange. The ICAB also communicates and represents the views of local community programs through participation of its representatives in the SLG, SCs, protocol teams, and other Network groups. The ICAB convenes regularly via conference calls and in person. The ICAB chair is accountable to the Network chair and the MOG.

See Section 5 for additional details on the ICAB.

2.2.2 Scientific Service Cores

Two scientific service cores provide expertise integral to the design, conduct, and analysis of IMPAACT studies, from early planning through protocol development, via a consultative model.

The Social Behavioral Service Core ensures that IMPAACT studies are designed and implemented with appropriate consideration of social-behavioral factors that may influence outcomes of interest or success of the study and that state-of-the-art approaches and measures are used. The core is led by a chair and composed of internationally recognized experts in adherence measurement and analysis, as well as engagement in care, retention, and decision making, with specific emphasis on child, adolescent, and maternal health.

The Pharmacometric Service Core's responsibilities are to provide expertise in the design of pharmacometric studies including developing initial pharmacokinetic (PK) and pharmacodynamic (PD) models, continually updating these models as new information becomes available, and applying statistical methods to optimize study design. They also perform, in collaboration with the LC's Specialty Pharmacology Laboratories and other specialty laboratories, PK analyses of IMPAACT study data, exploratory PK/PD analysis, and PK/pharmacogenetic studies. The core is led by a chair and composed of PK/PD modeling experts in pediatrics, obstetrics, HIV, TB, and other therapies used in IMPAACT

studies. As needed, they work in collaboration with industry sponsors to ensure appropriate utilization of the most up-to-date adult PK and PD characteristics to ensure optimal design of IMPAACT studies.

The chairs of both cores are selected by the SLG; members are chosen by the chair and confirmed by the SLG. The cores are accountable to the SLG.

2.2.3 External Scientific Advisory Group (EAG)

An external scientific advisory group may be convened periodically to provide constructive feedback on the Network's current and planned scientific agenda, including identifying gaps and providing recommendations for prioritization and future directions. The group may convene either via conference call or in person. The group should include diverse expertise and experience relevant to the Network's research agenda, including pediatric HIV therapy, pediatric TB/HIV co-infection, perinatal HIV transmission, pediatric HIV vaccines, pediatric immunology, HIV reservoirs, metabolic/neuropsychiatric complications of HIV and ARV therapy, and behavioral sciences. The group should also include community representation. Members must be currently unassociated with IMPAACT and have no current conflict of interest. The group is directly advisory to the SLG and will be led by a non-voting *ex officio* member of the SLG.

The external scientific advisory function may be fulfilled through alternative means as determined by the SLG.

2.2.4 Electronic Case Report Forms Committee

The Electronic Case Report Form (eCRF) Committee works closely with the SDMC to develop standardized data collection methods and eCRFs that collect the data required for IMPAACT studies in an accurate and efficient manner. The committee develops generic eCRFs for use across studies, promotes efficient data collection and data entry, and reduces collection of nonessential information.

The eCRF Committee is led by representatives of the SDMC and composed of representatives from the SDMC, LC, and Operations Center, as well as site representatives, including study coordinators, data managers, study nurses, and other clinicians. Members review and provide input on the design of new generic eCRFs and provide input on study-specific eCRFs for new studies as needed. Committee activities focus on review of generic eCRFs (done on monthly calls) and study-specific eCRFs (done as needed and by email).

2.3 Central Resources

The central resources of the IMPAACT Network include:

- Leadership and Operations Center (LOC), located at Johns Hopkins University (JHU) and FHI 360
- Statistical and Data Management Center (SDMC), located at the Harvard T.H. Chan School of Public Health and Frontier Science Foundation
- Laboratory Center (LC), located at the University of California Los Angeles (UCLA)

These groups coordinate closely with each other in the development, implementation, and oversight of Network studies and other Network activities.

2.3.1 Leadership and Operations Center

The Leadership and Operations Center (LOC) supports the Network leadership, structure, and functioning and is responsible for helping to shape the Network's scientific agenda and plays a key role in all phases of science generation and protocol development. Oversight of the LOC is the responsibility of the Network chair. The LOC includes functions across two institutions: the IMPAACT Finance and Contracts Office (at JHU) and the IMPAACT Operations Center (at FHI 360).

The Finance and Contracts Office administers and disperses grant and other funding for support of the Network leadership, protocol chairs, clinical research sites, specialty laboratories, the Operations Center, and other central resources. The Finance and Contracts Office also executes contracts with pharmaceutical companies and other collaborators to support Network studies.

The Operations Center provides a central point of coordination, communications, and support for all aspects of the Network. The Operations Center supports the scientific agenda; coordinates the development, implementation, and reporting of IMPAACT studies; supports all Network groups, committees, and protocol teams; and arranges and supports all Network meetings and leadership travel. The Operations Center Director serves as a voting member of the SLG and MOG.

The LOC's responsibilities, by functional area, are summarized in Table 2-1.

2.3.2 Statistical and Data Management Center

Through a separate but linked and fully collaborative grant with the LOC and the LC, the Statistical and Data Management Center (SDMC) is responsible for helping to shape the Network's scientific agenda and plays a key role in all phases of science generation and protocol development. The SDMC also provides comprehensive biostatistical and data management leadership, specifically in the design and implementation of Network studies and in the collection, quality control, and analysis of study data in accordance with study protocols and in collaboration with other team members, following the principles of Good Clinical Data Management Practices (GCDMP) and Good Clinical Practices (GCP).

The SDMC is comprised of a Statistical and Data Analysis Center (SDAC), located at the Center for Biostatistics in AIDS Research at the Harvard T.H. Chan School of Public Health, and a Data Management Center (DMC), located at Frontier Science Foundation. The SDMC PIs have fiscal responsibility for the SDMC grant, are accountable to the NIAID Program Officer and the Network chair, and serve as a voting member (one representative) of the SLG and MOG.

The SDMC's responsibilities, by functional area, are summarized in Table 2-2.

2.3.3 Laboratory Center

Through a separate but linked and fully collaborative grant with the LOC and the SDMC, the Laboratory Center (LC) is responsible for helping to shape the Network's scientific agenda and plays a key role in all phases of science generation and protocol development. The LC is also responsible for leadership, oversight, and support of laboratory aspects of Network studies and other activities including NIAID site laboratory preparedness and performance and coordination and oversight of the Network's specialty laboratories. Westat supports laboratory activities for NICHD sites. The LC plays a leadership role in cross-network activities, updating, harmonizing, and streamlining laboratory procedures used in other networks and groups.

The LC is located at the University of California Los Angeles (UCLA). The LC PI has fiscal responsibility for the LC grant, is accountable to the NIAID Program Officer and the Network chair, and serves as a voting member of the SLG and MOG.

The LC staff maintains regular communication with IMPAACT sites and confirms that sites are able to perform study-required laboratory procedures and tests prior to site activation for the study. The LC staff also visit sites, as necessary, to assess laboratory facilities and procedures.

The LC's responsibilities, by functional area, are summarized in Table 2-3.

Table 2-1. IMPAACT LOC Operational Responsibilities

Functional Area	Responsibilities
Leadership and governance	• Serve on and provide logistical and administrative support to the SLG, MOG, SCs, ICAB, Social Behavioral Service Core, and other Network committees and groups • Participate in the overall management of the Network and development of the IMPAACT scientific agenda • Provide operational leadership to the Network • Coordinate the development and management of the Network MOP • Coordinate and support Network evaluation processes (see Section 18)
Protocol management and support See Section 4 for a full listing of roles and responsibilities for the protocol CRM.	• Facilitate the development, review, approval, and tracking of concepts, ancillary studies, and other related study proposals • Assign a clinical research manager (CRM) to each IMPAACT protocol • In collaboration with the protocol chair, plan and manage protocol team business in consultation and with the support of other protocol team members • Facilitate communication between protocol teams, study sites, Network leadership, and other Network and sponsor entities as needed
Technical assistance to sites	• Coordinate the development and implementation of study-specific training plans as well as training related to Network policies and procedures • Coordinate and facilitate responses to inquiries from site staff on logistics and procedures for IMPAACT studies in collaboration with protocol team members and other Network entities, as applicable
Coordination of, facilitation of, and participation on oversight committees	• Serve as member of and coordinate activities of oversight groups • Facilitate preparation and distribution of relevant review materials; prepare and distribute review outcome reports and associated communications, as applicable
Community engagement See Section 5 for a full description of roles and responsibilities for the Operations Center community program staff.	• Facilitate broad community involvement through community representation on key Network committees and groups and, as applicable, by working with sites to develop and enhance the IMPAACT Community Advisory Board (ICAB) • Support the work of the ICAB and IMPAACT CAB Leadership Group (ILG)

Table 2-1. IMPAACT LOC Operational Responsibilities

Functional Area	Responsibilities
Communication and information dissemination	• Develop and maintain the IMPAACT website, including relevant information on sites and IMPAACT studies • Support and coordinate Network-level communication through conference calls, in-person meetings, electronic and written materials, announcements, and postings on the IMPAACT website and social media outlets • Support and organize Network meetings • Develop and maintain email groups and directories for the IMPAACT communication system in collaboration with the DMC • Maintain inventory of site- and study-related information and provide requested information to Network leadership and other committees as needed • Support the NIAID Clinical Research Management System (CRMS) and The Division of AIDS (DAIDS) Regulatory Support Center (RSC) by providing current study-specific information and documents in real time
Financial management and support	• Evaluate the adequacy of financial resources provided to sites, as necessary • Assist NIH Grants Management Branch (GMB), DAIDS Prevention Sciences Program (PSP), OCSO, and IMPAACT leadership in analysis of site funding requests and all other Network financial matters • Develop an annual funding plan based on the needs of the scientific agenda implemented during the funding cycle • Administer and disperse grant and other funding for support of Network activities • Execute contracts with pharmaceutical companies and other collaborators to support Network studies

Table 2-2. IMPAACT SDMC Operational Responsibilities

Functional Area	Responsibilities
Leadership and governance	• Serve on the SLG, MOG, SCs, and other Network committees and groups • Participate in the overall management of the IMPAACT Network and development of the IMPAACT scientific agenda • Provide statistical and data management leadership to the IMPAACT Network • Contribute to the development and management of the Network MOP • Contribute to Network evaluation processes (see Section 18)
Protocol management and support See Section 4 for a full listing of roles and responsibilities for the statistician, PDM, and LDM.	• Participate in the review of concepts, ancillary studies, and other related study proposals; track status of analyses being performed by the SDMC • Assign a statistician, a protocol data manager (PDM), and a laboratory data manager (LDM) to each IMPAACT protocol • Participate in the protocol-related groups, as applicable • Design and maintain the study databases • Provide centralized data entry and data management • Provide reports to fulfill Investigational New Drug (IND) reporting requirements, as applicable • Review and provide study data and reporting to pharmaceutical partners under the terms of the Clinical Trials Agreement (CTA), as applicable • Develop and implement data quality control (QC) systems • Provide needed information to DAIDS to assist with site-monitoring visits
Technical assistance to sites	• Participate in the development and implementation of study-specific training plans • Develop, coordinate, and implement training related to data management for Network members • Respond to inquiries from site staff in collaboration with protocol team members and other Network entities, as applicable • Provide operational assistance to sites, the LC, and protocol teams for specimen tracking and retrieval, including labeling and specimen tracking sheets to facilitate specimen entry into the specimen tracking system, the Laboratory Data Management System (LDMS), and reports of LDMS entry errors and discrepancies between LDMS and CRF databases
Information technology support	• Develop and maintain software systems and related procedures for transmitting, receiving, processing, analyzing, and storing study data and meeting reporting requirements • Assist sites in set-up and maintenance of data collection material relay systems
Participation on oversight committees	• Serve as a member of oversight groups
Clinical data safety monitoring	• Review relevant laboratory and safety data for accuracy, consistency, and completeness • Provide QC and coding of adverse event (AE) data • Verify completeness of expedited adverse event reporting through reconciliation of AEs reported to DAIDS and those reported to the SDMC

Table 2-3. IMPAACT LC Operational Responsibilities

Functional Area	Responsibilities
Leadership and governance	• Serve on the SLG, MOG, SCs, and other Network committees and groups • Serve on and provide logistical and administrative support to the Pharmacometrics Service Core • Participate in the overall management of the Network and development of the IMPAACT scientific agenda • Contribute to the development and management of the Network MOP • Contribute to Network evaluation processes (see Section 18)
Protocol management and support See Section 4 for a full listing of roles and responsibilities for the LC representative and LT. See Section 17 for a full listing of roles and responsibilities for the Laboratory Center.	• Participate in the review of concepts, ancillary studies, and other related study proposals • Assign an LC representative to each IMPAACT protocol; facilitate assignment of an LT, in consultation with Laboratory Technologist Committee, to each IMPAACT protocol • Review and define appropriate laboratory testing methods and materials to be used in IMPAACT studies • Participate in protocol-related groups, as applicable • Collaborate with other NIH-sponsored HIV clinical trial networks to harmonize laboratory methods and maximize the efficiency of protocol development, implementation, and analysis • Collaborate with IMPAACT specialty labs to perform protocol-specified testing
Technical assistance to sites	• Participate in the development and implementation of study-specific training plans • Respond to inquiries from site staff in collaboration with protocol team members and other Network entities, as applicable (Westat may also respond to laboratory-related inquiries from NICHD site staff, as needed) • Provide operational assistance to sites, the SDMC, and protocol teams for specimen tracking and retrieval, including labeling and tracking specimen sheets to facilitate specimen entry into the specimen tracking system, the LDMS, and reports of LDMS entry errors and discrepancies between LDMS and CRF databases
Participation on oversight committees	• Serve as a member of oversight groups

2.4 Oversight Groups

Additional Network groups provide oversight on behalf of the SLG and MOG:

- Multidisciplinary Protocol Review Group (MPRG)
- Study Monitoring Committee(s) (SMC)
- Network Evaluation Group (NEG)
- Publications Review Group (PRG)

These committees have both standing and *ad hoc* members and convene via conference call as needed.

2.4.1 Multidisciplinary Protocol Review Group

The Multidisciplinary Protocol Review Group (MPRG) reviews protocols on behalf of the SLG prior to submission to the NIAID Sciences Review Committees. The purpose of the MPRG review is to ensure IMPAACT protocols are scientifically rigorous, accurate, consistent, complete, and standardized to the extent possible. The MPRG critically reviews protocols for scientific and design integrity; operational feasibility, focusing on key issues such as site participation, infrastructure, and capacity; relevance to the community; and any ethical, logistical, or potential regulatory concerns. The review is multidisciplinary to streamline and avoid multiple sequential review steps. This group has authority to approve protocols, request revision and re-submission, or to disapprove them, based on Network-specified criteria.

See Section 9 for additional details on the MPRG.

2.4.2 Study Monitoring Committee

In support of the management and oversight functions of the MOG, for designated studies a Study Monitoring Committee (SMC) monitors participant safety and the progress and quality of IMPAACT study conduct. The scope of SMC reviews varies across studies, reflective of protocol specifications.

See Section 13 for additional details on the SMC.

2.4.3 Network Evaluation Group

The Network Evaluation Group (NEG) develops and conducts the Network evaluation program on behalf of the MOG. Evaluation reports are shared with the entities whose work was evaluated and with Network sponsors, as appropriate. A primary component of evaluation is the CRS Performance Report. This report focuses on critical aspects of study implementation at the site level, such as participant accrual and retention, data quality, laboratory performance, and regulatory issues. At the request of the MOG, the NEG may evaluate and report on other Network entities in a similar manner.

See Section 18 for additional details on the NEG.

2.4.4 Publications Review Group

The Publications Review Group (PRG) reviews all abstracts and manuscripts reporting on Network studies and related investigations prior to submission to a conference or journal to ensure high quality products and publications and scientific rigor.

See Section 19 for additional details on the PRG.

2.5 Protocol Teams

Protocol teams assume primary responsibility for scientific leadership in the development, implementation, and day-to-day oversight of IMPAACT studies; protocol teams are also responsible for timely dissemination of study results.

See Section 4 for additional details on the composition and functions of protocol teams.

2.6 Clinical Research Sites

IMPAACT studies are conducted at clinical research sites (CRSs) worldwide and are funded by NIAID and NICHD. Investigators and other representatives of these sites, including community representatives, participate in all levels of the Network structure. The active participation of site representatives is critical to IMPAACT's scientific mission. These sites bring extensive clinical trials capacity and a wealth of experience for implementation of the Network's scientific agenda.

IMPAACT sites are experienced in implementing clinical trials, monitoring for and reporting adverse events, achieving high participant retention rates, and rigorously adhering to study protocols. Site staff are skilled in applying the principles of Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) in all aspects of study conduct. These practices include obtaining informed consent and assent; performing clinical, pharmacy, and laboratory study procedures; maintaining study product accountability; performing data management and quality management processes; and collecting, labeling, processing, testing, storing, and shipping biological specimens. In addition, each site obtains community input on the research process through its community advisory board(s), although a site may refer to this structure by another locally chosen name or establish an alternative structure.

Staffing at each site may vary based on the structure of the site, the number and type of studies being conducted, and any local requirements. Some staff members may have general functions that apply across studies and others may have study-specific responsibilities. Site staff often include the following:

- CRS Leader and CRS Coordinator
- Study-specific Investigators of Record (IoR) and sub-investigators
- Study-specific Coordinators
- Pharmacist of Record, study-specific Pharmacists of Record, and other pharmacists and pharmacy technicians
- Research nurses and clinicians
- Data managers and technicians
- Laboratory directors, managers, technologists, and technicians
- Counselors and social workers
- Community educators and liaisons
- Participant outreach, recruitment, and retention staff
- QA/QC staff
- Administrative staff

2.6.1 NIAID Sites

The Division of AIDS (DAIDS) at NIAID funds sites worldwide to participate in Network studies. Each site is part of a Clinical Trials Unit (CTU); CTUs may be comprised of multiple sites. NIAID provides resources to fund research infrastructure and study implementation through cooperative agreements with CTUs and through the LOC.

2.6.2 NICHD Sites

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds sites worldwide to participate in Network studies. NICHD provides resources to sites to fund research infrastructure and study implementation through the NICHD coordinating center.

2.6.3 Protocol-Specific Sites

Sites that are not affiliated with the Network through NIAID or NICHD may be engaged and supported to implement specific Network studies if needed to meet the study objectives, such as to reach special populations or expand capacity.

See Section 10 for additional details.

3 GOOD DOCUMENTATION PRACTICE

3.1 Introduction to Good Documentation Practices within the IMPAACT Network

Good Documentation Practices (GDP) play an important role to ensure effective communication between all IMPAACT Network members, clearly illustrate document histories, and demonstrate compliance with Good Clinical Practice (GCP) guidelines (International Council on Harmonisation Good Clinical Practices, ICH E6(R2)). This section sets minimum standards for GDP compliance within the IMPAACT Network. Each Network organization (Leadership and Operations Center (LOC), Laboratory Center (LC), Statistical and Data Management Center (SDMC), and Clinical Trials Unit/Clinical Research Site (CTUs/CRSs)) may have additional, specific requirements.

Documentation includes all records—in any form—that describe or record the methods, conduct, and/or results of a study, the factors affecting a study, and the actions taken. They are created throughout the protocol lifespan, from protocol development through publication and close-out. Applicable documents may include, but are not limited to, the following:

- Regulatory submissions and approvals
- Protocol documents (protocols, Letters of Amendment, Clarification Memoranda, Full Protocol Amendments, Summaries of Changes)
- Site selection documents
- Training materials, attendance sheets, and presentations
- Study-specific Manuals of Procedures
- Laboratory Processing Charts
- Study Progress, Data, and Safety Monitoring Plans
- Statistical Analysis Plans
- Site-specific Study Activation Checklists
- Data collection instruments
- Call summaries
- Monitoring reports
- Operational guidance documents (e.g., fact sheets, Frequently Asked Questions (FAQs), infographics)
- Monitoring Committee (SMC or DSMB) reports and responses
- Notes to file and other study memoranda
- Personnel qualification and training records

Documents must be accurate and written in a manner that ensures both internal document consistency and consistency with other applicable reference documents. If documents are to be used together, then each should clearly reference the other.

The use of electronic systems/software to create, sign, date, track and/or store study records is permitted by the applicable Network organization or CTU/CRS. Division of AIDS (DAIDS) guidance and recommendations for electronic systems to be used in the conduct of IMPAACT studies is provided in the Electronic Information Systems (EIS) Policy, which is available at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

Throughout this Manual, guidance is provided on the assigned primary author(s), required Network or protocol team member reviews, and the associated review and approval steps of various Network and protocol documents. It is the assigned primary author's responsibility to ensure timely updates, distribution, maintenance, version and change control, and record management. Each primary author must comply with applicable policies, guidelines, and/or standard operating procedures (SOPs) for their organization. Additionally, all documents developed for IMPAACT studies should follow the guidelines included in this section.

This section outlines the principles and guidelines for good documentation practices. These guidelines apply to all site and central resource staff working on IMPAACT studies. For additional guidance, the DAIDS Good Documentation Policy and job aid are available at: https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent.

3.2 General Guidelines for Document Creation, Review, and Management

Consistent with good documentation practices, all study documents should meet the ALCOA+ elements, as shown in Figure 3.1.

Figure 3.1. ALCOA+ Elements to Ensure Good Documentation Practices

A	**Attributable**	It should be obvious who created a document and when it was created. Similarly, if any changes were made, it should be obvious who made the change, when the change was made, and why.
L	**Legible**	The document should be easy to read.
C	**Contemporaneous**	Information should be recorded as it was observed. When signatures are required, all signatures/initials should be attached to a date indicating when the signature was added to the document.
O	**Original**	Records should be original and not a photocopy.
A	**Accurate**	Study records should have a high level of integrity and honesty to what was truly observed. Records should be thorough and correct and checked for unintentional errors.
+		Complete: Documentation should be thorough and free from losses and omissions of key information. Consistent: Information should be recorded and presented in the expected manner and sequence. Enduring: Records must be maintained throughout the entire lifecycle of a study and in accordance with all applicable laws and regulations. Available: Information should be accessible whenever needed or requested.

3.2.1 Document Identifiers

Every controlled document, tool, template, etc., should contain unique identifiers. "Controlled document" refers to any document, either digital or paper, that must be managed in a way that protects the integrity of the document's content through revisions. If a document is not final, it should be clearly marked as a draft.

Documents should include a title to allow for rapid identification of the document; in general, the following identifiers should also be included:

- Brief title of the document (For study-specific documents, the study number, e.g., "IMPAACT ####", should be included in the title)
- Page numbers, following the standard of "X of Y", with Y indicating the total number of pages, for multipage documents (Note: For PowerPoint or other presentation slides, page numbers may be excluded)
- Date (using unambiguous formatting, e.g., 12 APR 2023 rather than 04/12/23)
- Version number (if applicable; Note: For PowerPoint or other presentation slides, version numbers may be excluded)
- Roles (author and approver, as applicable)

A table of contents is recommended for long documents to facilitate finding specific sections within the document. (Note: Per Electronic Common Technical Document [eCTD] requirements, any protocol document that is five or more pages must include a table of contents.)

3.2.2 Document Review and Approval

Document review and approvals follow standard procedures as outlined in other sections of this Manual. To assist with compliance to good documentation practices, documents should generally be reviewed by a secondary author or designated Network or protocol team member to ensure that the information is correct and accurate.

Confirmation that a review has taken place and approval from required members should be documented and include the approval date. The primary author should follow their organization's guidelines and/or SOPs on obtaining approvals. If the organization does not have established procedures, approval may be obtained through written electronic communications (e.g., an email or scanned wet signature) unless a signature is required pursuant to FDA predicate rules. Any confirmation of review and approval must include the approval date, based on receipt of the email, electronic signature, or handwritten date on a wet signature approval form.

The following signature best practices are encouraged when obtaining necessary approvals:

- Include a printed or typed name along with the signature on documents requiring sign-off, using blue ink if handwritten. (If using a 21 CFR Part 11 compliant system, the typed name and date of signature will automatically be generated by the signature software.)
- When using a 21 CFR Part 11 compliant electronic platform, select the appropriate reason for sign-off from the software options (e.g., "I am the document author," "I am the document approver," "I have read and understand this document," or "I have trained on this document").
- Optional: A person's title or role on the study may also be included.
- Ensure, to the extent possible, that a handwritten date accompanies a handwritten signature and is in an unambiguous format (e.g., 12 APR 2023 rather than 04/12/23).

DAIDS has provided guidance outlining signature requirements for documents submitted to the DAIDS Protocol Registration Office, which may be used as guidance for additional documents: https://rsc.niaid.nih.gov/resources/signature-requirement-guidance.

3.2.3 Document Distribution

Once finalized, all documents that are not to be altered or used as tools should be saved in portable document format (PDF) prior to distribution. The PDF helps to prevent inadvertent changes in the document post finalization. Document distribution should occur as efficiently as possible post document finalization to ensure the document remains contemporaneous and up-to-date. The primary author is responsible for ensuring the document is distributed to the required and/or most appropriate persons. Electronic distribution by email is the preferred method of the IMPAACT Network to distribute finalized documents.

3.2.4 Reviews, Updates, and Management

Documents are reviewed and updated, as applicable, per procedures as outlined in relevant sections of this Manual. A periodic review of documents may be completed to ensure documents are kept current; this review is the responsibility of the primary author(s).

When modifications must be made to finalized documents, the revised version must be saved with indicators reflecting the revised nature of the document; for example, a new version number and/or date that follows the logical sequence of the prior distribution. Edits affecting content should be reviewed, and confirmation of the review and approval of the edited document should be obtained. Unless otherwise required, minor grammatical edits or small corrections do not require a formal review and approval.

Once the revised document is finalized, the document should be distributed with a summary of changes, including (when appropriate) the reason for the correction(s). The summary of changes may be communicated within the text of an email; however, a cover page, separate summary of changes document, or a version control and document history table within the document are preferred.

To ensure the most up-to-date version is used, all prior versions of documents should be archived and individuals receiving the updated document should be notified as such.

3.2.4.1 Corrections

Any correction or modification to any applicable documents that does not result in issuance of an updated document should include a single line through the original entry, with initial and date. If needed (e.g., source document), an explanation of the change should be included.

3.2.5 Document Storage

Documents should be filed in a consistent and logical way for easy retrieval upon request. To the extent possible, files should be maintained in a secure manner with limited access and be protected from physical damage and loss. All study documents should be stored through study implementation, study closeout and as required by the study protocol, study sponsor, Institutional Review Board/Ethics Committee (IRB/EC), and regulatory authorities. See Section 14 for additional details related to document retention.

3.2.6 Trial Master Files

The Trial Master File (TMF) is a collection of documents that individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with GCP standards, as well as with other applicable regulatory requirements.

As of May 2021, DAIDS utilizes a decentralized approach for new TMFs. TMF documents will be stored in multiple DAIDS-approved electronic systems maintained by Electronic System Owners. DAIDS is responsible for communicating which IMPAACT Network studies require creation and maintenance of a TMF. Individual IMPAACT Network groups are responsible for maintaining sponsor-delegated documents in study TMFs, according to their applicable organizational policies and as assigned by DAIDS. The study sponsor is ultimately responsible for the full TMF for all IMPAACT studies after study closure and ensuring suitable archive is available.

4 PROTOCOL TEAMS

Protocol teams assume primary responsibility for scientific and operational leadership in the development, implementation, and oversight of IMPAACT studies and dissemination of study results. This section outlines the selection process of protocol chair, the selection and assignment of other team members, the responsibilities of protocol team members, and the protocol team's relationship with IMPAACT oversight and scientific committees. IMPAACT scientific and oversight committees and groups are outlined in Section 2 and Section 13, respectively; the protocol development process is further detailed in Section 9.

4.1 Protocol Chair and Vice Chair

Key protocol team members are proposed in study concept sheets, and proposed protocol chairs and vice chairs are reviewed by the IMPAACT Scientific Leadership Group (SLG) at the time of concept review.

4.1.1 Protocol Chair and Vice Chair Selection

One protocol chair and one vice chair are typically proposed in the concept sheet. Exceptions are assessed by the SLG on a case-by-case basis (e.g., co-chairs or multiple vice chairs). As noted in Section 9, the SLG evaluates and confirms the proposed protocol chair and vice chair based upon past leadership performance, current commitments, and relevant expertise and experience. Selection as protocol chair or vice chair does not imply that a site with which a chair is affiliated will be selected for study participation (see Section 10).

The SLG also considers whether proposed chairs have the capacity to serve concurrently as chair or vice chair of multiple IMPAACT studies and/or network committees. Protocol chairs need not be affiliated with an IMPAACT study site or other IMPAACT organization. Network resources are allocated to support these critical positions.

4.1.2 Protocol Chair and Vice Chair Responsibilities

The protocol chair provides scientific leadership during the development, implementation, and reporting of the study. They assume responsibility for completion of protocol team responsibilities and other study activities within the approved budget and timeline. Protocol chairs may often delegate specific areas of responsibility to the vice chair, but decision-making authority and ultimate responsibility for the execution of the study rest with the protocol chair.

Protocol chairs must familiarize themselves with IMPAACT processes as outlined in the IMPAACT Network Manual of Procedures (MOP) and adhere to them. A list of study responsibilities is included in

the scope of work, which is part of the contractual agreement that provides network resources to support each protocol chair and vice chair.

Protocol team activities are planned and managed by the protocol chair and the clinical research manager (CRM), in consultation and with the support of other protocol team members. Specifics of protocol team management vary according to the needs and type of study, the number and location of sites involved, and individual leadership and management approaches.

General Responsibilities (throughout the life cycle of the study):

- Ensuring study compliance with Good Clinical Practice (GCP) guidelines (International Council on Harmonisation Good Clinical Practices, ICH E6(R2)) and IMPAACT policies and procedures in the Network MOP
- Managing the study's overall operations in coordination with the CRM
- Developing meeting agendas and leading protocol team meetings and calls
- Coordinating the establishment and dissolution of study-specific groups as necessary to achieve efficiency in the development, implementation, and reporting of the study
- Working with the CRM to identify study targets, milestones, and timelines
- Coordinating protocol team member activities to meet study targets and timelines
- Collaborating with protocol team members on the development and execution of study activities and materials, as outlined in Table 4-1
- Monitoring progress in relation to established timelines and working with protocol team members as needed to address delays that may be encountered
- Monitoring the quality and progress of study conduct and working with protocol team members and study sites as needed to address study implementation issues
- Providing status updates to IMPAACT leadership, as needed
- Acting as a liaison between the protocol team, the study sponsor, and network leadership and oversight groups
- Providing active and timely scientific and operational guidance to support participating study sites

Pre-Implementation:

- Leading protocol development in coordination with the CRM
- Working with the CRM to complete the study site selection process
- Working with Operations Center staff to develop the study budget
- Working with the CRM to determine the training plan, develop the training materials, and participate in training sites on protocol requirements
- Ensuring timely development and sign-off of required key study implementation plans and materials
- Providing scientific expertise and facilitating final decision making within the protocol team to achieve agreement on scientific or operational issues brought before it; if agreement cannot be reached, referring the issue to the MOG/SLG

Study Implementation:

- Participating in study data reviews consistent with the study monitoring plan
- Together with the protocol statistician(s), reporting on the status of the study to the Study Monitoring Committee (SMC) and/or Data and Safety Monitoring Board (DSMB)
- Ensuring timely development of study closure plans and materials

Publications:

- Overseeing analysis and writing teams (e.g., designating writing team members, reviewing schedules, monitoring progress, prioritizing analyses, communicating publication plans, responding to IMPAACT Publications Committee reviewer comments, advocating for additional resources as required), as further described in Section 19
- Ensuring review and approval of all study-related manuscripts, abstracts, and presentations

4.2 Protocol Team

Protocol teams assume primary responsibility for scientific and operational leadership in the development, implementation, and oversight of IMPAACT studies and dissemination of their results.

4.2.1 Protocol Team Membership

The protocol team will be established following study approval by the SLG and the selection of a protocol chair. Investigators involved with the development of the concept sheet may not necessarily be invited to be a member of the protocol team. The protocol chair identifies investigators with expertise relevant to the study. The Operations Center coordinates and communicates the protocol team formation to protocol team members. Team members need not be affiliated with an IMPAACT study site or other IMPAACT organization. Membership of each protocol team will vary according to the protocol, but membership should generally include:

- Protocol chair (and/ vice chair)
- DAIDS medical officer (MO)
- NICHD MO
- NIMH MO (if applicable)
- CRM(s)
- Statistician(s) (and/or epidemiologist(s))
- Protocol data manager(s) (PDM)
- Laboratory data manager(s) (LDM)
- DAIDS protocol pharmacist(s) (if applicable)
- Community representative(s)
- Laboratory Center (LC) representative(s)
- Pharmaceutical or industry representative(s) (if applicable)
- Laboratory technologist (LT)
- Westat representative (if applicable)
- Investigator(s)
- Site investigator from each participating Clinical Research Site (CRS)

Additional members, as required for a specific protocol, may include a pharmacologist (or pharmacometrician), virologist, behavioral scientist, immunologist, etc.

4.2.2 Protocol Team Responsibilities

Although individual protocol team members have different roles in fulfilling specific protocol team responsibilities (see Table 4-1), all members are expected to provide scientific, operational, or site-specific input, as appropriate, to protocol team activities.

Table 4-1. Roles of Key Protocol Team Members

Team Member	Primary Roles and Responsibilities
Protocol chair	• Hold ultimate responsibility for execution of the study and final decision-making authority • See Section 4.1.2 for further details of chair responsibilities
Vice chair	• Collaborate with the protocol chair for execution of the study • See Section 4.1.2 for further details of vice chair responsibilities
Medical Officer (DAIDS, NICHD, or NIMH)	• Participate fully in protocol team discussions and decisions • Facilitate communication between protocol team and relevant NIH groups and staff • Provide timely review of study documents and response to queries • Provide oversight of safety monitoring during study implementation • DAIDS MO to review and sign-off on each study-specific MOP version
Clinical Research Manager (CRM)	• With protocol chair, provide scientific and operational input to the protocol and coordinate and lead protocol development and any subsequent protocol modifications, as applicable • Organize and document protocol team conference calls and meetings • Prepare study budget with Operations Center financial staff, in collaboration with the protocol chair and, as applicable, with input from other protocol team members and site representatives • Submit protocol for required IMPAACT and DAIDS reviews (Multidisciplinary Protocol Review Group (MPRG), applicable Scientific Review Committee, Regulatory, MO, Regulatory Affairs Branch) and manage the response/revision process, as needed (see Section 9) • Coordinate the site selection process (see Section 10) • Develop and produce the study-specific MOP with input from the Data Management Center (DMC), LC, and other protocol team members, as applicable (see Section 11) • Collaborate with protocol team members to coordinate the completion of study open to accrual requirements (see Section 11) • Coordinate and develop the training plan and materials and provide study-specific training with DMC, LC, and other protocol team members, as applicable (see Sections 11 and 16) • Coordinate the site activation process (see Section 11) • Assess the performance of and provide operational guidance to sites during study conduct, enabling the sites to respond to problems and issues that arise during implementation of studies and dissemination of findings • Provide information on study progress to the sites, protocol teams, Network leadership, pharmaceutical representatives (if applicable), and/or DAIDS • With the SMC or DSMB coordinator, collaborate with Statistical and Data Management Center (SDMC) on SMC and/or DSMB reviews and reports • Contribute to study close-out procedures (see Section 14) • Participate in publication activities and facilitate, as needed (see Section 19) • See Section 2 for further details of Operations Center responsibilities

Table 4-1. Roles of Key Protocol Team Members

Team Member	Primary Roles and Responsibilities
Statistician	• Provide design, statistical, and scientific input during protocol development and throughout the conduct of the study • Lead development of statistical components of the protocol • Collaborate on protocol development and protocol-related materials • Develop randomization and enrollment plan, as needed • Lead development and implementation of the Study Progress, Data, and Safety Monitoring Plan (SPDSMP), including routine reports (see Sections 11 and 13), in collaboration with the PDM and LDM • Lead development and implementation of the Statistical Analysis Plan (SAP), in collaboration with the protocol chairs, MOs, and other protocol team members • Lead development of Analysis Implementation Plan (AIP), as needed • Conduct data analyses and generate interim analysis reports for the SMC or DSMB, in collaboration with the PDM and other protocol team members • Conduct data analyses and generate final analysis reports, in collaboration with the PDM and other protocol team members • Contribute to study close-out procedures (see Section 14) • Collaborate on publication activities and lead analyses, as needed • Submit study results to ClinicalTrials.gov • See Section 2 for further details of SDMC responsibilities
DAIDS Protocol Pharmacist (if applicable)	• Lead development of pharmacy and study drug/product components of the protocol • Collaborate with the CRM to develop and produce the MOP, with primary responsibility for pharmacy sections (see Section 11) • Conduct study-specific training on pharmacy requirements • Advise protocol team on all study product-related issues, including study drug/products and associated materials for administration • Collaborate with CRM on review of site-specific study activation requirements related to pharmacy requirements prior to study activation • Interact with pharmaceutical companies, Clinical Research Products Management Center (CRPMC), and sites to ensure study product supply and materials are available, as needed • Monitor timely study product shipment to study sites • Monitor drug supply, expiration dates, and budgets for drug, where necessary
Investigators	• Provide scientific input during protocol development • Provide input and review clinical-related sections of study implementation documents, as applicable • Provide investigator-specific expertise, as applicable • Participate in publication activities, as applicable
Pharmaceutical or industry representative	• Provide input during protocol development and implementation, as applicable and as outlined in network and/or sponsor agreements

Table 4-1. Roles of Key Protocol Team Members

Team Member	Primary Roles and Responsibilities
Protocol Data Manager (PDM)	• Collaborate in the development of the protocol • Collaborate with the CRM to develop and produce the MOP, with primary responsibility for data management, reporting, and randomization sections • Lead the development of Clinical Data Interchange Standards Consortium (CDISC)-compliant data collection instruments (e.g., case report forms [CRFs], computer-based questionnaires) and instructions, in collaboration with LDM and statistician, as needed • Collaborate with CRM on review of site activation requirements related to data management prior to activation • Conduct training on data management and data collection instrument completion • Collaborate with statistician and LDM to develop and implement the SPDSMP (including development and distribution of routine reports) • Collaborate with LDM, pharmacologist, and statistician in the development and implementation of the PK data management plan, when applicable • Collaborate with statistician to generate interim analysis reports for the SMC or DSMB and final analysis reports • Provide support for data collection and management • Monitor study data in accordance with the protocol requirements and issue site queries as needed for quality assurance • Collaborate with CRM to provide support for operational matters that may influence study data • Assess site data quality and report results to protocol team, as needed • Conduct data management site visits, as needed • Contribute to study close-out procedures, including data collection and cleaning (see Section 14) • Participate in publication activities and facilitate, as needed • See Section 2 for further details of SDMC responsibilities
Laboratory Data Manager (LDM)	• Collaborate in the development of the protocol • Collaborate with PDM to develop data collection instruments and instructions • Collaborate with the LC representative and LT on development of the Laboratory Processing Chart (LPC; see Section 11) • Lead development and implementation of the LDMS Quick Add Templates • Collaborate with the statistician and PDM to develop and implement the SPDSMP • Lead development and implementation of the PK data management plan with the pharmacologist, statistician, and PDM, when applicable • Monitor laboratory data for the study in accordance with the protocol requirements and issue lab queries as needed for quality assurance • Assess the quality of laboratory data for the study, including but not limited to, specimen completeness, in collaboration with the PDM, and report results to protocol team, as needed • Coordinate specimen shipping requests and data transfer agreements for receipt of resulting assay data, as needed • Contribute to study close-out procedures (see Section 14) • Participate in publication activities and facilitate, as needed • See Section 2 for further details of SDMC responsibilities

Table 4-1. Roles of Key Protocol Team Members

Team Member	Primary Roles and Responsibilities
Community representative(s)	• Provide perspective of community and potential participants during protocol development, study implementation, publications, and results dissemination • Facilitate communication with the IMPAACT Community Advisory Board (ICAB), throughout the life of the study • Work with protocol team and community advisory boards (CABs) to develop and implement plans for dissemination of study results to the community, as needed
LC Representative	• Collaborate in the development of the protocol • Develop and produce the LPC with input from the LT, LDM, and other protocol team members, as applicable (see Section 11) • Collaborate with LT to provide laboratory expertise in development of data collection instruments • Collaborate with CRM on review of site-specific study activation requirements related to laboratory requirements prior to study activation; for NIAID sites, confirm laboratory readiness (for NICHD sites, laboratory readiness is confirmed by Westat) • Collaborate with LT to conduct training on study-specific laboratory procedures and processes • Collaborate with CRM and LT to provide support for operational matters that may influence laboratory procedures or results • Participate in publication activities and facilitate, as needed • See Section 17 for further details of LC responsibilities
Laboratory Technologist (LT)	• Collaborate in the development of the protocol • Collaborate with the LC representative and LDM on development of the LPC (see Section 11) • In collaboration with LC representative, LDM, and PDM, provide laboratory expertise in development of data collection instruments • In collaboration with LC representative and other protocol team members, identify study-specific laboratory requirements and materials • In collaboration with LC representative, conduct training on study-specific laboratory procedures and processes • Collaborate with CRM and LC representative to provide support for operational matters that may influence laboratory procedures or results • In collaboration with LC representative and CRM, develop and review laboratory related sections of the MOP • Participate in publication activities, as needed
Westat Representative(s) (if applicable)	• For studies with NICHD site participation, facilitate communication between protocol team, Westat colleagues, and NICHD sites • For Westat laboratory colleagues, collaborate with CRM on review of site-specific study activation requirements related to laboratory requirements prior to study activation; for NICHD sites, laboratory readiness is confirmed by Westat

Table 4-1. Roles of Key Protocol Team Members

Team Member	Primary Roles and Responsibilities
Site investigator from each participating CRS	• Provide site-informed input on protocol development and implementation • Review and comment on study implementation materials and data collection instruments • Participate in publication activities, as needed

4.2.3 Study-Specific Groups

The protocol chair may identify study-specific groups to address specific needs/activities during protocol development and study conduct and appoint protocol team members or external investigators to these study-specific groups. Examples might include study-specific groups to address:

- Development and/or oversight of specialized behavioral procedures for a study
- Development and/or oversight of specialized clinical procedures for a study
- Development of specialized data collection modules (in collaboration with SDMC)
- Ongoing support of site clinicians regarding toxicity management and study drug dosing, such as a Clinical Management Committee (or Core Team)
- Review of safety assessments and reports or determination of outcome measures (e.g., external safety review groups or outcome review groups)
- Drafting and submission of manuscripts and presentations (see Section 19)

The CRM facilitates and generally participates in the conference calls and meetings of these study-specific groups. Where applicable, the CRM provides summaries to the protocol team for the study-specific group meetings and conference calls. Delegation of responsibilities for ongoing, study-specific groups is outlined in the protocol during development; membership and roles and responsibilities of these groups is generally described in the SPDSMP. Network leadership review of membership on atypical study-specific groups may be required.

When protocol chairs are not included in the group membership, a group chair is typically identified to assume leadership responsibilities and decision-making authority. When the CRMs are not included in the group membership, a group member is designated to assume group management and documentation responsibilities of key decisions; see Section 12 for details on quorum and documentation requirements.

4.3 Relationship of Protocol Team to IMPAACT Management Oversight Group (MOG)

The MOG monitors each IMPAACT protocol team with regard to protocol development, implementation, analysis, and reporting. This oversight is accomplished through the SMC, Operations Center, LC, and SDMC by a mixture of formal reviews of key documents produced by the protocol teams (e.g., study protocol, protocol summaries, open reports to the SMC or DSMB, and primary and secondary manuscripts) as well as review of prepared reports.

In addition to oversight provided by the SMC or DSMB, as detailed in Section 13, routine MOG oversight includes:

- Evaluation of study progress in relation to key implementation benchmarks established by the MOG and information from the protocol teams (e.g., timeliness of enrollment and follow-up targets, routine reports to the SMC or DSMB, and progress in data analysis and reporting). The MOG identifies and

communicates recommended actions on delayed protocols and unexpected problems during protocol implementation.
- Assistance to DAIDS in determining the need for additional resources, for example, because of unexpected costs associated with planned study procedures.
- Adjudication of conflicts that cannot be resolved within the protocol teams (see Section 4.4).

The SLG may also provide scientific guidance, as needed. In particular, protocol changes including significant changes to the scientific goals, study objectives, or design must be approved by the relevant SC and SLG, as described further in Section 9.

4.4 Conflict Resolution within Protocol Teams

Conflicts within IMPAACT are handled by referring the issue in dispute to the next level of the IMPAACT organizational structure.

If a conflict arises within a protocol team and cannot be resolved between the members involved, the issue is referred to the protocol chair. If the protocol chair cannot resolve the issue with the protocol team, the issue is referred to the MOG. If all reasonable attempts to adjudicate conflicts or address problems with the protocol team do not result in resolution of the conflict, the MOG may direct that the protocol team membership or its leadership be modified.

5 COMMUNITY PARTICIPATION AND ENGAGEMENT IN THE IMPAACT NETWORK

Community participation and engagement are critical in scientific research. There is mutual benefit to communities and researchers when all parties work together throughout the scientific research process. In the IMPAACT Network, community participation occurs at the Network, community, and site levels through various mechanisms that include representation on the Network committees, protocols teams, and cross network community activities.

The IMPAACT Operations Center Community Engagement Program staff oversee IMPAACT's community engagement activities. Local engagement is typically done by clinical research sites with community partners who operate on a local level.

The IMPAACT Operations Community Engagement Program staff are responsible for the following:

- Ensuring an IMPAACT Community Program Manager (CPM) is assigned to each protocol team and Scientific Committees (SCs)
- Facilitating appropriate community input into the scientific agenda and the research process with Network leadership, including the Scientific Leadership Group and Scientific Committees, as well as within protocol teams
- Developing mechanisms for sharing experiences, lessons learned, and best practices in community involvement in research
- Building capacity for local communities to provide input into research at IMPAACT sites
- Facilitating training and capacity building sessions for community staff and CAB members
- Working with other IMPAACT Operations Center staff to ensure that community representatives are adequately prepared prior to launch of new studies, study milestones and results, to assist them in managing expectations and communicating study outcomes at the community level.

5.1 Confidentiality

All IMPAACT Community Advisory Board (ICAB) members are required to adhere to confidentiality standards and may be asked to sign confidentiality agreements. Members must agree to acknowledge the sensitive nature of IMPAACT discussion by refraining from:

- Disclosing confidential information, including concept sheets, protocols in development, study participant data and identifiers, and unpublished study results
- Sharing unpublished product data or other confidential proprietary information
- Sharing or distributing personal usernames and passwords to IMPAACT-related websites
- Sharing or distributing draft ICAB documents. Members can share documents for community review once approved timelines for such review have been set

Members are responsible for making certain an item can be shared or made public. If a member is in doubt, that member MUST clarify the issue of confidentiality. Clarification can come from the provider of the information, the chair of the relevant IMPAACT committee or protocol, or the chairs of the ICAB. Members must also respect confidentiality of disclosures by any member of the clinical trials networks (for example, the sharing of photographs, personal stories, HIV status, etc.).

Breach of confidentiality by any member may result in disciplinary action, up to and including loss of membership privileges. Disciplinary actions are determined by ICAB leadership.

5.2 IMPAACT Community Advisory Board (ICAB)

The ICAB includes representatives from areas in which IMPAACT works, including Asia, Africa, and the Americas, and assists clinical research site (CRS) Community Advisory Boards (CABs) with capacity building, training, and development. The role of the ICAB is to provide HIV/AIDS live experience expertise that positively impacts the formulation and implementation of research by community representation at the Network and cross- network levels.

The purpose of the ICAB is to ensure that community participation is the foundation of all community engagement activities at a CRS and to facilitate community participation throughout the research process (concept development, protocol development, study implementation, results dissemination, and post-trial access to interventions that are found to be effective).

The ICAB's goals are to:

- Provide HIV/AIDS lived experience that assists in the development and implementation of research
- Develop ways to share challenges and solutions, best practices, experience, and lessons learned
- Build community capacity to provide input and support to the IMPAACT scientific agenda
- Foster involvement of community members who represent diverse study communities within the Scientific Leadership Group (SLG), SCs, and protocol teams
- Provide information and guidance regarding community-related matters to the SLG, SCs, and protocol teams
- Provide guidance and actively promote Network initiatives related to research and training that focus on community participation across all levels of IMPAACT research

5.2.1 ICAB Membership

There are two ICAB representatives from each IMPAACT CRS – one a local CAB member and the other a site staff liaison (commonly a community educator/community liaison [CE/CL]). Typically, the local CAB elects or nominates the CAB member to serve on the ICAB while the CRS Leader or designee appoints the CE/CL. The CE/CL supports and facilitates the CAB member's participation in the ICAB.

Standing membership in the ICAB includes:

- Voting members (one vote each)
  - ICAB chair
  - ICAB vice chair
  - One CAB representative from each CRS
- Non-voting members
  - One CE/CL from each CRS
  - Emeritus ICAB chair (unless the Emeritus ICAB chair is an ICAB representative for their CRS)
  - IMPAACT Operations Center Community Engagement Program staff

5.2.2 ICAB Roles and Responsibilities

The roles and responsibilities of the ICAB include:

- Advocating for IMPAACT scientific priorities that reflect the needs of people living with HIV/AIDS, including community research priorities
- Advocating for innovative, efficient, and timely clinical trials
- Protecting the interests of research participants
- Promoting effective CAB(s) at every IMPAACT site
- Facilitating information flow between the sites and Network, including new and emerging research and study results, when available
- Bringing site and regional community issues to the ICAB Leadership Group (ILG) for further discussion with the IMPAACT Network
- Participating on protocol teams, when applicable
- Training and mentoring CAB members with assistance from site staff, the ILG, and IMPAACT Operations Center
- Electing the membership of the ILG

5.2.3 ICAB Participation Requirements

Active participation is expected and necessary to achieve the goals of the ICAB. Members of the ICAB are expected to attend and contribute to scheduled conference calls and/or webinars. If neither of a CRS's ICAB representatives is available, another site staff member or local CAB representative should be identified to participate on the call/webinar and report back to the CRS's ICAB representatives.

ICAB members are expected to attend the annual IMPAACT Network Meeting and the ICAB face-to-face meetings. Upon their return, they should report on both the community-specific and scientific content of those meetings to the local CAB and other site staff.

Participation in protocol team and other Network committee conference calls and meetings occur as appropriate. Additionally, study-specific ICABs may be established for some IMPAACT studies. See Section 5.6.1 for more information.

5.3 ICAB Leadership Group (ILG)

The ILG provides guidance and support to the ICAB and advises IMPAACT leadership on matters concerning community engagement in the IMPAACT research agenda. The ILG serves as a conduit of information between the IMPAACT ICAB, IMPAACT leadership, and IMPAACT SCs.

The ILG's goals are to:

- Respond to time-sensitive requests for community input
- Inform and guide the development of a community-centered, relevant, effective, and ethical research agenda
- Proactively identify challenges related to community engagement and/or research implementation to uphold scientific integrity and ethical standards
- Through the ICAB chair,
  - Inform the IMPAACT SLG of the ICAB's decisions, concerns, and activities
  - Advise the IMPAACT SLG on strategies to address challenges and issues of concern
- Develop mechanisms for sharing experiences, lessons learned, and best practices for community engagement in IMPAACT research

5.3.1 ILG Standing Membership

The standing membership of the ILG includes:

- Voting ILG members
  - ICAB chair
  - ICAB vice chair
  - Two at-large members for each of the IMPAACT SCs
- Non-voting ILG members
  - IMPAACT Operations Center Community Engagement Program staff
  - Emeritus ICAB chair

5.3.2 ILG Membership Requirements

While membership in the ILG is open to all ICAB members, it is important that the ILG is representative of the IMPAACT research communities. Therefore, people living with or affected by HIV are encouraged to join, including:

- Women and people who are pregnant and postpartum
- Parents/caregivers of infants, children, and young people
- Adolescents and young people

The qualifications of ILG members include:

- The ability to provide daily life experience-based expertise on living with HIV/AIDS
- The ability to read, speak, and write English at a conversational or fluent level
- Access to a device (e.g., computer, smart phone, tablet) with dependable internet capability, whether at home or the research site
- Time flexibility for participation in international conference calls (US time zones)

- A history of positive ICAB contributions, if applicable
- Strong public speaking and presentation skills
- A basic understanding of scientific protocols
- The ability to quickly respond to time-limited requests

Regional and Site Representation on the ILG

It is important that the ILG impartially represent communities from the geographical regions that participate in IMPAACT research. For this reason, only one ICAB representative from any one CRS can serve on the ILG. This policy is ensured during the ILG solicitation and election process by:

- Alternating geographic representation between the ICAB chair and ICAB vice chair (see Section 5.3.4 for more information)
- Making ineligible the participation in the ILG by the second ICAB representative from the same site as an elected ILG member. If the ICAB vice chair chooses to become the ICAB chair, the second ICAB representative from the site is not eligible to apply for a position on the ICAB until the ICAB chair's one term of two years expires.
- When both the community representative and site liaison apply for a position within the ILG, both may be entered into the open election. The applicant with the most votes will be appointed to the ILG.

If the ILG's membership is not composed of at least one representative from each geographical region, the ILG may petition volunteers from the unrepresented region(s) for assistance and guidance to ensure that input and feedback into IMPAACT research and projects include the perspective of communities from all regions.

5.3.3 ILG Member Term Limits

ICAB Chair

After one term of two years, the ICAB chair moves into an emeritus chair role where they continue to actively participate in the leadership and direction of the ILG but through mentorship and guidance.

ICAB Vice Chair

After one term of two years, the ICAB vice chair may choose to be automatically moved into the position of ICAB chair where they will serve a two-year term. If the ICAB vice chair chooses not to move forward in the role of ICAB chair, the position of ICAB chair will be opened to receive applications followed by an election from the ICAB.

At-Large Members

At the end of one term of two years, an elected at-large ILG member may re-apply for a second term. At-large members may only serve up to two consecutive two-year terms. Members who have served two consecutive terms must rotate off the ILG for two years.

Emeritus Chair

The emeritus chair serves for one, one-year term in which they actively participate in the leadership and direction of the ILG through mentorship and guidance. The emeritus chair is not a voting member of the ILG. If re-elected as the ICAB representative of their CRS, they may, after rotating off the ILG for two years, seek election as an ILG at-large member.

5.3.4 ILG Membership Selection Process

The positions of ICAB vice chair and the at-large membership of the ILG are filled through an open solicitation made to the full ICAB. Those interested in serving as an ILG member must complete a multi-component application process. This process is designed to identify the best qualified individuals from the pool of applicants.

The process may include:

1. Completion of an application form which assesses the desired qualifications for the position.
2. Submission of a performance checklist that is to be completed by either the CE/CL, CRS leader, or designee. The performance checklist evaluates the ICAB member's performance and interaction with their site and site CAB by assessing:
    - Active participation and regular attendance in site CAB meetings.
    - Responsiveness to emails and requests made by the site and/or CAB.
3. Submission of a one-page Statement of Interest that clearly describes the candidate's experience with HIV/AIDS, history working within a community advisory board structure, and any other information the candidate feels relevant and important to this selection process.

The IMPAACT Operations Center Community Engagement Program staff review all application packets for completeness. Applications that meet all requirements will advance to the final stage of the application process, which is a popular vote, open election.

The voting membership of the ICAB are asked to vote for their preferred leadership group members by selecting their top choices.

The ICAB representative may base their vote solely upon their own preferences or discuss the qualifications of candidates with their site's CE/CL or site CAB. CEs/CLs are responsible for ensuring that their site's voting ICAB member votes when requested. If necessary, the CE/CL may consult the voting ICAB member and submit a ballot on their behalf.

If the ICAB vice chair opts to move into the position of ICAB chair, the candidate with the most votes from an alternate geographic region becomes the new ICAB vice chair. For example, if the person moving into the ICAB chair is from the Americas region, the candidate with the most votes from the Asia or Africa region would be eligible for the position.

If the ICAB vice chair opts NOT to move into the position of the ICAB chair, the candidate who receives the highest number of votes will fill the position of the new ICAB chair. The candidate with the next highest number of votes from an alternate geographic region will become the new ICAB vice chair.

5.3.5 ILG Roles and Responsibilities

The roles and responsibilities of the ICAB Leadership Group include:

- Participating in monthly ILG calls and periodic face-to-face meetings
- Developing ICAB agendas
- Planning trainings with the ICAB and IMPAACT Operations Center
- Seeking opportunities that allow ICAB members to actively participate in the process of generating science as well as collaborate more closely with the various committees, working groups, and

protocol teams in supporting community-focused HIV, tuberculosis, and any other emergent areas of research
- For at-large members, participating in SCs
- For the ICAB chair and vice chair, participating in the SLG and leading ICAB meetings

If ILG members are unable to meet these roles and responsibilities, they may be asked to consider stepping down, and an election may be held to replace the ILG member to ensure adequate community representation.

5.3.6 ILG Scientific Committee Representation

Each at-large ILG member serves as an ICAB representative to one of the SCs. The roles and responsibilities of the SC representatives are to:

- Review and provide feedback on all new concepts within the SC
- Inform and advise the ILG on issues of concern
- Regularly participate in virtual and periodic face-to-face meetings

5.4 IMPAACT Site Community Advisory Boards

Typically, a CRS obtains community input into the research process through its CAB, although a CRS may refer to this structure by any locally chosen name or establish an alternative structure. Community representatives provide input to protocol teams, particularly in reviewing protocols in development, adapting sample consent forms for local use, and developing other study-related materials.

ICAB representatives may be asked to submit site update report forms to the Operations Center Community Engagement Program staff. The site update report form captures the site CAB's activities, accomplishments, and challenges that can be shared with the full ICAB for cross-learning and development. Routine CAB updates are also provided on ICAB conference calls.

To ensure their autonomy and to reduce possible conflicts of interest, CAB members are volunteers from the CRS community and are not paid staff members at the site. They must adhere to CAB by-laws and governance regarding roles, responsibilities, and meeting attendance. They are expected to participate meaningfully so that issues requiring community dialogue receive appropriate attention. CAB members and community partners involved in review of protocols and related documents sign a statement of confidentiality to ensure the confidentiality of proprietary information and to protect members and study participants from HIV-related stigma.

The CRS supports CAB members as they share their community expertise and gain new skills through face-to-face meetings and conference calls. CAB members are reimbursed for legitimate costs associated with participating in the advisory process, such as transportation, childcare, and meals, at a level deemed appropriate by the individual CRS. This reimbursement should not be construed as payment. The CRS staff and other IMPAACT members (such as Clinical Research Managers [CRMs], protocol chair, protocol team members, the IMPAACT Statistical and Data Management Center or the IMPAACT Laboratory Center) who are conducting training or assessment visits at study sites should be available to participate in CAB meetings as needed. The CRS is expected to support representatives of the CAB to participate in the IMPAACT meetings, protocol-specific training, and community workshops.

5.5 Community Input Throughout the Study Lifecycle

Community input and consultation is obtained throughout the study life cycle, with specific reviews and processes during concept development, protocol development, study implementation, and results dissemination.

5.5.1 Concept Development

When a concept is initially received for SC review, the assigned Operations Center representative(s) works with the assigned Community Program Manager (CPM) to determine an appropriate timeline for community review, depending on the date scheduled for SC review of the concept as well as the concept's scope. The ILG review of the concept may occur concurrent with or following SC review but must be reviewed by the ILG prior to submission for Scientific Leadership Review (SLG). Regardless of the timing, the ICAB SC representatives are responsible for providing feedback as part of the SC review of the concept.

The ILG will typically review a concept during a conference call where the proposing investigator(s) are invited to join the call to briefly introduce the concept, providing additional information that may help facilitate ILG feedback. The CPM will work with the ILG to determine call scheduling, as part of routine calls or ad hoc. Following the call, the ICAB SC representatives, with assistance from the CPM, summarize and provide the ILG feedback to the proposing investigators; this feedback is also shared with the ILG.

The ICAB chair, serving as the ICAB representative on the IMPAACT SLG, shares the community's feedback with the SLG during their review of the concept.

5.5.2 Protocol Development

As further described in Section 9, critical input is sought from site representatives, community representatives, and other stakeholders throughout the protocol development process, as needed, to ensure both the appropriateness and the operational feasibility of the study. Community input from representative sites is initiated once a protocol team has completed site selection. The assigned CPM will solicit 1-2 ICAB representatives from participating sites to serve as community representatives on the protocol team; primary roles and responsibilities for the community representatives are described in Section 4.

Prior to or concurrent with the IMPAACT Multidisciplinary Protocol Review Group (MPRG), the CPM in collaboration with the CRM(s) and community representatives sends the draft protocol to the ILG and to the ICAB representatives from selected sites for review and comment. Written review comments are generally requested within 10 working days. During this time, the CPM, with the CRMs, may arrange a conference call with the protocol chairs or designees and the ILG and ICAB site representatives to discuss the protocol and obtain community feedback. The CPM consolidates and provides the ICAB comments to the protocol chairs and CRMs as well as to the ICAB representative to the MPRG (generally the ICAB chair). The ICAB representative to the MPRG may use the comments to inform their response during the MPRG review.

If community input is requested before site selection is complete, the ILG and select ICAB representatives will provide feedback.

5.5.3 Study Implementation

The community representatives on the protocol team are actively engaged throughout the study lifecycle. In addition, a study-specific ICAB may be established as needed for studies that are larger or include more complex or unique procedures, populations, study designs, or interventions, depending on the study-specific community needs. They are generally comprised of ICAB members from the CRSs selected to conduct the study. Study-specific ICABs are responsible for enhancing study-specific community strategies and identifying possible study implementation challenges. They also assist in the following activities:

- Development of study-specific educational toolkits (e.g., informed consent flipcharts, flyers, Dear Participant letters)
- Development of plans to disseminate information intended to keep community members informed of protocol updates
- Support site-specific community involvement activities
- Facilitate community preparedness and ongoing engagement activities and ensure the successful conduct of studies through local or site-specific partnerships

5.5.4 Results Dissemination and Potential Next Steps

As described further in Section 19, the release of study results provides an opportunity to share findings that could influence the standard of care in the communities where IMPAACT studies are conducted or the design and/or conduct of ongoing or future trials. Protocol teams are responsible for determining appropriate plans and timing and generally include directions for CRSs to share with study participants, CAB members and other community partners, country officials, and other key stakeholders.

In addition to planned publications based on the study primary and secondary objectives, the CRS CE/CL and CAB members are encouraged to develop publications (such as abstracts, manuscripts and posters) describing community efforts that contributed to the successful implementation of the research.

5.6 Cross Network Collaborations and Community Partners

The ICAB works with other Division of Acquired Immune Deficiency Syndrome (DAIDS) research networks by having representation in the DAIDS Office of HIV/AIDS Network Collaboration (HANC) Community Partners (CP) group. Community Partners promotes effective representation of the many communities within which the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases-sponsored HIV clinical trials networks conduct research. ICAB members selected and appointed to the CP participate in monthly conference calls and utilize online tools such as email and a web portal system that allows for document collaboration and use of discussion boards.

The ICAB works with HANC CP and other research/community groups and organizations when it deems the partnership beneficial to IMPAACT. The ICAB identifies and selects members to work on these collaborations. Opportunities for cross-network collaborations are encouraged within the ICAB.

ICAB members may also collaborate with other community groups from NIH and non-governmental organizations. Through these relationships, the ICAB identifies HIV/AIDS research needs and issues across networks and institutes and works toward their effective resolution.

6 NETWORK MEETINGS AND COMMUNICATIONS

Communications and information dissemination are critical to the successful management of a large, international, multicenter network such as IMPAACT. IMPAACT uses a variety of approaches to enhance communication within the Network about study-specific and Network-wide research initiatives. The Operations Center supports and coordinates much of the communications within IMPAACT through conference calls, in-person meetings, electronic and written materials, and announcements and postings through IMPAACT's website. The website serves as a main driver of general and public communication, where study-specific information and postings about Network-wide activities can be found. The Network also distributes a newsletter and utilizes social media platforms for communication purposes.

6.1 Meetings

6.1.1 Annual Network Meeting

In collaboration with IMPAACT leadership, the Operations Center organizes an annual Network meeting to bring together IMPAACT members and collaborators to discuss study designs and research goals, review data from ongoing trials, examine cross-cutting issues, and provide an overview of the IMPAACT scientific agenda. In addition, the meeting provides opportunities for training, identifying key issues, defining and discussing Network procedures, and clarifying roles and responsibilities of IMPAACT members. The meeting generally includes plenary sessions to update IMPAACT members on the latest scientific research related to the Network's mission and agenda. The Network Scientific Leadership Group (SLG), Management Oversight Group (MOG), Scientific Committees (SCs), IMPAACT Community Advisory Board (ICAB), and protocol teams schedule meetings in conjunction with this yearly event. Additionally, the annual Network meeting may provide National Institutes of Health (NIH) training opportunities.

The Operations Center is responsible for the overall logistics of the meeting, preparation of agendas and background materials and, subsequently, dissemination of any required materials for the SLG, MOG, SCs, protocol teams, and protocol-specific sessions in collaboration with the chair of the respective group, committee, board, or team.

6.1.2 In-Person Meetings

Network leadership groups, protocol teams, and other groups may meet in person at the Annual Meeting, on some other set schedule, or at key times, such as during protocol development (see Section 9 for more information about the appropriate timing of protocol development meetings). In-person meetings may

require adaptation to or replacement by a virtual meeting format, if needed, due to travel restrictions, social distancing requirements, or other unforeseen circumstances.

In-person meetings of Network leadership groups (SLG, MOG, and SCs) are generally convened annually. The purpose of these meetings is to discuss the priorities and direction of the IMPAACT Network. The Operations Center is responsible for the overall logistics of the meetings including preparation of agendas and background materials.

The clinical research manager (CRM) assigned to the protocol, with assistance from other Operations Center staff, is responsible for the overall logistics of any in-person protocol team meetings, including identifying times and assisting with the development and distribution of agendas and background materials. Documentation needs and requirements will vary based on the meeting and may include attendee rosters, written summaries, audio and/or video recordings, emailed summaries of action items, or other methods.

Ad hoc meetings of other groups can also be coordinated, based on need, with assistance from the Operations Center.

6.1.3 Conference Calls

In between or in lieu of in-person meetings, conference calls are used extensively to facilitate the Network's research activities. Joining conference calls over the internet using web-based platforms is the preferred approach, and when appropriate, webinar technology should be utilized to facilitate interactive slide presentations and other media-rich methods for sharing information and data. Organizers of each call should aim to provide toll-free numbers to all US participants and, when available, to international participants. Where a toll-free number is not available, alternate arrangements for connecting international participants should be made (e.g., dialing out to participants).

Routine call schedules may be established for IMPAACT study teams, groups, and committees, depending on project needs and the availability of key IMPAACT members involved in protocol or committee work. Prompt responses to these scheduling requests is required for efficient set-up of conference calls. Depending on the purpose and content of the call, quorum requirements as outlined in Table 12-2 of this MOP may apply. For protocol-related calls, prior to any call, participants should agree on a plan for documentation, including whose responsibility it is, as described in Section 4. Documentation needs and requirements will vary based on the call and may include written call summaries, audio and/or video recordings, emailed summaries of action items, or other methods.

As with in-person meetings, the Operations Center can provide a broad range of administrative and technical support for conference calls, if needed.

6.2 Communication Mechanisms and Material Distribution

Staff of the IMPAACT central resources (Leadership and Operations Center, Statistical and Data Management Center [SDMC], and Laboratory Center) disseminate IMPAACT information and study materials using a variety of methods including email, website postings, mail, and express mail services. To help ensure the successful transfer of information, each Network organization must:

- Have the capacity to send, access, and receive materials distributed using the above methods
- Ensure that IMPAACT communications and materials are distributed to all appropriate staff members
- Maintain all key study and IMPAACT communications in a well-organized filing system

Key IMPAACT information is posted on the IMPAACT website for access by all Network members and the public. Information from central resources and from the NIH is included and maintained regularly to ensure the timeliness of materials availability and dissemination. Other websites with information relevant to the Network include:

- DAIDS Regulatory Support Center (RSC): https://rsc.niaid.nih.gov/
- Office of Human Research Protections (OHRP): https://www.hhs.gov/ohrp/
- US Food and Drug Administration (FDA): http://www.fda.gov/
- National Institutes of Health (NIH): https://www.nih.gov/
  - National Institute of Allergy and Infectious Diseases (NIAID): https://www.niaid.nih.gov/
  - *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): https://www.nichd.nih.gov/
  - National Institute of Mental Health (NIMH): https://www.nimh.nih.gov/
- HIV/AIDS Network Coordination (HANC): https://www.hanc.info/
- US Centers for Disease Control and Prevention (CDC): https://www.cdc.gov
- World Health Organization (WHO): https://www.who.int/

6.2.1 Network Website

The IMPAACT website (http://impaactnetwork.org) provides a wide range of materials.

The general philosophy governing the design, maintenance, and content of the website is to provide a site that: (1) contains useful and up-to-date information on the Network organization and studies; and (2) accommodates various internet connections and software and hardware limitations across this multinational Network.

When materials are posted on the IMPAACT website, an appropriate file type will be chosen based upon the document. If an alternate file type is needed (e.g., if a file is posted as a PDF, but a Word version is required), requests can be sent to the Operations Center. Documents generally open in new tabs, thus providing viewers with easy access back to the main website. Information on the IMPAACT website is updated frequently. This may include IMPAACT protocols, letters of amendment, full protocol amendments, and study-specific materials including laboratory processing charts, manuals of procedures, training presentations, and study implementation materials. Study-specific pages are developed to suit the needs of each particular study. An updated list of site names and numbers and a list of protocols (numbers and titles) that includes participating sites and the status of each study is also posted. The website also features a searchable IMPAACT publications database.

The design and maintenance of the IMPAACT website is the responsibility of the Operations Center. Document posting requests or design/structure update requests are sent to the website manager. Questions and comments on the website may be sent to: IMPAACT.webcontact@fstrf.org.

6.2.2 Newsletter and Social Media

The IMPAACT Network routinely distributes a newsletter to members, which generally includes study and other updates, a listing of new publications, ICAB updates, and a staff spotlight.

The Network also utilizes social media to keep members and the public aware of news and content related to the Network's scientific agenda. IMPAACT has a presence on Facebook, Twitter, and LinkedIn.

6.3 Release of Information to the Public

This section describes the public information policy of the Network as well as procedures and guidance related to press releases and public announcements. Policies and procedures related to dissemination of study results and the Network's compliance and support of the NIH Public Access Policy can be found in Section 19.

6.3.1 Public Information Policy

Investigators and site staff may have access to proprietary and sensitive information as a result of their participation in IMPAACT studies. The following guidelines relate to disclosure of product and study-related information to the public. These guidelines are in keeping with the policies and procedures of the DAIDS Office of Program Operations and Scientific Information, the NIAID Office of Communications and Government Relations (OCGR), and the NIAID News and Public Information Branch (NPIB).

Inquiries from the press, community representatives, and public officials concerning general study status may be addressed by the study investigators to whom questions are directed; however, investigators may not provide public comments related to study outcomes or adverse events, except in coordination with the protocol team and the sponsor.

Press inquiries more specifically or generally about IMPAACT activities should be referred to the IMPAACT Operations Center (IMPAACT.OperationsCenter@fstrf.org) in consultation with Network leadership and NIH.

Proprietary information about study products in development or used in a trial conducted under an Investigational New Drug (IND) application may not be discussed publicly by anyone without written permission of the product's manufacturer.

6.3.2 Disclosure of Study Results

The release of study results provides an opportunity to share findings that could influence the standard of care in the communities where IMPAACT studies are conducted or the design and/or conduct of ongoing or future trials. As outlined in Section 19, the protocol team, in coordination with Network leadership and NIH, develop materials and plans for results dissemination.

6.3.3 Press Releases and Public Announcements

All Network-related press releases and public statements will be developed or approved by NIAID, NICHD, and NIMH and, as appropriate, by its co-sponsors. When such materials are developed by the sponsor(s), the DAIDS Medical Officer and IMPAACT Operations Center will coordinate review by Network and/or study leaders as needed. When these materials are developed within the Network, the DAIDS Medical Officer and IMPAACT Operations Center will ensure that they are reviewed and approved by required groups, including representation from the relevant protocol team. Before any materials undergo NIH review, the IMPAACT Operations Center ensures they have been reviewed and/or approved by relevant parties within the Network. Study-related press releases and materials must be approved by the protocol chair and the IMPAACT Network chair.

To ensure accuracy of information and proper identification of IMPAACT, NIH, and other funding sources, all press releases generated by the Network must be reviewed by the IMPAACT Operations Center, which will coordinate additional review by the appropriate funding institutes, as necessary. Investigators should allow sufficient time for this process.

When study results are to be published or presented at a scientific meeting, the IMPAACT Operations Center, in collaboration with NIH and other relevant sponsors, may coordinate press announcements with the authors and the publishing journal or scientific meeting organizer to comply with all required embargo guidelines. For studies conducted under a Clinical Trials Agreement (CTA) with a product manufacturer, the publication guidelines and procedures described in the CTA must also be followed. In cases of specific points of discordance between CTA requirements and this policy, the CTA requirements shall be followed.

Review and issuance of press releases developed outside the IMPAACT Network (e.g., pharmaceutical, biomedical industry, or external collaborators) will follow the terms included in any applicable CTAs with DAIDS.

All press releases, statements, and public announcements must properly acknowledge that the activities of the IMPAACT Network are performed cooperatively with NIAID, NICHD, and NIMH.

7 IMPAACT General Policies and Procedures: Funding, Conflict of Interest, Certificate of Confidentiality, and ClinicalTrials.gov

7.1 IMPAACT Funding Procedures

The IMPAACT Network leadership and central resources (Operations Center, Statistical and Data Management Center [SDMC], and Laboratory Center [LC]) are funded through cooperative agreements (UM1 awards) with the National Institute of Allergy and Infectious Diseases (NIAID). Each clinical research site (CRS) is funded by NIAID or the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). NIAID sites receive funding directly from NIAID (through the Clinical Trials Unit [CTU]) and through the IMPAACT Finance and Contracts Office at Johns Hopkins University (JHU); NICHD sites receive funding from NICHD through a contracted coordinating center.

7.1.1 IMPAACT Funding Process for Pharmaceutical Company-Supported Studies

The IMPAACT Network may receive funding from pharmaceutical companies to support the conduct of a study. The funding level can vary depending on the study; a study may be fully funded by the pharmaceutical company or only partially funded, in which case costs are shared with the Network. In either case, the pharmaceutical company provides funding directly to the IMPAACT Finance and Contracts Office, which then funds the CRSs through a task order. For studies supported by pharmaceutical companies, the IMPAACT Finance and Contracts Office provides funding to the CRSs for both personnel and non-personnel study costs. The development of study budgets for these studies follows the same process as the Network-supported studies, and Management Oversight Group (MOG) approval is required (see Section 11). Once the MOG has approved the study budget, the Operations Center works with the IMPAACT Finance and Contracts Office to enter the budget into the pharmaceutical company's template and submit it to the pharmaceutical company for review and approval. Once approved, the IMPAACT Finance and Contracts Office receives funding based on milestones or a payment schedule defined in the funding agreement. Pharmaceutical funding is not included in the annual funding plan submission request to NIAID; however, enrollment projections and spending estimates are compiled during the annual budgeting and mid-course correction processes.

7.1.2 IMPAACT Funding Process and Timeline for NIAID-Funded Sites

NIAID funds CRSs as part of CTUs through UM1 awards. CTUs receive core (infrastructure) funding from NIAID for their administrative center and their CRSs. CTUs also receive study-specific (protocol) funding for the CRSs through their UM1 award to support site personnel effort specific to protocols; non-personnel study-specific (protocol) funding is provided to the CRSs through the IMPAACT Finance and Contracts Office in the form of a task order. Protocol funding for both personnel and non-personnel costs is provided by the IMPAACT Finance and Contracts Office directly to protocol-specific sites. Sites submit invoices to the IMPAACT Finance and Contracts Office for payment based on schedules presented in task orders executed between the IMPAACT Finance and Contracts Office and the sites.

- **Core funds** are provided to maintain scientific and administrative expertise and infrastructure at the CTU and at each affiliated CRS. Continued core support is based on satisfactory evaluation by the Network and NIAID. Costs in this category include:
  - CTU Principal Investigators (PIs) to maintain CTU administration and scientific contribution
  - CTU Coordinators and other CTU administrative, financial, and oversight staff
  - Regulatory, pharmacy, data management, and laboratory oversight staff
  - Quality management staff and activities
  - Community education and engagement staff and activities
  - Maintenance and replacement of equipment
  - Travel to Network meetings
  - Mentoring and training of staff

- **Study-specific (protocol) funds** are provided in addition to core funds to support study-specific preparatory activities (as "start-up funding"), implementation, and close-out for each IMPAACT protocol. Prior to review and approval by the MOG, study-specific budgets are developed by the IMPAACT Operations Center in collaboration with the SDMC, LC, protocol chairs, other team members, site representatives, and JHU. Protocol funding needs are projected for the Network annually based on these budgets, together with study-specific timelines and participant accrual plans; resulting protocol funding plans are submitted to NIAID by the IMPAACT Finance and Contracts Office. As needed, mid-course correction updates to the annual budget are also developed based on the criteria above and submitted to NIAID by the IMPAACT Finance and Contracts Office. The mid-course correction is normally requested at the mid-point of the award funding period. Costs in the protocol funding category include:
  - Study-specific regulatory, clinical, laboratory, pharmacy, statistical, and data management activities not otherwise supported by core funds
  - Study-specific community education and engagement activities
  - Study-specific participant recruitment and retention activities
  - Study-specific participant reimbursement
  - Study-specific evaluations (including but not limited to laboratory assays performed at site laboratories)
  - Study-specific equipment and supplies
  - Clinical trials insurance (if legally required; see Section 11 for further details)
  - Additional Community Advisory Board (CAB) support/activities, as needed

The Division of AIDS Office of Clinical Site Oversight (OCSO) representative and Grants Management Specialist send a letter to the CTU PIs to provide guidance on budget development for the coming year.

IMPAACT leadership develops an annual protocol funding plan based on study-specific budgets, anticipated study initiation dates, number of studies planned to be implemented by each CTU, number of participants, and other factors that have cost implications. The recommendations are submitted to NIH

Grants Management Branch (GMB) and NIAID (OCSO and the Prevention Sciences Program Chief). The IMPAACT Finance and Contracts Office works closely with NIH partners to ensure adequate review and compliance. DAIDS informs IMPAACT leadership of the protocol funding level it intends to provide and requests a plan to allocate the funding to NIAID-funded sites. Given the role of DAIDS in the funding of the IMPAACT scientific portfolio, IMPAACT and DAIDS leadership engage in an ongoing dialogue to ensure adequate funding levels to support the Network's scientific agenda.

Each year, CTUs complete a non-competing grant progress report (PHS 2590 package), including a budget and budget justification for the coming year. Unless otherwise instructed, this package is due 60 days prior to the annual anniversary date (i.e., 1 October for a 1 December award date). The format and forms for this package are available at: https://grants.nih.gov/grants/forms/report_on_grant/progress_reports.htm.

In addition to submitting the renewal package, CTUs must also account for expenditures by funding source(s) through their annual Federal Financial Report (FFR). The FFR also includes information on unliquidated balances (funds obligated to the CTU, but not expended). The CTU is required to file the FFR within 90 days of the calendar quarter in which the funding cycle ends. This report is submitted directly to NIH's Office of Financial Management (OFM).

The Network may request a carryover of unspent funds in its annual Research Performance Progress Report (RPPR) submission. GMB staff cannot act on any carryover requests received until OFM notifies them that the FFR has been accepted.

If a CRS identifies a need for additional funds, CTU and CRS leadership should first review the CTU award to determine if there are funds that can be re-budgeted to cover the proposed costs, which they can manage given their expanded authority. If re-budgeting is not possible, the CTU/CRS should submit a request including the amount needed, along with a detailed justification, to the IMPAACT Finance and Contracts Office. The IMPAACT Finance and Contracts Office will determine if there is sufficient funding within the award to fund the additional request. Depending on the amount requested, approval by the IMPAACT MOG may be needed.

7.2 Conflict of Interest and Financial Disclosure Policies

The IMPAACT Network seeks to maintain objectivity in all of its research by ensuring that the selection of products for testing, as well as the design, conduct, and reporting of Network studies is not biased by financial interests. In accordance with the provisions of the US Code of Federal Regulations (CFR), the Network adheres to the following policies:

- *NIH HIV/AIDS Clinical Trials Networks Financial Disclosure Policy and Procedure*: This policy is in compliance with 42 CFR 50/F and 45 CFR 94; see Section 7.2.1.
- *United States Food and Drug Administration (FDA) Financial Disclosure by Clinical Investigators*: This policy is in compliance with 21 CFR 54 and applies to studies conducted under an Investigational New Drug (IND) application; see Section 7.2.2.

Figure 7-1 summarizes these policies as they relate to IMPAACT Network members. Depending on their Network roles and responsibilities, members may be subject to the requirements of one or both policies.

Figure 7-1. Financial Disclosure Requirements and Responsibilities for IMPAACT Network Members

<table>
<tr><th>HIV/AIDS Clinical Trials Networks
Financial Disclosure Policy and Procedure</th><th>FDA Financial Disclosure by Clinical Investigators</th></tr>
<tr><td>• All members of IMPAACT leadership and oversight committees (MOG, Scientific Leadership Group (SLG), Scientific Committees, Multidisciplinary Protocol Review Group (MPRG), Study Monitoring Committee (SMC)</td><td rowspan="2">For each IND study conducted at a CRS, all study site personnel listed on Form FDA 1572</td></tr>
<tr><td>• Protocol chairs and other protocol team members who make direct and significant contributions to or decisions about a study and/or study data, as determined by Network leadership</td></tr>
<tr><td colspan="2">Note: Pharmaceutical company representatives and US Federal government employees who are protocol team members are required to report under other Federal guidelines.</td></tr>
</table>

7.2.1 NIH HIV/AIDS Clinical Trials Networks Financial Disclosure Policy

All Network members who are required to disclose financial information under the HIV/AIDS Clinical Trials Networks Financial Disclosure Policy and Procedures (see Figure 7-1) must complete the "Statement of Financial, Equity, and Intellectual Property Interests" at least annually or when joining a protocol team or committee. The office of HIV/AIDS Network Coordination (HANC) coordinates collection of these disclosures. Further guidance is provided in the NIH HIV/AIDS Clinical Trials Network Financial Disclosure and Conflict of Interest Guidelines Standard Operating Procedure which is available at: https://www.hanc.info/resources/sops-guidelines-resources/site-management.html#fdcoi.

Members of a protocol team who do not have key decision-making roles are not required to disclose under this policy.

7.2.2 FDA Financial Disclosure by Clinical Investigators

Separately from the NIH disclosure policy described in Section 7.2.1, sponsors of IND studies are required to disclose to the FDA certain financial arrangements between sponsors and clinical investigators, as well as certain interests of clinical investigators in the study product or in the sponsor of the study. To fulfill this requirement, CRSs are required to maintain documentation of certain financial arrangements and interests for IND studies.

DAIDS policy on *Collection of Financial Disclosure by Clinical Investigators Conducting DAIDS-Sponsored IND Trials* applies to all investigators and sub-investigators (individuals listed on Section 6 of Form FDA 1572) participating in any DAIDS sponsored and/or supported study where DAIDS is the IND holder. Financial disclosure forms must be completed for each IND study at the timepoints noted in Figure 7-2.

Disclosures should be indicated on behalf of the staff member as well as the staff member's spouse and dependent children. Financial disclosure documentation must be maintained and updated, as applicable, throughout the period of study implementation. The original forms and any updated forms should be available on site for review. Further guidance on the requirements for collection and monitoring of financial disclosure forms is available in the Collection of Financial Disclosure by Clinical Investigators Conducting DAIDS-Sponsored IND Trials policy, available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

IMPAACT has developed a financial disclosure form template that may be used to meet FDA requirements (available on the IMPAACT website or through the Operations Center). Alternatively, an equivalent form provided by a pharmaceutical company co-sponsoring an IMPAACT study may be used, or a study-specific financial disclosure form may be developed. The DAIDS Sponsor's Authorized Representative (SAR), in consultation with the pharmaceutical company (if applicable) and protocol team, will make the final decision regarding which financial disclosure form will be used. The IMPAACT Operations Center clinical research manager (CRM) will inform participating sites of which type of form will be used for a given study.

Figure 7-2. Financial Disclosure Requirements and Responsibilities for IMPAACT Network Members

Timepoint to Complete Financial Disclosures	Staff Required to Complete
Prior to site-specific study activation (at the time a site completes the Form FDA 1572, as described in Section 11)	Site IoR and all site staff listed on the Form FDA 1572
At any time when a new study staff member is added to the Form FDA 1572 (also applies to name changes)	New site staff member who is added to the Form FDA 1572
At any time when the financial interests of a site staff member listed on the Form FDA 1572 change	Applicable site staff member
At any time when a site staff member is removed from the Form FDA 1572	Site staff member who is removed from the Form FDA 1572
At any additional time, as required by the sponsor, i.e., as part of study close-out procedures	Site IoR and all site staff listed on the Form FDA 1572

If required, DAIDS, through the Operations Center, will collect the completed forms.

7.2.3 Subrecipient Financial Conflict of Interest

Under 42 CFR 50/F, institutions carrying out Public Health Service (PHS)-funded research must maintain an up-to-date, written, enforced policy on financial conflict of interest (FCOI). In addition, if an institution carries out such research through a subrecipient (e.g., subcontractor or consortium member), the institution must take reasonable steps to ensure that any subrecipient investigator complies with the regulation. The institution must either require that subrecipient investigators comply with the institutional policy or the subrecipient must certify that its policy complies with the regulation.

IMPAACT Finance and Contracts Office staff are required to verify that the subrecipient institution has the required institutional FCOI policy in place prior to issuance of a subaward. The IMPAACT Finance and Contracts Office maintains a list of IMPAACT Member Institutions (IMIs) that are currently listed in the Federal Demonstration Partnership (FDP) Clearinghouse. Any IMPAACT subrecipient that is not listed in the FDP Clearinghouse must complete "The Johns Hopkins University School of Medicine Significant Financial Interest Statement for JHU SOM Subrecipients Conducting PHS-Funded Research" form. Forms must be updated on a yearly basis. Subaward agreements will not be issued without FCOI verification.

7.3 NIH Certificate of Confidentiality

A Certificate of Confidentiality (CoC) is deemed issued under the IMPAACT Network NIH award. Documentation of NIH funding or support, the NIH CoC Policy (NOT-OD-17-109), the NIH Grants Policy Statement (See 4.1.4.1), and subsection 301(d) of the Public Health Service Act, serve as documentation of the issuance of a Certificate for a specific study. The certificate protects the privacy of

IMPAACT study participants at US sites whose personal information has been or will be collected. Effective 1 October 2017, in compliance with Section 2012 of the *21st Century Cures Act* and updated NIH policy, all NIH-funded studies are automatically included in the certificate.

All participating US investigators are required to protect the privacy of all study participants and shall not:

- Disclose or provide, in any US federal, state or local civil, criminal, administrative, legislative or other proceeding, the name of such individual or any such information, document or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document or biospecimen pertains; or

- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research, unless the disclosure is intended for the purposes of other scientific research that is in compliance with applicable US federal regulations governing the protection of human subjects in research.

The CoC does not cover voluntary disclosures made by study participants, the reporting of suspected harm to others or self, or requests by authorized US Department of Health and Human Services (HHS) personnel. IMPAACT protocols incorporate sample informed consent forms that contain language describing the CoC and its limitations for study participants at US sites; US site staff inform participants of the limitations of coverage of the CoC during the informed consent process.

For more information on the CoC, refer to the law pertaining to the Certificate of Confidentiality [Public Health Service Act 301(d)] and the NIH Certificates of Confidentiality Kiosk, including information on 42 U.S.C. 241(d), as amended by Public Law No. 100-607, Section 163 (4 November 1988).

7.4 Processes for Registration and Results Entry for IMPAACT Studies in ClinicalTrials.gov

ClinicalTrials.gov is a US government-funded clinical trials registry.

In September 2007, the US Food and Drug Administration and Amendments Act (FDAAA) mandated that certain types of clinical trials be registered in ClinicalTrials.gov and that results be entered for all trials except for Phase I and observational studies. This mandate applied to all trials initiated or ongoing as of 26 December 2007. In September 2016, the US Department of HHS issued a Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) which clarifies and expands the regulatory requirements and procedures for submitting registration and summary results information of clinical trials on ClinicalTrials.gov, in accordance with FDAAA 801. Also in September 2016, NIH issued a final policy to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTrials.gov. Under this policy, every clinical trial funded in whole or in part by NIH is expected to be registered on ClinicalTrials.gov and have summary results information submitted and posted within one year after the Primary Completion Date (PCD), whether the clinical trial is subject to FDAAA 801 or NIH policy (see Section 7.4.3 for the PCD definition). This policy is effective for applications for funding, including grants, other transactions, and contracts submitted on or after 18 January 2017. For the NIH intramural program, the policy applies to clinical trials initiated on or after 18 January 2017. In addition, some journals require that studies (including Phase I) be registered on ClinicalTrials.gov.

7.4.1 Division of AIDS ClinicalTrials.gov Protocol Checklist

For all IMPAACT studies (IND and non-IND), study CRMs and the Statistical and Data Analysis Center (SDAC) work to complete and submit the DAIDS ClinicalTrials.gov Protocol Checklist during protocol development. Around the time of Clinical Sciences Review Committee (CSRC) review, the CRM drafts the checklist and emails it, along with the draft protocol, to SDAC (ct.gov@sdac.harvard.edu). SDAC colleagues confirm the details of the draft checklist, including whether results will be required and the anticipated PCD as provided by the study statistician; they will then finalize the checklist. The final checklist is sent back to the CRM. If mandatory informed consent language is required as indicated on the checklist, the CRM ensures that appropriate language is included in the protocol. As noted in Section 9, the completed checklist must be included with each protocol submitted for DAIDS Regulatory Review. During regulatory review, the Regulatory Support Center (RSC) verifies the content of the form aligns with protocol language and communicates any discrepancies to the protocol team. Any issues with the checklists are forwarded to SDAC (ct.gov@sdac.harvard.edu). The anticipated PCD is also shared with the DAIDS RSC Clinical Study Information Office (CSIO) for entry into the NIAID Clinical Research Management System (CRMS).

7.4.2 ClinicalTrials.gov Registration for IMPAACT Studies

All IMPAACT studies are registered.

- For IND studies, where the IND is held by DAIDS, the sponsor is DAIDS, and the study is registered and maintained by DAIDS.
- For non-IND studies, the sponsor is the Network (ACTG or IMPAACT), and the study is registered and maintained by the Network.

For non-IND studies, the Operations Center is responsible for drafting the initial registration record. For IND studies, the Operations Center sends the final protocol, along with the ClinicalTrials.gov checklist to DAIDS and their regulatory contractor, who is responsible for drafting the initial record and sending the draft to the study CRMs, copying IMPAACT.CTGOV@fstrf.org. Once the initial registration record is drafted, the study CRM sends the document for review by the protocol chairs and protocol statisticians. Review comments are requested within five business days. The study CRM coordinates integration and resolution of comments with the Operations Center staff responsible for the registration (non-IND studies) or with the DAIDS contractor (IND studies).

Per FDAAA, protocols must be registered no later than 21 days after the first participant is enrolled. To meet International Committee of Medical Journal Editors (ICMJE) requirements to publish with one of their journals, protocols must be registered prior to the first participant enrollment. In general, sub-studies and observational studies do not need to be registered, although protocol teams may register them if desired. See Section 11 for timing of study registration in ClinicalTrials.gov in relation to other open to accrual requirements.

For non-IND studies, once the record has been made public, the Operations Center forwards the National Clinical Trial (NCT) number, affiliated protocol number, and any updates to the anticipated PCD to the RSC CSIO. Studies will appear on the DAIDS automated email six months before the PCD is met. This email is sent to the SDAC ClinicalTrials.gov representative and each Network ClinicalTrials.gov email listserv. Once a study appears on the automated email list from DAIDS, the SDAC ClinicalTrials.gov representative contacts the study statistician to check the accuracy of the PCD. In addition, if studies are terminated prematurely or if actual PCDs occur more than six months before the anticipated PCD, study

statisticians notify the SDAC ClinicalTrials.gov email alias (sdac.ct.gov@sdac.harvard.edu). Notification of any changes are sent to the RSC CSIO (CSIO@niaid.nih.gov) to update the NIAID CRMS.

7.4.3 Results Entry for ClinicalTrials.gov

Results for IMPAACT clinical trials must be submitted within one year of the PCD, defined by ClinicalTrials.gov as the "date on which the last participant was examined or received an intervention to collect data for the primary outcome measure. Whether the clinical study concluded according to the protocol or was terminated does not affect this date." This date may coincide with the "closed to follow-up" date or may occur earlier than the "closed to follow-up" date, depending on the study. For studies which have multiple primary outcome measures, the PCD is the latest date meeting the definition above; there is only a single PCD for a study.

The NIH definition of a clinical trial is "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes." Further information is available at: https://grants.nih.gov/policy/clinical-trials/definition.htm.

When the PCD has been met for a study, the activities shown in Table 7-1 are initiated.

Table 7-1. Activities and Responsibilities to Ensure Compliance with ClinicalTrials.gov Requirements following PCD

Timeframe	Activity	Responsible Group
Within two months after PCD	• Finalize the list of sites that had participants in the study on ClinicalTrials.gov • Submit protocol documents and Letters of Amendment	• Network contacts or DAIDS contractor
Six months after PCD	• Take ownership of the protocol record and initiate results entry (documented by email between IMPAACT.CTGOV@fstrf.org and CT.GOV@sdac.harvard.edu); note that only one owner is allowed to be in the record at any given time	• SDAC
Before starting results entry	• Review and update the entire protocol record	• SDAC
Within one year after PCD	• Submit study results • Notify RSC CSIO of the ClinicalTrials.gov study results submission date to update in NIAID CRMS	• SDAC
Once results have been made public	• Notify IMPAACT.CTGOV@fstrf.org that ownership of the study has been transferred back to the Network	• SDAC

SDAC is responsible for responding to all queries from the ClinicalTrials.gov editor as the activities shown in Table 7-1 are completed. To help with this process, SDAC enters the designated Network contact information in the Results Point of Contact fields of the ClinicalTrials.gov protocol record. The Network contacts will communicate with the appropriate parties and respond to the query.

For studies where a second round of results entry will be required, e.g., when participant follow-up continues after the PCD and/or when results for secondary outcomes are delayed, SDAC will retain ownership of the record until all results have been made public.

7.5 Letters of Support

For funding applications or other support requests for projects relevant to IMPAACT's research agenda, proposing investigators may request a letter of support from the Network. These requests are reviewed by the Network Chair and others as needed to determine if a letter of support is warranted. For proposals/funding applications for projects involving use of IMPAACT data and/or specimens, letters of support typically state the intention to make requested data/specimens available through the Network's ancillary studies program through which specific requests (NWCS, DACS and DRs) are reviewed and approved as outlined in Section 15. This approach facilitates the timely provision of letters of support for relevant grant applications, allows tracking of proposals to which the Network has committed, and precludes the Network from obligating itself to participate in studies that do not have adequate budgetary support.

Investigators are responsible for submitting requests for letters of support to the Network by emailing the Network Chair or IMPAACT.capsubmssions@fstrf.org ideally at least six weeks ahead of the grant application deadline. Submitted materials should include an introductory letter or message, draft letter of support, and a copy of the specific aims of the grant application. Proposals for which IMPAACT co-funding may be requested must be negotiated in advance; see Section 9 for more information on collaborative studies.

The Network chair reviews letter of support requests for alignment with the IMPAACT Network research agenda and requests input from others (SDMC PI or LC PI) if network resources are being requested; other considerations may include the following:

- Whether the proposed research is already being addressed
- If there may be potential negative impacts on ongoing protocol data analyses or specimen use priorities
- If specimens are requested, the proposed research falls within the general research usage of stored specimens under which participants have consented

If network resources are being requested, the SDMC PI reviews for resource needs, e.g., time estimate for preparation of data and/or specimen requests. If substantial resources are requested, support for the SDMC will be required in the grant application, if applicable, or through an identified funding source.

If approved, the Operations Center will finalize the letter of support for the grant applicant. If not approved, the Operations Center will inform the investigator(s).

8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Applicable US Federal Regulations and Guidelines

IMPAACT studies are funded by the United States (US) National Institutes of Health (NIH) and therefore all studies must be conducted in accordance with applicable sections of the US Code of Federal Regulations (CFR) as described below.

CFR Title 45, Part 46 (45 CFR 46): All IMPAACT studies must be conducted in accordance with 45 CFR 46 entitled "Protection of Human Subjects," which includes subparts related to:

- Review of research by Institutional Review Boards/Ethics Committees (IRBs/ECs)
- Requirements for obtaining and documenting informed consent
- Additional protections and requirements when the following types of human subjects are involved in research:
  - 45 CFR 46 Subpart B: Pregnant women
  - 45 CFR 46 Subpart B: Human fetuses
  - 45 CFR 46 Subpart B: Neonates
  - 45 CFR 46 Subpart C: Prisoners
  - 45 CFR 46 Subpart D: Children

Health Insurance Portability and Accountability Act (HIPAA): US sites participating in IMPAACT studies must also comply with CFR Title 45, Parts 160 and 164, which cover the "Standards for Privacy of Individually Identifiable Health Information" (also known as the "Privacy Rule") and includes subparts related to:

- Standards for use and disclosure of protected health information (PHI)
- Authorizations to use and disclose PHI or waivers of authorization
- Tracking of PHI uses and disclosures

Investigational New Drug (IND): IMPAACT studies conducted under an IND application are subject to additional regulation by the US Food and Drug Administration (FDA) and must be conducted in accordance with:

- 21 CFR 11 Electronic Records, Electronic Signatures
- 21 CFR 50 Protection of Human Subjects
- 21 CFR 54 Financial Disclosure by Clinical Investigators
- 21 CFR 56 Institutional Review Boards
- 21 CFR 312 Investigational New Drug Application
- 21 CFR 314 Applications for FDA Approval to Market a New Drug

Form FDA 1572: The Investigator of Record (IoR) is the individual at each site for an IMPAACT study who is responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable US federal regulations, in-country regulations, and any provisions imposed by the reviewing IRB/EC/other regulatory entity. The IoR is the signatory for the Form FDA 1572 for studies conducted under an IND (or the Division of AIDS [DAIDS] Investigator of Record Form for non-IND studies).

The IoR is required to sign either a Form FDA 1572 (for IND studies) or a DAIDS Investigator of Record Form (for non-IND studies) to formally document agreement to conduct the study in accordance with the study protocol and applicable US regulations. The forms are completed and submitted to the DAIDS Protocol Registration Office (PRO) as part of the protocol registration process described in Section 11. The forms are available at https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms, and guidance for completing them is provided in the DAIDS Protocol Registration Manual available at: https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual.

In addition to signing either the Form FDA 1572 or the DAIDS Investigator of Record Form, the IoR must sign a study-specific Protocol Signature Page to formally document agreement to conduct the study in accordance with the protocol and all applicable protocol-related documents, and in compliance with US regulations; standards of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP); IRB/EC determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

8.2 Training Requirements: Good Clinical Practice and Human Subjects Protection

DAIDS requires that all IMPAACT studies be conducted in accordance with *ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (hereafter referred to as "GCP"): https://www.ich.org/page/efficacy-guidelines.

IMPAACT sites must comply with the DAIDS requirements for Human Subjects Protections (HSP) and GCP Training, as per the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

The IoR is responsible for ensuring that site staff have completed HSP and GCP training before delegating any study-specific duties/tasks to them, and complete training every three years thereafter. For new site personnel, documentation of required training must be completed within 90 days of assignment to an IMPAACT study and prior to functioning without direct supervision, unless HSP and GCP training were completed within the past three years and supporting documentation is available. Documentation of HSP and GCP training must be maintained on-site and made available upon request to DAIDS personnel, study monitors, sponsor or regulatory authority representatives, site IRBs/ECs, and other US, local, and international regulatory entities.

The SCORE Manual requires HSP and GCP training for individuals who:

- "Interact with living individuals by performing invasive or noninvasive procedures for research purposes (e.g., drawing blood, collecting other biological samples, dispensing drugs, administering other treatments, employing medical technologies, utilizing physical sensors, utilizing other measurement procedures)" or
- "Obtain individually identifiable private information that is considered to be engaged in research."

All other personnel who have minimal involvement in the conduct of the research or minimal study-related contact with participants should receive training that emphasizes the protection of participant privacy and confidentiality. Minimally involved personnel may include drivers, couriers, clerical staff, and administrative staff.

Several acceptable training resources and methods are described in the DAIDS policy, including training modules on the DAIDS Learning Portal, which can be accessed at https://daidslearningportal.niaid.nih.gov; DAIDS may also sponsor or support other applicable training sessions to meet these requirements. Other options and guidance related to training are available at:

- CITI Program (GCP and/or HSP)
- Association of Clinical Research Professionals (HSP only)

Online or in-person training sessions offered by site institutions (e.g., university or hospital programs) and/or other commercial programs may also be used to meet these requirements.

As a condition for site-specific study activation, IoRs must document that all study site staff are appropriately qualified and trained to carry out their delegated duties per the study-specific delegation of duties log. IoRs also must maintain adequate documentation of staff having completed required training as described in this section and Section 16.

DAIDS also requires that other DAIDS collaborators complete HSP and GCP training, as outlined in the DAIDS Policy on Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training Requirements, which can be accessed at https://www.niaid.nih.gov/sites/default/files/gcp_hsp_policy.pdf. Note that this policy applies to DAIDS collaborators, excluding Network clinical research sites, participating in NIAID DAIDS-supported clinical research, including DAIDS-sponsored research.

8.3 IRB/EC Review and Approval

All IMPAACT studies must be reviewed and approved by IRBs/ECs responsible for oversight of research involving human subjects conducted at a site. A responsible IRB/EC registered with the US Office for Human Research Protections (OHRP) under a Federal Wide Assurance (FWA) must oversee IMPAACT research conducted at each site. In many cases, more than one IRB/EC is involved, for example, if a site is funded through a US institution with one or more sites in other countries. In such cases, all responsible IRBs/ECs must review and approve all required study-related documentation (as described further below). All studies must be reviewed and approved by all responsible IRBs/ECs prior to the initiation of study implementation. Thereafter, all studies must undergo continuing review at least annually.

45 CFR 46 requires sites located in the US to rely upon approval by a single IRB (sIRB) for cooperative research. To fulfill this requirement, the IMPAACT Leadership and Operations Center (LOC) selects an sIRB to provide oversight of IMPAACT studies conducted at US sites. The LOC coordinates submissions to and other communications with the sIRB. The sIRB reviews IMPAACT protocols and provides approvals applicable to participating US sites. The sIRB reviews and approves each participating site's informed consent and assent forms; additional reviews may occur if required by site local and/or institutional IRBs/ECs. As needed, the LOC and sIRB will arrange for training on sIRB policies and procedures to be provided to IMPAACT site staff and will similarly ensure that relevant sIRB materials are made available to site staff.

All IRBs/ECs responsible for oversight of a given study must be listed on the Form FDA 1572 or the DAIDS Investigator of Record Form signed by the IoR. The IRBs/ECs responsible for oversight of IMPAACT studies must meet the requirements of 45 CFR 46 and 21 CFR 56 (as applicable) and must be associated with an institution/organization that has received an FWA from OHRP, which formalizes the institution's commitment to protect human subjects. Additional information related to assurances is available on the OHRP website: https://www.hhs.gov/ohrp/. US regulations and the ICH Guideline for GCP specify the documents that sites are required to submit to their IRBs/ECs when obtaining initial and continuing review. Some IRBs/ECs may require additional documentation in support of their reviews; sites must comply with all IRB/EC requirements.

Documentation of all submissions to and all approvals from all responsible IRBs/ECs — and any other IRB/EC correspondence — must be maintained in on-site essential document files for each study. In addition, DAIDS requires submission of IRB/EC approval documentation and other documents to the PRO using the DAIDS Protocol Registration System (DPRS). Further information on the protocol registration process is provided in Section 11 and in the DAIDS Protocol Registration Manual. DAIDS requires all IRB/EC approval documentation to be labeled with the full protocol title, including the network protocol number, the DAIDS study ID number, the protocol version number, and the protocol version date. Although not required, sites are encouraged to request that IRBs/ECs note the effective and expiration dates of all approvals.

Table 8-1. Required IRB/EC Submissions for Initial Review and Approval (Prior to Study Activation)

Documents Sites Must Submit to IRB/EC	Written Approval Required*
Protocol Version 1.0 (or first implementation version of the protocol, if not Version 1.0)	Yes
Site-specific Informed Consent Forms (ICF) and Assent Forms (all applicable languages) *Note: IMPAACT study ICFs typically contain information on participant reimbursement amounts and schedules; however, these may be approved through submission of separate materials.*	Yes
Investigator's Brochure(s)** or Package Inserts**	No
Other Safety-related Information (if applicable)	No
Investigator of Record Current Curriculum Vitae	Yes
Participant Recruitment Materials Developed Prior to Study Initiation	Yes
Other Written Information for Study Participants Developed Prior to Study Initiation	Yes
Other Documentation Required/Requested by the IRB/EC	If required by IRB/EC
*Based on US regulations and the ICH Guideline for GCP, written approval is required for these documents. Additional approvals may be required by IRB/EC policies and procedures. If so, the required approvals must be obtained and filed. **Required for studies with investigational products. Note: All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the site. Documentation of all submissions and approvals from all responsible IRBs/ECs must be maintained in on-site essential document files.	

45 CFR 46.109 requires that research be subject to continuing IRB/EC review at intervals appropriate to the degree of risk, but not less than once per year.

IoRs are responsible for ensuring timely submission of continuing review requests to IRBs/ECs, including the sIRB if applicable, so that no lapse in approval occurs for ongoing studies. The Clinical Trials Unit Principal Investigator is responsible for ensuring that the IoR fulfills this responsibility. As specified in the DAIDS Protocol Registration Manual, if a lapse occurs, the research at the site must stop, unless the IRB/EC finds that it is in the best interest of individual participants to continue participating in the research interventions or interaction. Enrollment of new participants cannot occur after the expiration of IRB/EC approval(s). Sites should contact their appropriate institute representative and/or institute program officer when there is any lapse and for additional guidance and information. Sites should submit IRB/EC lapse documentation (i.e., the site's documentation of the lapse to the IRB/EC and the IRB's/EC's response) to DAIDS PRO.

Continuing reviews must be conducted consistent with all applicable US and local regulations and IRB/EC policies and procedures. IoRs must submit documentation for review consistent with these regulations, policies, and procedures. IoRs must also submit documentation of continuing review to DAIDS PRO through the DPRS.

8.4 Other Regulatory Entities

In addition to oversight by IRBs/ECs, research conducted at many IMPAACT sites is subject to oversight by other regulatory entities. The DAIDS Protocol Registration Manual defines this type of entity as "any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific ICFs prior to implementation at a site." For example, in some states within the US, institutional approvals are required since these states have research regulations in addition to the federal

human subjects protection regulations detailed in US federal regulations (45 CFR 46). Additionally, at many non-US sites, other approvals may be required in addition to the local IRB/EC approval, which include but are not limited to approvals from ministry of health, national regulatory agency, in-country drug control council, national IRB/EC, or other government agency.

All regulatory entities responsible for oversight of a given study must be listed on the Form FDA 1572 or the DAIDS Investigator of Record Form signed by the IoR.

IoRs or designated study staff are responsible for preparing submissions to and obtaining required initial and continuing review approvals from regulatory entities and for submitting documentation of the required approvals to DAIDS PRO using the DPRS. DAIDS also requires that copies of clinical trial applications submitted to in-country national regulatory authorities be provided to the DAIDS PRO using the DPRS.

8.5 Informed Consent and Assent

Informed consent is a process by which an individual voluntarily expresses their willingness to participate in research after having been informed of all aspects of the research that are relevant to the decision. In the remainder of this section, persons who provide informed consent are referred to as "consenters." These individuals may be study participants or the parents, legal guardians, or legally authorized representatives of study participants.

Written informed consent must be obtained before any study-specific procedures are performed with a potential study participant. For many IMPAACT studies, written assent must also be obtained from potential participants who are not of legal age or are otherwise not able to provide independent informed consent. The age of assent will be determined by IRB/EC policy and local guidelines. All site staff involved in obtaining informed consent and assent must be designated on the study-specific delegation of duties log and listed on the Form FDA 1572 or DAIDS Investigator of Record Form for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR's delegation of responsibility for obtaining informed consent to these staff. See Section 11 for additional guidance related to the delegation of duties log.

For some IMPAACT studies, informed consent for both screening and enrollment is obtained in one step. For other studies, informed consent is first obtained for screening, and then informed consent for enrollment is obtained (in a second step) from participants found to be eligible during the screening process. Informed consent may also be requested for additional or optional procedures or for storage and possible future research use of biological specimens. Consenters may decline consent for optional procedures and still participate in a given study. ICFs may have separate sections to describe these procedures and separate signature blocks to document consent decisions for these procedures. Alternatively, a separate ICF may be used. Whenever a study involves human genetic testing, consenters must be provided with options to either consent to or decline this testing.

Because informed consent is considered an ongoing process, key elements of informed consent should be reviewed at all study follow-up visits.

For studies conducted at US sites, additional authorization to use or disclose PHI may be required if the site is regarded as a "covered entity" under HIPAA, and therefore subject to the Privacy Rule. This additional authorization may be included as part of the study ICF or may be a separate document. Authorization to use or disclose PHI must be approved by a responsible Privacy Board for the covered

entity. The Department of Health and Human Services (DHHS) Office for Civil Rights has developed tools to help entities determine whether they are covered entities and subject to HIPAA.

The DAIDS guidance on Review of Informed Consent Forms: Impact of the HIPAA Privacy Rule clarifies how DAIDS informed consent reviews and protocol registration will be managed in the context of HIPAA. DAIDS will review ICFs for compliance with the Common Rule and US FDA regulations and DAIDS requirements, but not for Privacy Rule compliance.

Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process is described below. Additional informed consent process information from DAIDS is available at https://rsc.niaid.nih.gov/clinical-research-sites/informed-consent-process-information. Refer to also Section 4.8 of the ICH Guideline for GCP and the DAIDS SCORE Manual.

All IMPAACT sites must establish and maintain standard operating procedures (SOPs) for obtaining informed consent and assent that address all aspects of the informed consent and assent processes consistent with all applicable regulations and guidelines, DAIDS policies and procedures, and site IRB/EC policies and procedures; sites should also note that SOPs may need to be modified and/or augmented to meet individual IMPAACT study protocol specifications (e.g., in study-specific addenda). Additional key considerations for SOPs established for IMPAACT studies include methods for:

- Ascertaining whether a potential participant is of legal age or is otherwise able to provide independent informed consent or assent
- Ascertaining legal guardianship
- Ascertaining whether a consenter is literate, and who may serve as a witness to informed consent processes conducted with consenters who are illiterate
- Ascertaining comprehension before proceeding to an informed consent decision
- Determining whether assent will be obtained in the presence of a parent or guardian
- Addressing the extent to which potentially sensitive information collected in studies of children and adolescents (e.g., drug and alcohol use, sexual activity) will be reported to parents or legal guardians
- Obtaining assent from participants who were enrolled prior to the age of assent
- Obtaining informed consent from participants who were enrolled prior to the age of independent informed consent

Sites are encouraged to incorporate Community Advisory Board (CAB) input into these SOPs and to seek IRB/EC review and approval of these SOPs.

US regulations (45 CFR 46 and 21 CFR 56) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and, by delegation, all study staff involved in conducting the informed consent process, to deliver all required information to consenters. Based on the reviews completed as part of the IMPAACT protocol development and study activation processes, there is assurance that once a site is activated for an IMPAACT study, a site's ICFs include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter comprehends the information
- Document the process

Further guidance related to each of these requirements and processes is provided in the subsections below.

8.5.1 Deliver all Required Information in a Manner that is Understandable to the Consenter

The informed consent process should be conducted in the consenter's preferred language and should reflect whether the consenter is determined to be literate per site SOPs.

If the consenter is literate, begin the informed consent process by providing the consenter with a copy of the ICF to read. Also provide the consenter with any other informational materials developed to complement the ICF. If the consenter is not literate, read the materials to the person. After the consenter has read (or has been read) the materials, verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, note the main points described in each paragraph of the ICF and ask if the consenter has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consenter and discuss these thoroughly. Take as much time as needed to address each question or concern.

If the consenter is not literate, an impartial literate witness must be present during the entire informed consent process. See Section 8.6.1 for more information regarding illiterate participants.

8.5.2 Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services (outside the study) will not be affected by the consenter's decision whether to take part in the study. Encourage the consenter to take as much time as needed — and to talk about study participation with others if the consenter chooses — before making a decision.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consenter, with emphasis on the fact that the witness is there as a protection for the consenter, not as an agent of the study per se.

8.5.3 Confirm that the Consenter Comprehends the Information

The consenter must not be asked to agree to take part in the study, or to sign or make their mark on the ICF, until they fully understand the study. Study staff are responsible for ensuring that each consenter understands all aspects of study participation before signing or marking the ICF.

A variety of approaches can be taken to assess comprehension. Unless a specific method is designated as required to be used in a given study, methods used should be as specified in site SOPs. These methods may include a semi-structured checklist to guide a discussion in which the consenter responds to open-ended questions designed to elicit understanding of key concepts; other types of documented discussions with the consenter; and structured knowledge quizzes administered to the consenter.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, study staff should review those aspects again until the consenter fully understands them. If after additional review and discussion the consenter is not able to demonstrate adequate understanding, the consenter should not be asked to sign or mark the ICF. Similarly, if the consenter has concerns about possible adverse impacts if they were to provide consent or indicates that they may have difficulty adhering to the study requirements, the consenter should not be asked to sign or mark the ICF unless or until such issues can be resolved to the satisfaction of the consenter and the IoR or designee.

8.5.4 Document the Process

US regulations require that informed consent be documented with the use of a written ICF approved by the responsible IRBs/ECs and signed and dated by the participant or the participant's legally authorized representative at the time of consent. In general, the same documentation conventions that apply to informed consent processes are expected to apply for assent processes.

All signature and date blocks on the ICF should be completed in ink. Legal names should be used. Fabricated or falsified names should never be used. Initials may not be used in place of a consenter's full surname, and it is strongly recommended that initials not be used in place of a consenter's full first name. However, if a consenter commonly signs their name using an initial for their first name, the initial may be used, provided this practice is acceptable per the policies of the site institution(s). Character symbols (e.g., Chinese characters) are acceptable in countries that use them.

If the consenter is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.

The DAIDS SCORE Manual lists detailed requirements and suggestions for documenting the informed consent process. Sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets (or other similar tools). Sites choosing to use coversheets should identify the coversheets as source documents in their SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consenter. All informed consent documentation must be maintained and kept on file as part of the participant's study records.

In addition to completing the documentation requirements of the ICF itself, each informed consent process should be documented in a signed and dated chart note. The note should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the informed consent requirements outlined in the DAIDS SCORE Manual. However, if an informed

consent coversheet (or other similar tool) is used, it is not necessary to transcribe information recorded on the coversheet (or other tool) into the chart note.

Data required to document informed consent and assent decisions will also be entered into study-specific case report forms.

Regulations require that consenters be given a copy of their signed ICF. If a consenter opts not to receive a copy, this should be documented, and the consenter should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF. The same approach should generally be taken, when applicable, with assent forms.

8.5.5 Reconsenting

As indicated above, IMPAACT site SOPs for obtaining informed consent should describe methods of obtaining assent from participants who were enrolled prior to the age of assent and for obtaining informed consent from participants who were enrolled prior to the age of independent informed consent. IoRs and designated study staff are responsible for determining when previously-enrolled study participants reach the age of assent and/or the age of independent informed consent and for conducting and documenting required assent and informed consent processes with these participants. If such criteria are met during follow-up, consent or assent should be obtained at the next study visit after the criteria are met and prior to performing study procedures at the visit. As assent and consent requirements change over time with participant age, the most up-to-date assent and consent decisions are taken to apply. For example, if a participant previously enrolled at 16 years of age is not willing to provide written informed consent for continued study participation when they reach 18 years of age, their decision should be taken to override the prior consent decision made when they were first enrolled in the study.

Over the course of a study, new information may become available that may affect prior informed consent and assent decisions. For example, protocol-specified procedures may be modified, or new safety- or risk-related information may come to light. In such cases, the study protocol, sample ICFs, and sample assent forms are typically amended, and study staff are required to obtain re-consent (and re-assent if applicable) for the continued study participation of previously-enrolled participants. Further detailed written guidance on re-consenting and re-assenting requirements is typically provided to sites by the protocol team. In addition, the DAIDS Protocol Registration Manual specifies that re-consenting is expected to occur immediately (i.e., without delay no later than five business days) upon obtaining all required IRB/EC and regulatory entity approvals of revised ICFs (and assent forms), usually by or at the participant's next study visit.

8.5.6 Storage of Informed Consent Forms

IMPAACT sites must maintain, in a confidential and secure manner, the complete, original, signed and dated ICFs (and assent forms if applicable), of all persons who are screened for and/or enrolled in IMPAACT studies, in accordance with the specifications of the study protocol and the study-specific manual of procedures (see also Section 8.7).

8.6 Special Populations

8.6.1 Additional Considerations for Consenting Persons who are Illiterate

US regulations and the ICH Guideline for GCP specify additional protections that must be in place when obtaining informed consent from persons who are illiterate. A witness who is literate in the language in

which the informed consent discussion is conducted must be present during the entire informed consent process undertaken with a consenter who is illiterate. The ICH Guideline identifies an impartial witness as a person who is independent of the study and cannot be unfairly influenced by people involved with the study. This witness need not be totally unaffiliated with the study. It may be possible, for example, to designate a participant advocate who would be available at each site. The witness will sign and date the ICF to attest that the information in the consent form was accurately explained to, and apparently understood by, the consenter, and that informed consent was given freely by the consenter. Site SOPs for obtaining informed consent should specify procedures to be followed when obtaining informed consent from persons who are illiterate and should define who may serve as the witness to the informed consent process. Refer to Figure 8-1 for a summary of considerations for obtaining informed consent from persons who are illiterate. Figure 8-2 provides an example of completion of informed consent signature blocks for consenters who are illiterate.

Additional considerations for documenting the informed consent process for persons who are illiterate are as follows:

- The study staff member who conducts the informed consent process should document the consenter's illiteracy in the study chart.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs (with the endorsement filed in study-specific essential document files), the study staff member who conducts the informed consent process should enter the consenter's name below the consenter's printed name block on the ICF, together with a signed and dated note documenting the name of the staff member who made the entry and the date of the entry. The consenter's signature date should be completed in the same manner.
- The consenter should make their mark (e.g., thumbprint) in the consenter's signature block.

Figure 8-1. Summary of Considerations for Obtaining Informed Consent from Persons who are Illiterate

- Sites must specify procedures for obtaining and documenting informed consent from persons who are illiterate in their SOP for obtaining informed consent. These procedures must be consistent with the DAIDS SCORE Manual and must be followed each time informed consent is obtained from a person who is illiterate. It is recommended that sites seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent process with a person who is illiterate. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should print the consenter's name below the consenter's printed name line on the informed consent form, together with a signed and dated note documenting the name of the staff member who made the entry and the date of the entry (see Figure 8-2).
- The consenter should make their mark on the consenter's signature line.
- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should enter the date upon which the consenter marked the ICF below the consenter's signature date line, together with a signed and dated note documenting the name of the staff member who made the entry and the date of the entry (see Figure 8-2).
- For more information, see Section 4.8 of the ICH Guideline for GCP and the DAIDS SCORE Manual.

Figure 8-2. Example of Completed Informed Consent Signature Blocks for Consenters who are Illiterate

SIGNATURES

Participant Name	Participant Signature	Date
Mary Phiri		**25 NOV 2014**

Participant name and date written by Martha Moore. MM 25 NOV 2014

Martha Moore		**25 NOV 2014**
Name of Staff Person Conducting Consent Discussion	Study Staff Signature	Date

Debra Ross		**25 NOV 2014**
Witness Name	Witness Signature	Date

8.6.2 Additional Considerations for Research Involving Pregnant People, Fetuses, and Underage Participants

IMPAACT studies frequently involve pregnant people, people who may become pregnant, fetuses, infants, and children.

45 CFR 46.201 specifies additional considerations for research involving fetuses, pregnant people, and neonates, and research involving children in Subparts B and D, respectively. These subparts outline additional requirements for IRBs/ECs when reviewing research involving these vulnerable populations and assessing the relative risks and benefits of the proposed research.

DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category from 45 CFR 46.404-407 and 21 CFR 50.51-54 and IRB/EC approval for involvement of children based on the determination specified by that category. This requirement applies to the initial and continuing reviews of study protocols and to any subsequent reviews of protocol amendments involving potential study risks or benefits. The documentation may be provided in IRB/EC approval letters or in other official correspondence from the IRB/EC and must be included in submissions to DAIDS PRO. Additional guidance can be found in the DAIDS Enrolling Children in Clinical Research Policy located at: https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent.

Obtaining and documenting consent for participation of infants and children may involve obtaining consent from one or both parents, a legal guardian, or other legally authorized representative. DHHS regulations at 45 CFR 46.102(I) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. Thus, under 45 CFR 46.102(I), the determination of who may be a legally authorized representative is a matter of state or local law. It is highly recommended that site SOPs for obtaining informed consent and assent, including defining the

minimum age for independent consent and assent and defining and ascertaining legal guardianship, be submitted for review and approval by responsible IRBs/ECs prior to initiation of IMPAACT studies involving infants and children.

8.6.3 Additional Considerations for Prisoners

IMPAACT does not plan to conduct any studies that recruit, screen, or enroll participants from a prison setting. However, it is possible that persons enrolled in IMPAACT studies could become incarcerated during follow-up. 45 CFR 46 Subpart C specifies additional considerations for protection of prisoners as subjects in biomedical and behavioral research including enhanced IRB/EC review requirements and a requirement to obtain approval for prisoner participation from the Secretary of the US DHHS. IMPAACT sites will comply with these requirements prior to involving prisoners in any IMPAACT study.

8.7 Confidentiality

Study site staff will make every effort to maintain the confidentiality of study participants and information that can be linked to them; however, absolute confidentiality cannot be guaranteed. Unless otherwise specified in the study protocol, sites shall not submit any of the following participant identifying information to the Statistical and Data Management Center or other external entity: participant names (including partial and initials), addresses, phone or fax numbers, email addresses, medical record numbers, health insurance beneficiary numbers, or account numbers.

Authorized representatives of the following organizations are granted access to participant study records as needed to assess the quality of study conduct:

- NIH
- Collaborating pharmaceutical companies
- Clinical site monitors
- IMPAACT Operations Center, Statistical and Data Management Center, and Laboratory Center
- Site IRBs/ECs and regulatory entities
- US OHRP
- US FDA
- Other US, local, and international regulatory authorities

In addition to efforts undertaken by site staff to ensure confidentiality, a Certificate of Confidentiality (CoC) is deemed issued for IMPAACT under the terms of the NIH award. The certificate protects US sites from being compelled to disclose study-related information by any US federal, state, or local civil, criminal, administrative, legislative act or other proceedings. The provisions of the CoC, as well as its limitations (e.g., in cases of reportable harm to self or others), will be included in the ICF and will be explained to participants during the informed consent process for each study to which the certificate applies. See Section 7 for further details regarding the CoC.

8.8 Participant Costs for Study Participation

Unless otherwise specified in the study protocol, IMPAACT study procedures are performed at no cost to study participants.

8.9 Participant Reimbursement for Study Participation

Pending IRB/EC approval, participants may be reimbursed for their time and effort when taking part in IMPAACT studies, and/or be reimbursed for costs associated with travel to study visits, time away from work, childcare, etc. Guidance should be sought from local community representatives on appropriate site-specific reimbursement types, amounts, and schedules prior to final IRB/EC approval.

8.10 Access to HIV-Related Care

8.10.1 HIV Counseling and Testing

Most IMPAACT studies involve HIV testing. All such testing will be provided in the context of HIV pre-test, risk reduction, and post-test counseling. Participants (or their parents or guardians) must receive their HIV test results and associated counseling to enroll in IMPAACT studies, as specified by study eligibility criteria.

8.10.2 Care for Participants Living with HIV

Most IMPAACT studies will identify persons living with HIV, either as part of the study screening process or during follow-up of enrolled participants. IMPAACT studies cannot provide long-term care and/or treatment to persons living with HIV; however, each protocol contains information on HIV-related care and support that may be available to study participants. Plans for post-study access to agents provided through an IMPAACT study from which participants are benefiting are discussed early in protocol development and addressed in each protocol.

All IMPAACT sites are required to be familiar with current local standards of care for HIV prevention and treatment and to maintain resource lists and SOPs for referral of persons newly diagnosed and living with HIV. Study participants should be actively referred to local standard of care providers for aspects of their care and treatment that cannot be provided through the study in which they are participating. This may include HIV-related care, reproductive health care, well baby, under five care, and specialized care to further evaluate and treat adverse events identified during study participation. Similar approaches should be taken for referral of participants to social service providers, e.g., for housing and food insecurity.

8.11 Local Reporting Requirements

IMPAACT study staff will comply with all applicable local reporting requirements such as communicable diseases and/or child abuse and neglect identified among IMPAACT study participants to local authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

9 PROTOCOL DEVELOPMENT AND MODIFICATIONS

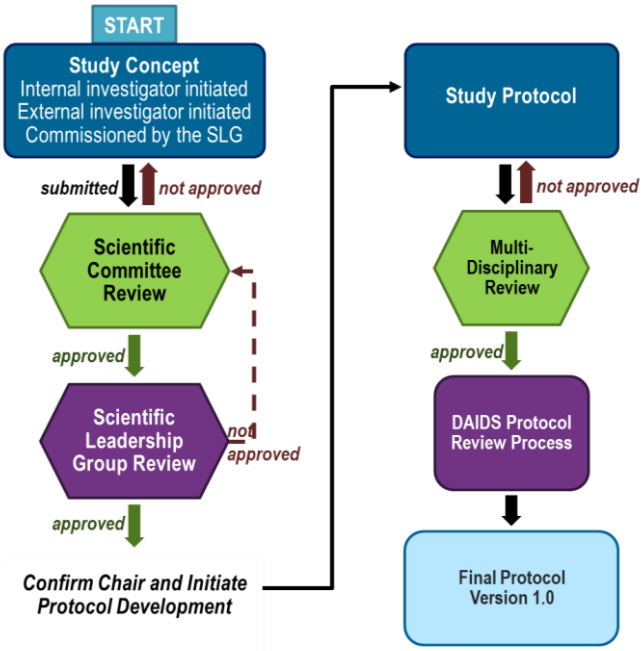
The IMPAACT Network has an open and iterative process for review of new study proposals designed to efficiently identify those of highest scientific merit, potential public health impact, and feasibility/sustainability within the Network for further development. Network studies are developed through multidisciplinary collaboration among investigators, the Scientific Committees (SC), the Scientific Leadership Group (SLG), the Management Oversight Group (MOG), the central Network resources (Operations Center, Statistical and Data Management Center [SDMC], and Laboratory Center [LC]), the IMPAACT Community Advisory Board (ICAB), site representatives, and external collaborators. The process involves sequential development and review steps for study concepts and protocols, as shown in Figure 9-1 and described in greater detail in the remainder of this section.

Scientific priorities for IMPAACT research are determined by the SLG in collaboration with the SCs, aligned with the Network's mission and research agenda (outlined in Section 1). New studies may be proposed by IMPAACT investigators, proposed by external investigators, or commissioned by the SLG. Regardless of origin, initial review and prioritization is the responsibility of the relevant SC (see Section 2 for more detail on SC roles and responsibilities). As depicted in Figure 9-1, new study development begins with development of a study concept. The study concept is reviewed to determine whether the Network should commit resources to full protocol development and study conduct (see Figure 9-2 for review criteria).

Throughout all reviews, from concept through protocol reviews, the IMPAACT SC, SLG, and the IMPAACT Multidisciplinary Protocol Review Group (MPRG) determinations are considered final.

The Network follows a strict conflict of interest policy throughout the concept and protocol review process. Any SC or SLG member involved in the development of a proposed study recuses themself from scoring and voting on that study and only participates in discussions of the study proposal when proposing investigators and/or protocol team members are expected to participate (e.g., in open sessions of review calls).

Figure 9-1. Protocol Development, Review, and Approval Process



*An early Scientific Review Committee (SRC) review may be required or requested.
Note: Each review step may require revisions and resubmissions.

Figure 9-2. IMPAACT Study Review Criteria

The criteria outlined here are used for study proposal review of concepts. For each of the three criteria, proposals are assigned numerical scores of 1 to 5, with 1 being the most favorable.

- Scientific merit
  - Study is aligned with IMPAACT's scientific agenda and priorities
  - Hypothesis is scientifically sound and can be appropriately tested with the proposed study design
  - Study design and methods will yield the proposed outcomes
- Potential public health impact
  - Study is relevant to one or more IMPAACT study populations (infants, children, adolescents, pregnant/postpartum people affected by human immunodeficiency virus (HIV))
  - Study will answer important public health questions or is in the critical path of research toward such answers
- Feasibility and suitability for Network implementation
  - Study population is available at IMPAACT-affiliated sites
  - Study conduct is feasible within the Network structure
  - Study will benefit from a multisite and multidisciplinary collaboration with Network support and oversight

9.1 Concept Development and Review

9.1.1 Development

Proposals for new studies are reviewed by the Network in the form of a concept. Concepts are developed using a template that is available on the IMPAACT website and includes the elements outlined in Figure 9-3. Concepts are expected to be approximately 5-10 pages in length (excluding references and budget estimate).

Figure 9-3. Elements of IMPAACT Concepts

- Title of proposed study
- Proposed protocol chair and vice chair
- Rationale
- Objectives and outcome measures
- Hypotheses
- Study design
- Treatment regimen(s), if applicable
- Key study population characteristics
- Approximate sample size to address the primary objective(s)
- Study duration (enrollment and follow-up)
- Laboratory assays required
- Anticipated study implementation at international sites and/or sites in the United States
- External support/collaboration/funding (if any)

Completed concepts should be submitted by the proposing investigator(s) to the Operations Center via the following email address: impaact.capsubmissions@fstrf.org. The concept is then assigned an identification number for tracking purposes and forwarded to the appropriate SC for review.

Concepts may be submitted at any time; however, they must be submitted at least two weeks in advance of the review date. These dates are shared with proposing investigators in advance of the deadline.

The Operations Center, SDAC, and LC may assign staff to provide limited support for the development of each concept. The Operations Center may provide administrative and coordination support to the concept development group. The SDAC statistician(s) may provide advice on study design and sample size calculations for the primary objective(s), and the LC may provide advice on laboratory evaluations, as needed. Proposing investigators may involve other collaborators with relevant expertise in the concept development team.

9.1.2 Scientific Committee Review

The Operations Center forwards each new numbered concept to the relevant SC chair and vice chair to begin the IMPAACT review process. Concepts received at least two weeks in advance of the next scheduled monthly SC call are typically reviewed on that call, unless otherwise determined by the SC chair. This lead time also allows for the ICAB representative on each SC to obtain more broad-based feedback on the concept from other ICAB members (as described in Section 5).

It is generally expected that the SC chair assigns committee members as primary and secondary reviewers of the concept. In addition, the SDAC representative (or designee) on the SC may provide a brief

statistical review. If needed, an external expert may be invited as either a primary or secondary reviewer. These reviewers provide written comments to the Operations Center at least three days in advance of the review call for distribution to the full SC and to the proposing investigators. The proposing investigators are invited to the call to briefly introduce the concept and respond to questions or requests for clarification; however, participation is not required. Assigned reviewers lead the discussion of the concept. Other SC members provide review comments during the call (or in writing in advance if they are not able to participate). These review calls include an open portion followed by a closed portion for SC members only. After the review call, SC members with no conflicts of interest vote (typically electronically) on next steps for the concept, per the following three categories:

(1) Approve for SLG review, with SC comments to be addressed as appropriate
(2) Revise and re-submit for SC review
(3) Discontinue development with the Network

Committee members base their reviews on the extent to which the proposed study is aligned with the committee's scientific priorities, as well as the criteria listed in Figure 9-2. More information on voting member designation and when voting can be considered complete is provided in Section 2.

The Operations Center coordinates with the SC chair and vice chair to distribute each concept for review, schedule the review, organize the committee voting process, and communicate the outcome of the review in writing to the proposing investigators and SC members.

- If the SC determines that a concept should be revised and re-submitted to the SC, the proposing investigators may be asked to provide a written response to the reviewers' comments along with the revised concept.
- If the SC approves a concept for submission to the SLG, the Operations Center helps coordinate the submission. When the SC review outcome is communicated to the proposing investigators, processes related to the Network's implementation of the Representative Studies Rubric (RSR; see Section 9.2) are shared.

The RSR tool is used to guide and monitor enhanced representation in clinical research. The RSR assesses individual studies for the extent to which they are designed to include or exclude underrepresented populations. The RSR is available on the IMPAACT website on the Manual of Procedures Page under *Training Materials and Resources.*

Note: As research priorities evolve over time in response to emerging science and changing standards of care, and because Network resources may fluctuate, a concept that was not approved previously may be submitted for re-consideration at a later time. In such cases, the proposing investigators are encouraged to discuss their plans with the relevant SC chair and vice chair in advance.

9.1.3 Scientific Leadership Group Review

The SLG generally reviews new study proposals (concepts) on an ongoing basis, either via conference call or during an in-person meeting. To allow adequate time for review, proposals must be submitted at least two weeks in advance of the scheduled SLG review. This lead time also allows for the ICAB SLG representative to obtain more broad-based feedback on the concept from other ICAB members (as described in Section 5).

For proposed studies deemed of especially high priority by the SC, for which there are external or other critical timeline considerations, the relevant SC chair may submit a written request for expedited SLG

review of a concept. Decisions regarding these requests are made on a case-by-case basis by the SLG chair and vice chair.

The Operations Center coordinates submission of concepts that have been approved by the respective SCs to the SLG. A primary, secondary, and statistical reviewer are assigned to each concept. Assigned reviewers submit written comments to the Operations Center 1-2 days in advance of the SLG review for distribution to the SLG, the relevant SC chair and vice chair, and the proposing investigators prior to the review. Reviews generally include an open portion followed by a closed portion for SLG members only (which may be held on a separate day). During the open portion, the relevant SC chair, vice chair, or designee (which may be one of the proposing investigators) briefly introduces the concept and responds to questions or requests for clarification; assigned reviewers may also briefly present their comments or overall evaluation. During the closed portion of the review, assigned reviewers lead the discussion of the concept. Other SLG members provide comments during the review (or in writing in advance if they are not able to participate). In some cases, all SC chairs and vice chairs are invited to participate in the review, for example, when the review is held during the IMPAACT Annual Meeting.

After the review, SLG voting members who participated in the review assign a priority score to the concept using the criteria specified in Figure 9-2 and vote on next steps for the concept, per the following categories:

(1) Approve for protocol development, with SLG comments to be addressed as appropriate
(2) Revise and re-submit for SLG review
(3) Discontinue development with the Network

The SLG evaluates and confirms through the voting process the proposed protocol chair and vice chair based upon past leadership performance, current commitments, and relevant expertise and experience. A maximum of 10-15% full time equivalent (FTE) direct support is provided for protocol team leadership (across both/all chair and vice chair positions). One chair and no more than two vice chairs will be endorsed. Section 4 describes the full roles and responsibilities for these protocol team leadership positions. The SLG may defer scoring or voting on a concept if it is determined that additional forthcoming information is critical to decision-making (e.g., results of another relevant study that is planned or underway). Concepts are considered approved for protocol development if at least 75% of voting SLG members vote for approval. While a detailed costing of the proposed study is not expected, approval of the concept for protocol development represents a commitment of resources from the Network to develop a full study protocol and the intention to conduct the proposed study within the Network. (See Section 11 for further details on the protocol budgeting process.)

If the SLG approves a concept for protocol development, SLG review comments are to be addressed in the study protocol; a separate response is not required unless specifically requested by the SLG. However, if SLG reviewers' comments are not addressed in the protocol, a separate response with an explanation is advised.

If the SLG determines that a concept should be revised and re-submitted, the proposing investigators are requested to provide a written response to the reviewers' comments along with the revised concept. Prior to re-submission, the documents should be reviewed by the SC chair and/or vice chair and the SDAC representative on the SC, as needed, to determine if further SC review is required before the revised concept and response are submitted to the SLG.

The Operations Center documents the review outcome and communicates the final result for each concept to the SLG, proposing investigators, SC chair and vice chair, and SDAC representatives (SDAC Director, Associate Director, and cbar.qb@sdac.harvard.edu) within approximately one week of voting completion.

For each concept approved for protocol development, the Operations Center assigns a protocol number which is included in the outcome notification for tracking purposes. When the outcome is communicated to the proposing investigators, guidance related to Division of AIDS (DAIDS) and IMPAACT policies and procedures, including ensuring use of non-stigmatizing language as described in the NIAID Language Guide (see Section 9.2), is shared. Guidance is also provided on whether formation of the protocol team and development of the study protocol may begin immediately or should be deferred for a specified period of time (e.g., due to timeframes for study product availability or competing demands for Network resources). Generally, proposing investigators should defer further protocol development work until the full complement of protocol team members are assigned to the study and the study clinical research managers (CRMs) have initiated protocol development work.

9.2 Protocol Development and Review

The protocol development and review processes detailed below are based on DAIDS guidance: https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent.

Protocol team members should refer to the following DAIDS policies and guidance documents related to protocol development. These are generally applicable to IMPAACT studies and can be accessed with job aids and recommended language at the link above:

- Enrolling Children in Clinical Research
- Good Documentation Practices
- Requirements for Informed Consent Forms
- NIAID Language Guide
- Representative Studies Rubric tool

9.2.1 Development

Protocol team formation begins per the timelines specified in the outcome notification documenting SLG approval of the study concept.

The assigned Operations Center CRM works with the protocol chair and vice chair to initiate the formation of the protocol team and contacts the SDMC, LC, DAIDS Program and Pharmacy Affairs Branch (PAB), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH) to determine their assigned representatives, as applicable. If specific expertise is needed on the team (e.g., pharmacologist, immunologist, behavioral scientist, virologist, etc.), recommendations may be sought from members of the relevant SC or SLG. As described in Section 10, representatives from each selected site are added to the protocol team once the site selection process has been completed to ensure adequate input on operations, feasibility, and other aspects of the study.

To initiate the development of the protocol document, the CRM incorporates information from the approved concept and any relevant review comments into the IMPAACT protocol template and works closely with the protocol chair to specify writing assignments and timeframes for drafting each protocol section, consistent with an overall timeline for protocol development reflective of Table 9-1. The CRM also requests a study ID number from DAIDS Clinical Study Information Office (CSIO). In consultation with the DAIDS Medical Officer (MO), the protocol team determines whether an early DAIDS Clinical Science Review Committee (CSRC) review should be arranged and, if so, that step is incorporated into the protocol development timeline. IMPAACT leadership and/or DAIDS may also request or require an early review. It is generally expected that most IMPAACT protocols will not require an early review.

When an early review is required, the review should occur prior to submission of the protocol for IMPAACT MPRG review.

Modifications of the study objectives, design, and/or schedule of evaluations that are significant and/or would substantively affect the size, scope, or cost of a study — relative to the previously-approved concept — require review and approval from the IMPAACT leadership. To avoid delays in protocol development, such approval should be sought prior to submission of the protocol for MPRG review. If such changes are proposed prior to MPRG review, team sign-off of the proposed modifications is not required.

The protocol chair and vice chair, CRM, and other protocol team members with writing assignments draft the protocol through an iterative process. The team communicates frequently via email and conference calls. An in-person or virtual protocol development meeting may also be convened to facilitate the process, with the appropriate timing agreed upon by the team. Protocol team members with key writing responsibilities are generally expected to attend such meetings; participation from all other protocol team members is optional. See Section 4 for further details on the composition and responsibilities of the protocol team.

For efficiency, the protocol team should prioritize development of the study schema, which includes the study objectives, the study design, and eligibility criteria first, followed by the schedule of evaluations. Development of other sections of the protocol (e.g., background and rationale) may proceed concurrently with work on the schema, eligibility criteria, and schedule of evaluations. However, it is often counter-productive to develop other sections before these three sections are fully discussed and agreed upon by the team. Once such agreement is achieved, these sections should generally not be re-visited. All other sections should then be developed based on the agreed-upon content of these sections, with a prioritization of statistical and clinical pharmacology sections. When drafting outcome measures, protocol teams should ensure alignment with the study objectives and should take into consideration requirements for submitting study results to ClinicalTrials.gov (processes related to ClinicalTrials.gov are described in Section 7).

Critical input is sought from site representatives, community representatives, and other stakeholders throughout the protocol development process as needed to ensure both the appropriateness and the operational feasibility of the study. Also, throughout the process, the CRM, along with the chairs and National Institutes of Health (NIH) representatives, monitor adherence to the protocol template and ensure that all applicable research regulations, guidelines, NIH policies, and IMPAACT policies and procedures are reflected in the protocol document. Likewise, the CRM works with the team to ensure that required elements of informed consent are reflected in the sample informed consent forms (ICFs) appended to the protocol. Version control is maintained by the CRM throughout the process and key decisions are documented for future reference as needed (e.g., in conference call and meeting summaries and in subsequent iterations of the protocol document).

The protocol chair and CRM are responsible for maintaining the protocol development timeline, communicating deadlines to team members, following up on pending items, and ensuring deadlines are met. Internal organizational reviews may also be conducted (e.g., SDAC, Operations Center, and/or pharmaceutical company reviews) but must be coordinated in keeping within the overall protocol development timeline. Although these reviews should largely take place in the background, the CRM should be made aware of all anticipated internal reviews well in advance, ideally at the start of the protocol development process. See Table 9-1 for an outline of the protocol development process and timeframes.

Table 9-1. Protocol Development Timelines

Protocol Development Steps	Timelines
IMPAACT Reviews	
Development of full draft protocol (including early CSRC review, if applicable, and internal SDAC reviews)	28-32 weeks
Protocol team sign-off	1 week
IMPAACT MPRG review (including advance submission and post-review revisions/response, including any second reviews)	8 weeks
Interim revisions (as needed to address all remaining comments and any comments from additional reviews; this time may be applied during other steps, based on team agreement, but should not exceed an additional 4 weeks)	4 weeks
DAIDS Reviews	
Protocol team sign-off	1 week
DAIDS Clinical or Prevention Sciences Review Committee Review (including advance submission and post-review revisions/response)	9 weeks
DAIDS regulatory review (including advance submission and post review revisions/response)	3 weeks
DAIDS Medical Officer review (including time for protocol team response)	3 weeks
DAIDS Regulatory Affairs Branch final review	10 working days
Total time from first team call to Final Protocol Version 1.0	~59-63 weeks

9.2.2 Protocol Development Oversight

Full draft protocols are expected to be submitted to the MPRG within the timeline outlined in Table 9-1. A high priority protocol may be identified by the SLG, in consultation with DAIDS, for accelerated development if there are urgent, time-sensitive considerations and the study must be implemented quickly in response to emerging scientific or clinical considerations. A limited number of studies may be prioritized at the same time, and the SLG may have to consider shifting priorities (delaying other studies) to accommodate accelerated timelines. Development of high priority studies will generally be accelerated by shortening the time for development of the full draft protocol (prior to MPRG review), by completing reviews concurrently when possible, and/or by reducing the turn-around times for DAIDS reviews (with approval from DAIDS).

The Operations Center provides monthly reports to update the MOG on protocol development statuses, and study implementation challenges and progress (see Section 13). Should a draft protocol become significantly delayed, a change in study team leadership may be required as determined by the MOG. If a protocol in development becomes irrelevant or no longer feasible due to emerging science or changing standards of care, a decision to stop development may be made by the SLG.

9.2.3 Team Review and Sign-Off

The draft protocol is distributed to all protocol team members for review prior to submission for MPRG review. Team members are asked to provide review comments and whether they approve or have any requested changes. Potential response categories may include the following:

(1) Approve
(2) Approve contingent on the following changes
(3) Approve with suggested changes
(4) Revise and redistribute for review

Following the protocol team review, the CRM incorporates any additional edits into the protocol and requests sign-off from one protocol chair (chair, co-chair, or vice chair), one statistician, and one DAIDS MO. Once sign-off requirements are met, the CRM submits the draft protocol to the IMPAACT MPRG at least two weeks prior to the anticipated review date (the CRM begins internal Operations Center coordination of the MPRG review 3-4 weeks prior to sign-off).

The sign-off process described above is also completed prior to submission for DAIDS scientific review (see Section 9.2.5). No other sign-off is routinely required from the protocol team during protocol development. Additional protocol team sign-off requirements for protocol modifications are described in Section 9.3.

9.2.4 IMPAACT Multidisciplinary Protocol Review Group

The purpose of the MPRG review is to ensure IMPAACT protocols are scientifically rigorous, accurate, consistent, complete, and standardized to the extent possible. The MPRG critically reviews protocols for scientific and design integrity, operational feasibility, and other key issues such as site participation, infrastructure and capacity, relevance to the community, and any ethical, logistical, or potential regulatory concerns. The MPRG conducts reviews on behalf of the SLG. The review is multidisciplinary to streamline and avoid multiple sequential review steps. The draft protocol is also reviewed concurrently by ICAB representatives, as described further in Section 5, and by Operations Center representatives prior to or concurrent with MPRG in the context of the Representative Studies Rubric (RSR).

The MPRG is comprised of the Network chair or vice chair (who serves as MPRG chair); the chair, vice chair, or other designated representative member of the relevant SC; standing representatives of the Operations Center, SDMC, LC, and ICAB; an IMPAACT pharmacist; designated NIH representatives; 1-2 external reviewers with expertise in the specific content area of the protocol (as available); an IMPAACT pharmacologist (for pharmacokinetic studies); and, as needed, a representative of the Social Behavioral Science Core.

Reviewers provide written comments on the protocol in advance of the review call, divided into major and minor comments. These are collated and distributed to all reviewers prior to the review call to facilitate the discussion. The MPRG agrees on the collective major comments to be included in the review summary and agrees on one of the following outcome options:

(1) Approved as written or with specific changes stipulated; no re-review required
(2) Re-submission/re-review required by the full review group or a subset (as determined by the chair) after required changes are incorporated and a response to the reviewers' comments is submitted
(3) Disapproved

The Operations Center summarizes the review in writing, distributes the draft to the MPRG and, following approval by the MPRG chair, provides the summary to the protocol team, typically within one week of the review.

Unless otherwise specified, a response to reviewers' comments and a revised version of the protocol are submitted to the MPRG in writing, ideally within 3 weeks of receiving the review summary. Typically, the team response and revised protocol are reviewed via email (another review call is not required), and any additional comments are conveyed with the final outcome/approval within one week of submission, with no additional response required. However, in some cases, an additional response and revised protocol are required before the final outcome is conveyed. The full MPRG review timeline, from submission to final outcome, is approximately eight weeks.

Typically, the protocol cannot proceed to the next review step until MPRG approval is obtained. In some limited circumstances, with prior approval from the MRPG chair and agreed upon with DAIDS, DAIDS SRC review may be concurrent or overlapping with MPRG review.

9.2.5 DAIDS Scientific Review

Upon completion of the MPRG review step (or concurrently with the final MPRG step), the updated draft protocol is distributed to all protocol team members for review prior to submission for DAIDS scientific review; sign-off is required prior to submission as described in Section 9.2.3.

IMPAACT protocols are reviewed by the DAIDS CSRC or Prevention Science Review Committee (PSRC), as determined by DAIDS. The SRC evaluates the research plans specified in each protocol on the basis of:

- NIAID's and other co-sponsoring institutes' research agenda, priorities, and other NIH clinical studies
- Scientific merit and study design
- Human subjects considerations and participant safety
- Compliance with US federal regulations and ethics
- Study oversight and monitoring
- Feasibility of timely completion
- Pharmacy and regulatory considerations
- When appropriate, plans for interim monitoring and analysis

The submission process differs for CSRC and PSRC review:

- *For protocols undergoing CSRC review:* When the protocol is ready for CSRC review, the CRM submits the protocol to the CSRC coordinator CSIO, along with the MPRG's comments and the team's response (if required), and the completed RSR. Every attempt will be made to hold the review by two weeks after the complete set of documents are received by the CSRC coordinator. The DAIDS MO may help with advanced scheduling to ensure timely reviews. Reviews are generally scheduled within three weeks of submission, but this varies depending on the CSRC schedule and time of submission.

- *For protocols undergoing PSRC review:* When the protocol is ready for PSRC review, the CRM submits the protocol to the DAIDS MO, along with the MPRG's comments and the team's response (if required). The DAIDS MO reviews the protocol and any accompanying documents for completeness (within one week) and forwards them to the PSRC coordinator at least two weeks (ten working days) prior to the scheduled PSRC review date.

CRMs may provide other materials to DAIDS (e.g., applicable package inserts) upon request. Protocol team representatives are generally invited to participate in an initial open session of the SRC review to provide a brief overview of the protocol and any major issues that they wish to highlight. Reviewers present their major comments to the protocol team representatives, followed by discussion of those of highest priority, as determined by the SRC chair. The SRC then proceeds in closed session.

The SRC review comments are summarized in a consensus memorandum that is provided to the protocol team typically within ten working days after the review. The memorandum identifies major and minor review findings along with one of three review outcomes:

(1) Approved for finalization and implementation: It is expected the protocol team will provide a revised letter of response addressing major comments and a revised protocol. (Note that DAIDS PSRC may request a letter of response addressing all comments).
(2) Decision deferred: It is expected the protocol team will provide a letter of response addressing major comments and submit a revised protocol for a second review.
(3) Not approved for further development or implementation.

The protocol team responds to the SRC review as specified in the consensus memorandum and submits response documents to the SRC through the SRC coordinator, ideally within 3 weeks of receipt of the SRC review memorandum; the updated draft protocol is also usually submitted. Written responses to review comments should include a description of any changes made in the protocol or justification for no change; confirmation of receipt is provided by the SRC coordinator. If the response and/or changes are deemed acceptable, the protocol team is notified in writing of SRC approval by DAIDS (generally one of the DAIDS MOs or Regulatory Support Center (RSC)) within approximately 1-2 weeks and the protocol moves forward to the next review step. If the team's response and revised protocol are not deemed acceptable, the protocol chair is notified and a plan for resolving the outstanding issues is developed in consultation with the DAIDS MO, Branch Chief, and others such as the SRC chair, Prevention Sciences Program Director, and key reviewers.

After SRC approval of the protocol is obtained, the final three steps of the DAIDS review process can begin. These steps are the DAIDS regulatory review, MO review and approval, and final DAIDS Regulatory Affairs Branch (RAB) review and approval, described below. Throughout these steps, the CRM works closely with other protocol team members to respond to review comments and make any necessary changes to the protocol.

9.2.6 DAIDS Regulatory Review

Once SRC approval is obtained, the CRM submits the revised protocol — labeled "Regulatory Review Version" — with the ClinicalTrials.gov checklist for regulatory review (copying CSIO). During this step, DAIDS (or its regulatory contractor) carries out a regulatory review of the protocol, completed with ten working days of protocol receipt. DAIDS (or its regulatory contractor) incorporates all comments into a review summary document and sends the document to the CRM.

For studies with more than one US site, the Operations Center will submit a draft of the protocol for an advisory review with the single institutional review board (sIRB), and address potential comments, prior

to the MO review. The intention of this review is to limit required protocol modifications that may arise from the sIRB protocol review.

9.2.7 DAIDS Medical Officer Review and Approval

The CRM, in consultation with the protocol chair or other protocol team members if needed, revises the protocol based on the regulatory review comments and prepares a response document, confirming that requested changes were made and providing justification if a requested change was not made.

Following the single IRB advisory review, if applicable, the CRM submits the revised protocol — labeled "Medical Officer Review Version" — with the response to the DAIDS regulatory review comments to DAIDS (or its regulatory contractor) for MO review and approval (copying CSIO). During this step, DAIDS (or its regulatory contractor) first reviews the protocol to ensure that all regulatory review findings have been satisfactorily addressed and then forwards the protocol for review by the MO, completed within ten working days of protocol receipt. The MO reviews the protocol to confirm an acceptable response to the regulatory review, including incorporation of any necessary changes into the protocol document, and to complete a final quality assurance check of the protocol on behalf of DAIDS. As a member of the protocol team, the MO has reviewed the protocol in detail multiple times prior to this step; therefore, few changes are generally expected. The possible MO review outcomes are:

(1) Approve as written
(2) Make changes as indicated and return to MO
(3) Make changes as indicated; do not return to MO

DAIDS (or its regulatory contractor) incorporates any review comments into a review summary document and sends the document to the CRM. The CRM, in consultation with the protocol chair or other protocol team members if needed, prepares a response to any MO comments and submits a revised protocol if needed, following the process described above for regulatory review. Once MO approval (option 1 or 3 above) is obtained, the CRM submits the protocol for final DAIDS RAB review and approval.

9.2.8 Final DAIDS Regulatory Affairs Branch Review and Approval

The CRM submits the protocol — labeled "FINAL Version 1.0" — to DAIDS (or its regulatory contractor) for final RAB review and approval (copying CSIO). RAB reviews the revised protocol and provides approval, completed within ten working days of protocol receipt. DAIDS provides a notification to the CRM when this review step has been completed; for Investigational New Drug (IND) studies, this includes notification that the final protocol has been submitted to the US Food and Drug Administration (FDA).

Once this review step is complete, the IMPAACT Operations Center sends the final protocol, along with the ClinicalTrials.gov checklist to DAIDS and their regulatory contractor as per Section 7.4.2.

9.2.9 Distribution of Version 1.0

Following notification from DAIDS (of approval for non-IND studies or of submission to the FDA for IND studies), the CRM distributes the final approved protocol to the protocol team and participating sites (copying CSIO). The final protocol is also posted on the IMPAACT website.

Many pre-implementation activities begin during the protocol development process, while others are dependent upon the distribution of the final, approved protocol. See Section 11 for details regarding pre-implementation activities.

9.3 Protocol Modifications

Consistent with DAIDS Guidance for Implementing Protocol Changes and other DAIDS policies and procedures, IMPAACT protocols may be clarified or modified by the following methods:

- Clarification Memorandum (CM)
- Letter of Amendment (LoA)
- Full Version Protocol Amendment
- Urgent Safety Notification

These methods, which are described in further detail below, are used for both IND and non-IND protocols. The protocol team determines the method to use in conjunction with the DAIDS MO, based on the guidance posted by DAIDS (or its regulatory contractor) (https://rsc.niaid.nih.gov/networks-protocol-teams/developing-protocols). See Table 9-2 for additional requirements and procedures.

As with Version 1.0 of the protocol, the Operations Center CRM is responsible for working with the protocol team to develop the relevant protocol document (e.g., CM, LoA), ensuring that the applicable review steps are completed with required protocol team sign-off, as summarized below:

- Prior to submission of draft LoAs to DAIDS (either for DAIDS scientific review, if required, or for DAIDS regulatory review; see Section 9.3.2)
- Prior to submission of draft Full Version Protocol Amendments to DAIDS (either for DAIDS scientific review, if required, or for DAIDS regulatory review; see Section 9.3.3)
- Prior to distribution of final Urgent Safety Notifications (e.g., Dear Investigator or Dear Participant letters; see Section 9.3.4)

Once all applicable reviews and approvals are obtained, the CRM is responsible for issuing final versions to the team and participating sites. Copies of all final protocol documents are posted on the IMPAACT website.

While protocol modification documents are in development and under review, study implementation proceeds according to the specifications of the prior approved version of the protocol, including any previously approved LoAs and CMs. Protocol modifications specified in the modification documents may only be implemented after the documents are fully approved, as described below.

IMPAACT MOG/SLG Review of Amendments

Before a protocol team develops an LoA or a full version protocol amendment with significant changes to the scientific goals, study objectives, or design, SLG review and approval must be obtained. The team should develop a memorandum detailing the rationale for the proposed amendment, summarizing the proposed scientific/study design changes, and describing study timeline implications; ideally, budgetary implications should also be described. The process of preparing, obtaining review and sign-off (see Section 9.2.3), and submitting this type of memorandum is coordinated by the CRM. SLG review may be waived at the Network chair's discretion or in the case of design changes due to regulatory requirements (e.g., FDA comments) with protocol team unanimity; in both exceptions, no memorandum is required; the

Operations Center notifies the SLG, typically by providing relevant documentation (e.g., team response to FDA comments, draft summary of changes document).

For draft amendments with significant budget increases, MOG review and approval of the updated budget must be obtained as early as possible and before draft amendment documents are submitted for DAIDS reviews (either SRC or regulatory review). The Operations Center works with the protocol chair(s) and other team members as appropriate to develop a memorandum summarizing the increased budget line items, corresponding protocol changes, and timeline implications.

Table 9-2. Requirements and Procedures for Protocol Modifications

Modification Requirements	Clarification Memorandum	Letter of Amendment	Full Version Protocol Amendment
Content involves change of risk-to-benefit ratio?	No	Yes, but impact should be minimal	Yes
Content must be reported to study participants?	No	Possibly, depends on content and requirements of site IRBs/ECs	Yes
Content requires change of informed consent form?	No	Possibly, depends on content and requirements of site IRBs/ECs	Yes
Content requires changes to study enrollment or study procedures?*	No	Possibly, depends on content	Possibly, depends on content
Results in change of protocol version number?	No	No	Yes
Requires approval by Medical Officer?	Yes	Yes	Yes
Requires approval by DAIDS SRC?	No	Yes, unless requirement waived by MO	Yes, unless requirement waived by MO
Requires DAIDS regulatory review?	No	Yes	Yes
Requires Medical Officer approval following regulatory review?	No	Yes	Yes
Requires RAB approval following Medical Officer review?	No	Yes	Yes
Requires approval by site IRBs/ECs?	No, unless required by site IRBs/ECs	Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained	Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained
Requires protocol registration?	No	Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained**	Yes, amended procedures may not be undertaken until after site IRB/EC approvals are obtained**

* -An LoA or full version protocol amendment is required for collection and entry of data in the study database for any procedure or evaluation that is not currently specified in the study protocol.
-An LoA or full version protocol amendment is not typically required for entry of additional data (i.e., additional detail/information) into electronic case report forms (eCRFs) for a procedure or evaluation that is already specified in the study protocol. However, sites must be officially notified via an appropriate mechanism (e.g., protocol CM) to enter the additional data into eCRFs from available source documentation. In some cases, an LoA or full version protocol amendment may be required if entry of the additional data necessitates eCRF changes, as determined on a case-by-case basis by the protocol team in consultation with the DMC and DAIDS RAB.

** Amendments including any revised site-specific informed consent forms should be implemented upon CRS receipt of all required IRB/EC approvals, unless otherwise noted in the LoA or summary of changes. Refer to the latest DAIDS Protocol Registration Manual, section "Amendment Registration," for details.

9.3.1 Clarification Memoranda

CMs typically are short documents prepared to provide further explanation or more detailed information related to current protocol specifications. CMs also may be used to correct minor errors and/or inconsistencies in a protocol. A CM cannot be used if the modifications would impact participant safety, the risk-to-benefit ratio of study participation, or the sample ICFs. IMPAACT CMs generally include:

(A) Instructions to sites regarding approvals and implementation
(B) Rationale for the modifications included
(C) A summary of how the modifications are being applied to the current protocol text

Because CMs should be implemented immediately, any study implementation materials affected by the CM (e.g., the study-specific Manual of Procedures) should be finalized prior to finalization and distribution of the CM. Although updates of these materials are generally not anticipated with changes implemented through a CM, this should be discussed and confirmed by the protocol team (including the DAIDS MO). Protocol team members who identify any such requirements are responsible for notifying the CRM and protocol chairs early in the CM development process.

The decision to use a CM is the responsibility of the DAIDS MO and does not require DAIDS RAB approval or sign-off; however, the MO may consult with RAB if there are questions related to the content proposed in a CM prior to making a final determination. Drafts are distributed to the protocol team for review by the CRM. Sign-off on a CM by one DAIDS MO is required prior to finalization. Once approved, the CRM distributes the final approved CM to the protocol team and participating sites (copying CSIO). The final CM is also posted on the IMPAACT website.

IRB/EC approval of CMs is not required by DAIDS; however, sites may submit CMs to their IRBs/Ecs for their information or, if required by the IRB/EC, for approval prior to implementation. All applicable IRB/EC requirements must be followed. CMs may be implemented by sites upon issuance unless their IRB/EC requires prior approval.

9.3.2 Letters of Amendment

LoAs typically are relatively short documents prepared to specify protocol changes that have minimal impact on participant safety and the risk-to-benefit ratio of study participation and include relatively minor (if any) modifications of ICFs. An LoA can be used when there are specific changes to the protocol that result in the addition of new information or the deletion of incorrect or unnecessary information. An LoA does not change the protocol version number and is considered part of the previously approved protocol version. LoAs typically incorporate the content of CMs previously issued under the same protocol version. IMPAACT LoAs generally include:

A) Instructions to sites regarding approvals and implementation
B) A summary of and rationale for the modifications included
C) A detailed account of where and how the modifications are being applied to the current protocol text

In the instructions to sites regarding approvals and implementation, specific guidance is provided regarding protocol registration and informed consent requirements associated with the LoA. Instructions for protocol registration requirements indicate whether 1) the LoA should be implemented immediately upon obtaining all required approvals, or 2) implementation should be deferred until after obtaining a notice of LoA registration from the DAIDS Protocol Registration Office (PRO), or 3) implementation should be deferred until after obtaining notification from the Operations Center (as described further below). The first (immediate implementation) is the standard approach. The CRM coordinates with the

protocol team, the DAIDS MO, and DAIDS RAB as needed to confirm the approach to be taken for each LoA.

Members of the protocol team may determine that modifications contained in the LoA require additional time for preparation of materials prior to implementation of the LoA. For example, additional time may be needed to make investigational study products available or to update the Study Enrollment System (SES or Stars) or eCRFs prior to implementation of the LoA. Protocol team members are responsible for identifying any such requirements and notifying the CRM and protocol chairs early in the LoA development process. The CRM then incorporates wording into the instructions to sites stating that implementation of the LoA occurs upon obtaining all relevant approvals AND issuance of notification that all operational requirements for implementation of the LoA have been completed.

Review and approval steps for LoAs are similar to the steps described for original protocols in Section 9.2. As noted above, LoAs do not generally require IMPAACT reviews (e.g., SC or MPRG review). Prior to submission to DAIDS for review, draft LoAs are distributed to the protocol team for review; sign-off is obtained from key protocol team members. The process for sign-off is identical to the process followed for protocols in development, as described in Section 9.2.3. The protocol team works with the DAIDS MO(s) to make an initial assessment of whether the proposed changes may be made using an LoA (rather than a full version protocol amendment); final determination regarding the appropriate method to be used is typically made by DAIDS RAB when the LoA is submitted for DAIDS regulatory review, and this determination is communicated by DAIDS (or its regulatory contractor) before the regulatory review is completed. If the collective changes being requested by the protocol team are extensive and cannot be implemented easily and immediately, DAIDS RAB may require a full version protocol amendment. DAIDS SRC review is not required for LoAs unless otherwise determined by the DAIDS MO in consultation other DAIDS staff. The DAIDS regulatory review, MO review and approval, and final RAB review and approval steps described in Sections 9.2.6-9.2.8 must be completed for all LoAs.

Following notification from DAIDS (of approval for non-IND studies or of submission to the FDA for IND studies), the CRM distributes the final approved LoA to the protocol team and participating sites (copying CSIO). The final LoA is also posted on the IMPAACT website.

LoAs must be reviewed and approved by site IRBs/ECs prior to implementation. LoAs include instructions to sites regarding IRB/EC review and approval and recommendations on how to notify participants of the changes made in the LoA, if applicable. However, it is responsibility of the responsible IRB/EC to determine whether and how participants are to be notified of changes and all IRB/EC requirements must be followed. In all cases, the LoA may not be implemented at a site until approval is obtained from all IRBs/ECs and other applicable regulatory entities responsible for oversight of research at that site. Sites are also required to register the LoA through DAIDS PRO (see DAIDS Protocol Registration Manual). Depending on the instructions to sites contained in the LoA, sites may be required to defer implementation until protocol registration is confirmed and/or until an implementation notice is issued for the LoA by the Operations Center.

9.3.3 Full Version Protocol Amendments

Full version protocol amendments are prepared when required changes to a protocol are substantive in number and/or nature. Modifications made via a full version protocol amendment are incorporated directly into the protocol document and result in a new protocol version number. A full version protocol amendment must also incorporate the contents of CMs and LoAs issued for the prior protocol version.

Examples of changes requiring a full version protocol amendment may include:

- Increase or decrease of more than 10% of the total number of participants to be enrolled
- Study design changes such as addition of a new study arm, a new study drug or formulation, an increase in dosage or dosing frequency of a study drug
- Substantive changes to the sample ICF(s)

Full version protocol amendments are developed by the protocol team as described above for original protocols and are accompanied by a summary of changes document. Summary of changes documents generally include:

A) Instructions to sites regarding approval and implementation
B) A summary of and rationale for the modifications included
C) A detailed account of where and how the modifications are being applied in the protocol text

In the instructions to sites regarding approvals and implementation, specific guidance is provided regarding protocol registration and informed consent requirements associated with the amendment. Instructions for protocol registration requirements indicate whether 1) the amendment should be implemented immediately upon obtaining all required approvals, or 2) implementation should be deferred until after obtaining a notice of amendment registration from the DAIDS PRO, or 3) implementation should be deferred until after obtaining notification from the Operations Center (as described further below). The first (immediate implementation) is the standard approach. The CRM coordinates with the protocol team, the DAIDS MO, and DAIDS RAB as needed to confirm the approach to be taken for each amendment.

Members of the protocol team may determine that modifications contained in the amendment require additional time for preparation of materials prior to implementation of the amendment. For example, additional time may be needed to make investigational study products available or to update the SES or Stars prior to implementation of the amendment. Protocol team members are responsible for identifying any such requirements and notifying the CRM and protocol chairs early in the amendment development process. The CRM then incorporates wording into the instructions to sites stating that implementation of the amendment occurs upon obtaining all relevant approvals AND issuance of notification that all operational requirements for implementation of the amendment have been completed.

Review and approval steps for full version protocol amendments are similar to the steps described for original protocols in Section 9.2. As noted above, amendments may require IMPAACT reviews (e.g., SC or MPRG review). Prior to submission to DAIDS for review, draft protocol amendments and summary of changes documents are distributed to the protocol team for review; sign-off is obtained from key protocol team members. The process for review and sign-off is identical to the process followed for protocols in development, as described in Section 9.2.3. Depending on the nature and extent of the modifications, DAIDS SRC review may be required as determined by the MO in consultation with the SRC chair and other DAIDS staff; if so, the procedures described in Section 9.2.5 are followed. The DAIDS regulatory review, MO review and approval, and final RAB review and approval steps described in Sections 9.2.6–9.2.8 must be completed for all amendments.

Following notification from DAIDS (of approval for non-IND studies or of submission to the FDA for IND studies), the CRM distributes the final approved full version protocol amendment and final summary of changes document to the protocol team and participating sites (copying CSIO). The final documents are also posted on the IMPAACT website.

Full version protocol amendments (new protocol versions and the accompanying summary of changes) must be reviewed and approved by site IRBs/ECs prior to implementation. Summary of changes documents include instructions to sites regarding IRB/EC review and approval and recommendations on how to notify participants of changes made in the amendment, if applicable. However, it is the responsibility of the responsible IRB/EC to determine whether and how participants are to be notified of the changes and all IRB/EC requirements must be followed. In all cases, the full version protocol amendment may not be implemented at a site until approval is obtained from all IRBs/ECs and other applicable regulatory entities responsible for oversight of research at that site. Sites are also required to register the full version protocol amendment through DAIDS PRO (see DAIDS Protocol Registration Manual). Depending on the instructions to sites contained in the summary of changes, sites may be required to defer implementation until protocol registration is confirmed and/or until an implementation notice is issued for the amendment by the Operations Center.

9.3.4 Urgent Safety Notifications

When there is a significant and immediate participant safety concern requiring notification of sites, investigators, IRBs/ECs and participants in an expedited manner, an urgent safety notification may be required. These notifications are typically written as "Dear Investigator" and "Dear Participant" letters developed by the protocol team, in consultation with DAIDS RAB; the DAIDS MO works with DAIDS RAB to determine if additional reviews and/or approvals are required prior to finalizing these types of notifications.

Urgent safety notifications include an explanation of and rationale for protocol changes and are distributed to sites for submission to IRBs/ECs and other applicable regulatory entities, with instructions regarding implementation. Recommendations for informing and re-consenting participants if needed is provided to sites by the protocol team; however, IRBs/ECs and applicable regulatory entities are responsible for determining the appropriate methods for this at each site.

Draft notifications are distributed to the protocol team for review; sign-off is obtained from key protocol team members, consistent with the requirements indicated in Section 9.2.3 (timelines may be truncated to allow for expediency). Once sign-off is obtained, the CRM distributes the final approved notifications to the protocol team and participating sites by the CRM (copying CSIO and DAIDS RSC).

9.4 Collaborative Studies

The IMPAACT Network recognizes that a thriving international network of researchers and collaborators is essential to ensuring rapid and continuing advancement of the Network's mission to improve health outcomes for infants, children, adolescents, and pregnant and postpartum people who are impacted by or living with HIV, tuberculosis, and other HIV-related conditions. The Network welcomes the opportunity to collaborate with other networks, researchers, and organizations on the development and implementation of studies consistent with its research agenda. Such cooperation enables IMPAACT to expand its scope, avoid duplication, enhance the interdisciplinary environment, and create opportunities for site participation/contribution. The mutual benefits include increased awareness of relevant activities and publications and identification of researchers with specific interests.

If an IMPAACT study is to be developed and/or implemented in collaboration with another research network or organization may require review by a scientific leadership group of the other network/organization, the review process must be agreed upon in advance by the respective leadership groups on a case-by-case basis. Typically, protocol team leadership includes representatives from each network/organization (e.g., as co-chairs), with other representatives from networks/organizations included as needed, and one of the networks' Operations Center, SDMC, and LC designated to take the lead to

avoid duplication of effort. In addition, both networks/organizations typically provide scientific and operational review of the protocol and oversight of the study, jointly or in parallel; however, the scope of the collaboration may vary and could be limited to support for IMPAACT site participation.

Collaborative studies may include those with co-funding through a non-network mechanism (e.g., a U01 grant, a pharmaceutical company), with the scope of the network's contributions determined on a case-by-case basis. Generally, the IMPAACT Network will consider collaboration with another entity if the study is of high interest, does not conflict with other IMPAACT studies, and is thought to be feasible for IMPAACT-affiliated site participation. The MOG may consider the need for and availability of IMPAACT resources; depending on the collaborative group, additional Memoranda of Understanding may need to be developed and approved.

When IMPAACT and another network, researcher, or organization plan to co-develop a protocol and implement a study, the roles and responsibilities of each entity are agreed upon in advance by the respective leadership groups on a case-by-case basis. A Responsible, Accountable, Consulted, Informed (RACI) matrix or alternative project management tool, may be used to set expectations for these studies.

When IMPAACT collaborates with a pharmaceutical company on development and/or conduct of a clinical trial, the roles and responsibilities are typically outlined in a Clinical Trials Agreement (CTA) with NIAID/DAIDS, a contract with the IMPAACT Finance Office and/or other types of agreements.

10 SITE SELECTION FOR IMPAACT STUDIES

This section describes the initial site selection process for IMPAACT studies in development, for adding new sites for ongoing IMPAACT studies, and for expansion to sites not affiliated with IMPAACT.

10.1 Initial Site Selection for New Studies

For each new IMPAACT study, a site selection process will be carried out by the protocol team, with oversight from the IMPAACT Management Oversight Group (MOG), to determine which clinical research sites (CRSs) will conduct the study. The site selection process is initiated after a study concept has been approved for protocol development and when the schema and eligibility criteria have been drafted (see Section 9 for more information on the protocol development process). The process will result in the development of a Site Selection and Accrual Plan for review and approval by the MOG. Objectives of the process include:

- Identifying the appropriate priority populations for enrollment into studies (e.g., pregnant people, people living with human immunodeficiency virus (HIV) and tuberculosis (TB))
- Distinguishing if sites have the resources to enroll the study population(s) and perform procedures as necessary; if not, the Network may be able to provide needed resources
- Involving site investigators and other key site staff early in protocol development and preparation for study implementation
- Enhancing the ability to predict the timing of key study milestones (e.g., completion of enrollment) based on specific enrollment projections provided by each site and, together, for the study overall
- Fostering site staff investment in and accountability for meeting study accrual targets and successful study implementation
- Optimizing allocation of Network resources
- Targeting study-related communications, training, and materials to participating sites

For most studies, a one-step site selection process utilizing a **study site application** will be undertaken by the protocol team. If the protocol team determines that additional implementation details are needed after reviewing the study site applications, then solicitation, review, and approval of a more extensive **site implementation plan (SIP)** may be appropriate, as described below. In some cases, a modified process may be utilized, such as in the context of follow-on studies proceeding directly from a prior study (at the same sites) and studies conducted in collaboration with sponsors other than Division of AIDS (DAIDS), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH). In the event that a modified process is utilized, deviations from the standard IMPAACT site selection processes described below should be documented in the Site Selection and Accrual Plan (See Section 10.1.4).

10.1.1 Study Site Application

To maximize site input and protocol team representation during protocol development, development and distribution of the study site application should begin as soon as possible after a study concept has been approved for protocol development. However, initiation of the process will require, at a minimum, a clear understanding of the study objectives, eligibility criteria, and any operational requirements that may impact site selection (e.g., access to a 24-hour pharmacokinetic processing facility, laboratory certification to perform certain assays, and the ability to ship specimens outside of the study site location, if central testing is required for a specific study). Site selection should generally be completed prior to submission of the protocol for review by the IMPAACT Multidisciplinary Protocol Review Group.

The purpose of the site application is to identify interested sites that meet minimum requirements to conduct a study (and to rule out those that do not) and to collect accrual projections that will be used by the protocol team to develop a Site Selection and Accrual Plan for review and approval by the MOG, as described below. For most studies, the site application is distributed to **all** IMPAACT-affiliated DAIDS and NICHD sites (emailed by the Operations Center to CRS leaders/site principal investigators [PI], copied to clinical trials unit [CTU] PIs, and the NICHD coordinating center), with an invitation to interested sites to complete the site application and return it to the protocol team for further evaluation. This is the preferred option. However, in some cases, site selection will be limited geographically, based on current standards of care, anticipated post-study access to the product or intervention, study design specifications, or other reasons. When limited based on one of these considerations, the site application distribution may be distributed only to representatives from sites in the specific countries and/or with the specific qualifications. The rationale for limitations should be clearly described in the Site Selection and Accrual Plan; if limited for scientific reasons or based on the study design, the rationale should also be included in the protocol.

Protocol team members will review all applications received. For NICHD sites, this includes representatives from NICHD coordinating center. Depending on the needs of the study and the number of applications received, teams may delegate this responsibility to a subset of team members, minimally including the protocol chair, vice chair(s), clinical research manager(s) (CRM), and NICHD coordinating center representative as needed. During the review, designated team members will determine which sites meet minimum requirements to conduct the study and how many total sites are required to ensure both high quality and timely conduct of the study. If more sites meet the minimum requirements than are needed for study implementation, the protocol team may consider other factors such as:

- Site capacity, experience, and past performance in other studies
- Laboratory capabilities, including any study-specific assays or assessments
- Study-specific pharmacy requirements (e.g., freezers)
- Country-specific approval requirements, and specimen shipment restrictions and approval requirements
- Concurrent participation in other studies that involve the same participant populations, staff, space/facilities, and/or other resources
- Optimal utilization of Network-affiliated sites and Network resources
- Preferences to expand or limit locations driven by scientific gaps and/or requests from collaborators (e.g., National Institutes of Health Intramural Research Program, collaborating networks, or pharmaceutical co-sponsors)

If a protocol team, or subset of team members, determines that additional information is needed to fully evaluate a site, the required information will be requested by the CRM. It is generally expected that site

selection will be limited to the number of sites needed to meet accrual targets and fulfill the study objectives.

10.1.2 Site Implementation Plan

As noted above, if the protocol team (or designated subset) determines that additional implementation details are needed after reviewing the study site applications, the CRM(s) will ask sites to complete a SIP. The purpose of this step is to obtain sufficient operational detail from each potential site to optimize selection of sites with respect to overall capacity, quality of study implementation, efficiency, and budgetary considerations. To achieve this goal, the protocol team develops a SIP tailored to the operational needs of the study.

As with the site application, all communications to and from potential study sites regarding SIPs will be coordinated by the CRM. However, NICHD-funded sites must submit their SIPs for review by the NICHD coordinating center prior to subsequent submission to the CRM.

Protocol team members will review all SIPs. Depending on the needs of the study and the number of SIPs expected, teams may delegate the review and approval responsibility to a subset of team members, including at minimum the protocol chair, vice chair(s), and CRM(s). Other team members may also review and approve selected portions of the SIP; for example, the Laboratory Center representative or laboratory technologist may review sections of the SIP related to specimen processing and other laboratory operations. Upon initial review of a SIP, if a protocol team determines that additional information is needed to fully evaluate a site, the required information will be requested by the CRM. When more sites meet the criteria for participation than are required to meet study objectives, the protocol team may rank the applicant sites based on available information and select the required number of sites based on this ranking.

10.1.3 Site Selection and Accrual Plan

Based on their study site application and SIP review (when utilized), the CRMs, with input from the protocol team, will develop a Site Selection and Accrual Plan for review by the MOG. In general, this plan should present an overview of the study and population of interest as well as the overall process of site selection, the criteria used to evaluate the applications received. The protocol team should specify which sites they propose for inclusion in the study and the total time expected to enroll all participants at the recommended sites. The MOG will determine whether to approve the plan as proposed or to recommend or require modifications. Once the plan is approved, the CRM will inform each site that submitted a study site application, and SIP if applicable, of the final review outcome.

10.1.4 Designation of Sites for Protocol Registration

Once final site selection decisions are made, and sites are informed of these decisions (as described above). The CRM will then designate the selected sites as permitted to register for the study in the DAIDS Protocol Registration System.

10.2 Addition of Sites During Accrual of Ongoing Studies

During the accrual phase of a study, a protocol team or the MOG may determine that additional site(s) are needed to enhance enrollment or otherwise meet the study objectives in a timely manner. However, the addition of sites is not the primary solution to resolving low accrual rates; rather, active management and involvement of the protocol team to facilitate participating sites in recruitment strategies should first be

undertaken. Because of the potential implications for Network resources, protocol teams must seek MOG approval before initiating a process to add sites to an ongoing study. A short memorandum outlining the rationale, proposed approach, and implications for the study timeline (including an updated study accrual plan) and a budget if there are budget or cost implications, is required. If approved, the team will proceed to contacting potential additional sites per the approved plan. It is generally expected that the two-step process described above will be followed to select additional sites; however, if a protocol team determines that a modified process would be more effective or efficient, an alternative approach may be proposed to the MOG. For example, a site that previously submitted a site application and SIP that met the requirements, but was not previously selected, may be approached first and asked to update their submission documents as needed.

10.3 Expansion Beyond the IMPAACT Network Affiliated Sites

In some cases, it may be necessary to engage sites that are not currently affiliated with IMPAACT to conduct a particular study. In such cases, additional capacity at sites affiliated with the other NIAID-funded networks would first be sought; this may be accomplished through a co-endorsement agreement with another network or through direct solicitation of sites affiliated with other networks (with permission of the leadership of those networks, as needed). If the required additional capacity cannot be identified among sites currently affiliated with other networks, engagement of sites by soliciting sites that are not associated with a NIAID-funded network or with NICHD, following DAIDS protocol-specific site expansion procedures.

For some studies, IMPAACT research partners or sponsors may specifically request inclusion of sites beyond those currently funded for IMPAACT studies by NIAID or NICHD. In such cases, the MOG's approval must be obtained, and the DAIDS protocol-specific site expansion procedures must be followed, regardless of funding source.

11 STUDY-SPECIFIC PRE-IMPLEMENTATION ACTIVITIES: OPEN TO ACCRUAL AND SITE-SPECIFIC STUDY ACTIVATION

Several pre-implementation activities must be completed before a study can be begin screening and enrollment of participants. These steps require active collaboration and communication between the Division of AIDS (DAIDS) staff, IMPAACT central resource groups, protocol team members, and site study staff.

There are a number of study-specific preparatory steps that must be completed before an IMPAACT study can be designated as **open to accrual**, as defined by the Division of AIDS (DAIDS) Study Statuses. These steps should be initiated during protocol development. While many of the steps cannot be completed prior to finalization of protocol Version 1.0, all should be completed as rapidly as possible following distribution of final protocol Version 1.0 to sites.

The clinical research manager (CRM) coordinates the site-specific study activation process for each study with relevant protocol team members, which is described in Section 11.2.

A study must open to accrual prior to any sites being activated; however, both processes proceed in parallel. Sites may only initiate implementation of an IMPAACT study after they have received a site-specific study activation notice.

11.1 Study Open to Accrual Requirements

This section describes requirements that must be met to open a study to accrual. The protocol chair and CRM work closely with other protocol team members to identify and track all requirements that must be met to open a study to accrual; while some requirements apply to all IMPAACT studies, others may be study-specific.

After all requirements have been met, the CRM announces that the study is open to accrual by notifying the protocol team and participating sites, the IMPAACT Data Management Center (DMC) Chief Data Manager, DAIDS Regulatory Support Center Clinical Study Information Office (RSC CSIO), and DAIDS Office of Clinical Site Oversight Monitoring Operations Branch (OCSO MOB).

Per DAIDS requirements, studies must open to accrual within 12 months of the DAIDS Scientific Review Committee (SRC) review approval date of the draft protocol; if an extension is needed, the CRM will coordinate with the DAIDS Medical Officer (MO) to request an extension or confirm that re-review is not needed.

11.1.1 Clinical Trial Agreements

A clinical trial agreement (CTA) is typically negotiated between a collaborating pharmaceutical company and DAIDS to document the responsibilities and rights of each party for the clinical trial. The agreement typically includes, but is not limited to, Investigational New Drug (IND) application sponsorship (if applicable), provision of study products, safety and data monitoring, and access to data. Terms in the CTA covering access to data should conform to DAIDS and Network policies.

When CTAs are required, the DAIDS CTA Team negotiates with the company. The DAIDS MO assigned to the study initiates the CTA development process internally at DAIDS during the protocol development process once it is determined that one or more pharmaceutical companies will provide study product and/or other support for the study (typically at the time of DAIDS SRC review). The CTA Team seeks input and review of CTAs by the protocol chair(s), MOs, and the Statistical and Data Management Center (SDMC) Principal Investigators (PIs), who consult, as needed, with the SDMC representatives on the protocol team, during the negotiation process. In some cases, the final study protocol cannot be distributed to participating sites until the CTA is finalized. The status of a CTA can be tracked on the National Institute of Allergy and Infectious Diseases Clinical Research Management System (NIAID CRMS, previously called DAIDS Enterprise System [ES]).

Copies of executed CTAs are provided to the collaborating pharmaceutical companies the IMPAACT Operations Center and the SDMC. They are not typically distributed to study sites, and sites are not expected to maintain copies of CTAs.

Additionally, a study may require a confidentiality disclosure agreement (CDA), which specifies the terms between a pharmaceutical company and DAIDS to exchange confidential information. If applicable for a study, a CDA will be coordinated by the DAIDS CTA Team.

11.1.2 ClinicalTrials.gov Registration for IMPAACT Studies

ClinicalTrials.gov is a United States (US) government-funded clinical trials registry. See Section 7 for a full description of the requirements and procedures for IMPAACT studies related to ClinicalTrials.gov.

The Sponsor and/or Responsible Party of the study is responsible for entering and maintaining the data in ClinicalTrials.gov:

- For IND studies, for which the IND is held by DAIDS, the sponsor is DAIDS and the study is registered and maintained by DAIDS (or its regulatory contractor).
- For non-IND studies, the sponsor is IMPAACT and the study is registered and maintained by the Operations Center.

As described in more detail below, the protocol statisticians are responsible for the development of a primary Statistical Analysis Plan (SAP); for studies with pharmacokinetics (PK) data as part of the primary and secondary outcome measures, the protocol pharmacologist(s) is responsible for development of a PK SAP. These SAPs are used to coordinate the submission of data to ClinicalTrials.gov.

In addition, the statisticians and pharmacologists are responsible for development of a PK results submission plan for ClinicalTrials.gov. The statisticians provide a template to the pharmacologists for submission of the PK results to the Statistical and Data Analysis Center (SDAC) for entry into ClinicalTrials.gov. The PK results submission plan should be discussed when the primary SAP is developed and completed soon after.

Per the Food and Drug Administration Amendments Act (FDAAA), protocols must be registered no later than 21 days after the first participant is enrolled. To meet International Committee of Medical Journal Editors (ICMJE) requirements to publish with one of their journals, protocols must be registered prior to enrollment. In general, sub-studies and observational studies do not need to be registered, although protocol teams may register them if desired.

Submission of IMPAACT study results to ClinicalTrials.gov is done by SDAC, as outlined in Section 19.

In general, studies must be registered to ClinicalTrials.gov, with receipt of a National Clinical Trial (i.e., NCT) number, prior to being opened to accrual.

11.1.3 United States Food and Drug Administration Review

If an IMPAACT protocol is submitted to the US Food and Drug Administration (FDA) under a new IND application, a minimum period of 30 calendar days must elapse before the study can be opened to accrual. Within this 30-day period, the FDA will review the protocol and notify the IND sponsor of any issues identified during this review. If the FDA is not able to complete its review within 30 days, the team may be informed that the timeline for the review has been extended; in this case, the study cannot be opened to accrual until further information is received from the FDA. IMPAACT protocols are typically distributed to participating sites to initiate local protocol submission processes (see Section 11.2.1), while awaiting the outcome of the FDA review.

If the FDA finds sufficient safety concerns, a Clinical Hold on the protocol may be issued. In this case, the study may not open to accrual until the concerns are resolved. The FDA may require that the protocol be amended or that additional data be submitted to justify why an amendment is not required. The

protocol team coordinates with the DAIDS MO and DAIDS Regulatory Affairs Branch (RAB) to respond to the FDA as soon as possible and within the timeframe specified by the FDA.

If no communication is received from the FDA within 30 days of the submission, or if questions or comments are received in the absence of a Clinical Hold, DAIDS will notify the Operations Center that the protocol is considered "Safe to Proceed."

In addition to the above, FDA review questions and comments may be received at any time during the lifecycle of a study. The protocol team coordinates with the DAIDS MO and DAIDS RAB to address any such questions and comments within the timeframe specified by the FDA.

11.1.4 Study Product Acquisition and Shipment to Sites

Study products for IMPAACT studies are typically received from the manufacturer or other sources, stored at the DAIDS Clinical Research Products Management Center (CRPMC), and distributed from the CRPMC to participating sites. General instructions for ordering study products from the CRPMC are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, which can be found at https://www.niaid.nih.gov/research/daids-clinical-research-pharmacy-and-study-products-management. For some studies, these general instructions may be supplemented with additional or alternative study-specific instructions provided by the DAIDS Pharmaceutical Affairs Branch (PAB).

Study product must be available for ordering at the CRPMC before a study can be opened to accrual. Questions regarding study product acquisition and shipment should be directed to the DAIDS protocol pharmacist for the study.

11.1.5 Laboratory Readiness

11.1.5.1 Laboratory Processing Chart

A Laboratory Processing Chart (LPC) is developed for most IMPAACT studies as a detailed laboratory-related companion document to the protocol. LPCs provide detailed instructions for specimen collection, handling, processing, storage, and shipping. The LPC also contains Laboratory Data Management System (LDMS) quick add templates, which are study-specific visit codes, specimen type codes, and applicable data collection material details. The quick add templates for specimen collection are finalized and available for site use in LDMS approximately two weeks after the LPC is final. The LPC also lists relevant contact information for collaborating laboratories and repositories.

LPC development typically begins when the protocol is in the final stages of development. The IMPAACT Laboratory Center (LC) representative is primarily responsible for developing the LPC in close collaboration with the protocol laboratory technologist (LT); the protocol laboratory data manager (LDM) and CRM also contribute to the LPC development. The full protocol team is responsible for reviewing the draft LPC when distributed by the LC representative.

The LC representative is responsible for ensuring quality control, appropriate versioning, and internal consistency of the LPC. The LC representative will distribute the LPC to the protocol team for final review and sign-off. Sign-off of the final LPC is required from one protocol chair (chair or vice chair), one LC representative, one LT, one LDM, and one CRM; if protocol virologist(s), pharmacologist(s), immunologist(s), or any other end testing laboratory representative(s) provided LPC instructions, their sign-off is also required. Sign-off is confirmed by the LC representative and must be completed before the LPC can be finalized and made available to participating sites. The LC representative is responsible for

ensuring all required sign-offs are received, ensuring compliance with good documentation practices, including appropriate version control, requesting that the LPC is posted to the study webpage, and distributing the LPC to sites. Additionally, the LC representative will share the LPC to applicable end testing laboratories. The final LPC must be available before the study is opened to accrual.

The LPC may be updated over time as experience with study implementation identifies aspects of the study protocol that may require further explanation, in response to frequently asked questions, or when protocol modifications impact LPC directions. When updates are required, the LC representative will coordinate that process. The LC will circulate updated LPC drafts to the protocol team, with the same sign-off requirements as the initial draft if significant changes are made. Sign-off is not required for LPC version changes to update staff or addresses. Updates will be documented using a version control log that will be made available with the updated LPC upon finalization of the updates. As with the initial version, the LC representative is responsible for ensuring all required sign-offs are received and ensuring appropriate version control.

The LC representative will notify the protocol team and participating sites of all LPC updates. It is the responsibility of the site Investigator of Record (IoR) to ensure that current versions of the LPC are maintained on site, in all relevant locations, and that updated LPC content is communicated to all applicable study staff in a timely manner.

Further details regarding the LPC may be found in Section 17.

11.1.5.2 Confirmation of Study-Specific Testing Specialty or Focus Laboratory Readiness

For any studies requiring clinical pharmacology (PK) testing, the Laboratory Center representatives will work with the designated PK testing laboratory(ies) to confirm laboratory readiness, including confirmation that required study drug assays have been validated and are listed on the Clinical Pharmacology Quality Assurance (CPQA) Program Drug Assay spreadsheet.

For any studies with protocol-specific testing at non-site laboratories (e.g., resistance testing), the Laboratory Center representatives will work with the designated testing laboratory(ies) to confirm laboratory readiness, as needed.

Teams may consider deferring these confirmations until close to the time of testing.

11.1.6 Participant Enrollment Materials

The DMC Study Enrollment System (SES) or Stars is used to enroll participants in IMPAACT studies. For most studies, the system is also used to track screening of potential participants. The system uses eligibility checklists that correspond to study-specific inclusion and exclusion criteria which must be programmed into the system for each study. In a process coordinated by the protocol data manager (PDM), draft versions of the checklists are distributed for protocol team review; sign-off is required from the protocol chair(s), DAIDS MO, and protocol statistician(s) prior to finalization.

For applicable studies, a prescription file must also be developed and programmed into the SES or Stars. For studies that involve randomization assignment, the prescription files set up programming for the randomization. For studies that involve the use of a study drug or product that will be provided, draft versions of prescription files are reviewed by the protocol pharmacist(s) and protocol statistician(s), with sign-off required prior to finalization.

Once the eligibility checklists and the prescription and randomization files are finalized, DMC staff program them into the SES or Stars and perform all necessary programming and system checks. Final programmed versions of the checklists and, as applicable, prescription and randomization files must be available before a study can be opened for accrual. Once final programmed versions are available, the DMC sends an announcement to the protocol team and participating sites informing them that the checklist is available for review but that the study is not yet open to accrual; see Section 11.1.7.

11.1.7 Data Collection Materials

Data collection instruments are used by study staff to record data needed to answer IMPAACT study questions. The DMC is responsible for developing the data collection instruments and associated materials (e.g., electronic case report form [eCRF] completion guide) needed for each study. Standard data collection instruments are used preferentially, but study-specific instruments are developed as needed to meet the data collection needs of each study as efficiently as possible.

IMPAACT data collection instruments are developed as follows:

- Development of the data collection instruments for a study typically begins when the protocol is in the final stages of development (i.e., following approval of the protocol by DAIDS SRC).
- The internal DMC study team puts together an eCRF completion guide, consisting of data collection forms schedule(s) and a listing of required data collection instruments based on protocol objectives, schedules of evaluations, and reporting needs. Scientific expertise is sought externally, as appropriate.
- The data collection instruments go through a series of reviews:
  - Protocol team review
  - DMC review, including Clinical Data Interchange Standards Consortium (CDISC) standards review, as needed
  - SDAC review
  - IMPAACT eCRF Committee (see Section 2)
  - Final team review and sign-off: final draft data collection instruments are distributed to the protocol team for review and comment; sign-off by the protocol chair(s), DAIDS MO, and statistician(s) are required to complete study builds.
- Once the data collection instruments have been reviewed by the team and final sign-off is received as outlined above, internal DMC processes are initiated for Clinical Trials Data Management System (CTDMS) finalization. This process requires six to eight weeks. The final data collection instruments are then posted to the DMC portal. The DMC notifies the protocol team and participating sites once the data collection instruments are available.

If select data collection instruments require translation into local languages after they are finalized in English, the DMC will work with site staff to prepare the local language translations and back-translations in accordance with site standard operating procedures (SOPs) and the guidance in Section 11.2.12. DMC staff will review back-translations to ensure that the translated data collection instruments retain the intended meaning of the original English language instruments.

The Chief Data Manager informs the Operations Center when all DMC materials (i.e., data collection and participant enrollment materials) are ready for study opening. These materials must be available before a study can be opened to accrual.

If the data collection instruments require updates during study implementation, the PDM will coordinate that process. Final sign-off by the protocol chair(s), DAID MO, and statistician(s) is required for new and updated data collection instruments.

11.1.7.1 Collection of Gender Identity

IMPAACT Network studies collect data on gender identity for all studies enrolling participants who are 12 years of age or older. The goals of this data collection are two-fold:

- Create a gender-affirming research environment that acknowledges individuals for how they identify
- Better understand the communities the Network serves

Data are collected through obtaining sex assigned at birth classifications from medical records and asking participants about their current gender identity, giving them a range of options to choose from or the ability to specify an identity themselves. Recognizing that sensitivities may arise related to gender dysphoria (the distress someone may feel when their gender identity is not the same as their sex assigned at birth) by asking these questions, sites are strongly encouraged to create SOPs that include appropriate referrals within their institution or to a community-based organization or specialist with knowledge, competency, and comfort in providing services to transgender and/or gender nonconforming youth. If no resources are available for these referrals or support, sites may opt out of this data collection procedure. The issue of resource availability will be addressed in the study-specific site selection materials or otherwise as requested (e.g., as part of site-specific study activation requirements).

If gender identity information is being collected, site SOPs should include options for staff training as needed, to better understand transgender communities and the importance of collecting these data. The Division of AIDS Cross-Network Transgender Working Group has developed a training curriculum for providing care to transgender persons in HIV research settings. The five-module eLearning series is available on the DAIDS Learning Portal (https://daidslearningportal.niaid.nih.gov/). In addition, there are materials on the DAIDS Learning Portal to conduct the trainings in person – including a presentation, facilitator's guide, and accompanying handouts.

To collect these data, a new IMPAACT Gender Identity Interview form is used in studies enrolling participants 12 years of age or older. The initial questions on the form ask if the interview was administered to the participant, and if not, why. Note that the interview should be administered to the participant only, without the parent or guardian present; informed consent forms will indicate that these questions are being asked without the parent or guardian present.

In general, all IMPAACT studies enrolling participants who are 12 years of age or older with protocols finalized after May 2019 include this evaluation, unless the protocol team determines that it is not appropriate to include for scientific or safety reasons. If protocol teams would like to opt out of this collection, they must seek approval from the IMPAACT Scientific Leadership Group (SLG) during the protocol development process.

11.1.8 Study-Specific Manual of Procedures

A study-specific manual of procedures (MOP) serves as an operational resource for implementation of IMPAACT studies. The purpose of a study-specific MOP is to supplement the protocol with further information to optimize adherence to study protocols and standardization of study procedures across sites.

Study-specific MOP development typically begins when the protocol is in the final stages of development. The CRM is responsible for coordinating the development and review of all MOP sections in close collaboration with the protocol chair and other protocol team members, some of whom are typically assigned primary authorship responsibilities, as outlined in Table 11-1. Regardless of primary

authorship assignments, the CRM will coordinate the development and finalization of all sections, requesting and incorporating input from other protocol team members and site staff as needed prior to finalization. The study-specific MOP is versioned in its entirety (i.e., Version 1.0, Version 2.0).

The full protocol team is responsible for reviewing draft sections of the study-specific MOP when distributed. Sign-off of all sections is required from the protocol chair, CRM, and DAIDS MO; sign-off requirements for other protocol team members are listed in Table 11-1. Sign-off requirements included in Table 11-1 should be considered minimum standards; protocol teams may specify additional requirements, beyond those specified in the table, if applicable. Sign-off requirements must be completed before the MOP can be finalized and made available to participating sites.

Topics typically included in a study-specific MOP are as follows:

- Study overview
- Site preparations for the study
- Study communications and resources
- Participant accrual and retention considerations
- Recruitment, screening, and enrollment considerations
- Study implementation, visits, and procedures considerations
- Informed consent and assent considerations
- Pharmacokinetic (PK) considerations, if applicable
- Pharmacy and/or study drug or study product considerations, if applicable
- Specimen collection and laboratory considerations, if applicable (the majority of laboratory considerations should be included in the LPC; see Section 11.1.5)
- Expedited adverse event (EAE) reporting considerations
- Clinical management considerations
- Data management considerations

The final study-specific MOP must be available before the study is opened to accrual.

The MOP may be updated over time as experience with study implementation identifies aspects of the study protocol that may require further explanation, in response to frequently asked questions, and/or when protocol documents (e.g., full amendments, Letters of Amendment [LoAs], or clarification memoranda [CMs]) are issued, as applicable. When updates are required, the CRM will coordinate that process. The CRM will draft or obtain required updated text and obtain review and sign-off from protocol team members as listed in Table 11-1; sign-off from the protocol chair and DAIDS MO are required for all updates. The CRM will document updates using a version control log that will be made available with the updated MOP upon finalization of the updates.

The CRM will notify the protocol team and participating sites of all study-specific MOP updates. It is the responsibility of the site IoR to ensure that current versions of the MOP are maintained on site, in all relevant locations, and that updated MOP content is communicated to all applicable study staff in a timely manner.

Table 11-1. Protocol Team Member Study-Specific MOP Responsibilities and Requirements

Protocol Team Member	Responsibilities and Requirements
Protocol Chair and DAIDS MO	Responsible for review and sign-off of all sections
PDM	Responsible for authorship, review, and sign-off of sections related to data collection and management
LC Representative and Protocol Laboratory Technologist	Responsible for authorship, review, and sign-off of sections related to specimen collection, processing, testing, shipping, and other related sections
Protocol Investigators	Responsible for input and review of sections related to clinical or other specialized procedures and safety reporting
Protocol Pharmacist	Responsible for authorship, review, and sign-off of sections related to study product and study product management
Protocol Pharmacologist	Responsible for authorship, review, and sign-off of sections related to PK procedures and considerations for study implementation, if applicable
CRM	Responsible for authorship and review of sections related to study overview, documentation requirements, accrual and retention, informed consent, study procedures, safety and clinical procedures, counseling, and any other sections related to study-specific requirements; responsible for review and sign-off of all sections
Protocol Statistician	Responsible for review of relevant sections

11.1.9 Study Monitoring Plans

Each IMPAACT study protocol specifies monitoring to be performed throughout the course of the study. Protocol statisticians and PDMs are responsible for developing a study progress, data, and safety monitoring plan (SPDSMP) that details the accumulating study data to be monitored; the type, frequency, and content of monitoring reports that will be generated; and responsibilities for generating, receiving, and reviewing database monitoring reports. The content of the SPDSMP must be consistent with relevant sections of the study protocol (e.g., safety-related roles and responsibilities, monitoring). Refer to the DAIDS Policy for Study Progress, Data, and Safety Monitoring Plan for additional information, which is available at https://www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring.

Drafts of the SPDSMP are distributed for protocol team review and input, in an iterative process as needed, to prepare a draft to be discussed during the initial Study Monitoring Committee (SMC) or Data and Safety Monitoring Board (DSMB) review. Input from all team members, and the SMC or DSMB, is incorporated into the final SPDSMP, with sign-off obtained from the SDMC protocol team members and one DAIDS MO. The SPDSMP is finalized before the study is opened to accrual. A near final version of the SPDSMP must be sent to the DAIDS MOs for review within 30 days of the release date of version 1.0 of the protocol, a full protocol amendment, or an LoA.

For studies that include PK evaluations, the LDMs are responsible for developing a Pharmacology Data Management Plan (PK DMP), in collaboration with the protocol pharmacologist(s), statisticians, PK testing laboratory representatives, PDMs, and the Study Data Tabulation Model (SDTM) specialist. In general, this plan should specify the process for monitoring PK sample collection, data quality, and sample shipping for the study, as well as content, format, schedule, and mechanism for transfer of PK assay results and parameter datasets (note that some elements describing data transfer may be included in data transfer agreements). The plan must be consistent with relevant sections of the study protocol and SPDSMP. Drafts of the PK DMP are distributed for protocol team review and input, in an iterative

process as needed, to prepare a near final draft to be discussed, with the SPDSMP, during the initial SMC or DSMB review. Input from all team members, and the SMC or DSMB, is incorporated into the final PK DMP, with sign-off obtained from the pharmacologist(s), statisticians, PDMs, LDMs, Laboratory Data Division Chief, Chief DM, and the SDTM specialist. The plan is finalized prior to opening the study to accrual.

Other study-specific database monitoring plans may be developed as described in the study protocol as applicable and will generally follow the same processes as described above for the SPDSMP.

11.1.10 Statistical Analysis Plan

The protocol statisticians are responsible for drafting a statistical analysis plan (SAP) that details the analyses to be performed to fulfill the study objectives. The primary SAP details the analyses to be performed for the primary and secondary objectives to be included in the primary study publication and for outcome measures to be submitted to ClinicalTrials.gov (regardless of the reporting timeline); when applicable, additional SAPs may be prepared for analyses to be performed for secondary publications. The protocol team receives a near-final draft of the primary SAP for review and comment. Input from protocol team members is incorporated into the final version of the primary SAP, which is approved by SDAC.

For studies with PK data as part of the primary and secondary outcome measures, protocol pharmacologists are responsible for developing a pharmacology SAP (PK SAP). The draft PK SAP is distributed to the protocol team for review. The pharmacologists incorporate input from protocol team members and provide the final PK SAP to the Operations Center to obtain sign-off documentation from the protocol pharmacologist(s) and one protocol statistician.

For select clinical trials, the National Institute of Allergy and Infectious Diseases (NIAID) requests that the SDMC provide the final primary SAP for approval by a NIAID statistician on behalf of DAIDS. If a PK SAP is developed for the study, the PK SAP is provided to DAIDS for concurrent review by a NIAID statistician.

The primary SAP and PK SAP (if applicable) are finalized before the study is opened to accrual.

11.1.11 Study Budget and Applicable Financial Agreements

Study-specific budgets are developed during protocol development and require review and approval from the IMPAACT Management Oversight Group (MOG) prior to opening a study to accrual. The Operations Center works with the protocol chair(s) and other team members as appropriate to develop the study-specific budget inclusive of site and protocol-specific specialty laboratory costs, costs for central resources (Operations Center, SDMC, and LC), and any other study-specific costs as needed. Typically, the study budget will be submitted to the MOG for review and approval soon after the draft protocol is reviewed by the Multidisciplinary Protocol Review Group (see Section 9), as significant changes affecting the budget may result from that review. If additional changes with significant budget implications are made after MOG review (e.g., resulting from subsequent protocol review steps such as DAIDS SRC review), the updated budget will be re-submitted to the MOG.

The Operations Center maintains study budgets and coordinates with the IMPAACT Finance and Contracts Office at Johns Hopkins University (JHU), which executes sub-agreements, sub-contracts, and other funding mechanisms to ensure all necessary components of the study are implemented per protocol. For example, some study procedures may require sub-contracts or sub-agreements to be developed, negotiated, and fully executed prior to opening a study to accrual. Studies with pharmaceutical funding

support may require a study-specific funding agreement with the pharmaceutical company to be finalized and fully executed prior to opening a study to accrual. Some study procedures or shipping of specimens during study follow-up may allow sub-agreements and sub-contracts to be developed during study implementation. The LC representative will ensure that all IMPAACT protocol-specific specialty laboratories and/or contract laboratories have been notified that they will receive and process study-specific samples. As part of determining the study-specific open to accrual requirements, protocol team members will determine which contracts or agreements must be fully executed or approved prior to opening the study to accrual. In general, any contracts or agreements needed to provide study product or complete real-time testing should be completed prior to opening to accrual.

Budget modifications needed during study implementation will be communicated to the Finance and Grants Office and may require MOG approval prior to finalization.

Protocol modifications, such as LoAs or full protocol amendments, may have implications on the study budget. The proposed modifications, along with any associated changes to the budget, must be reviewed and approved by the MOG per the guidance provided in Section 9.

11.2 Site-Specific Study Activation

During the process of protocol development, the protocol team compiles a study-specific listing of regulatory, operational, and other applicable requirements that must be met for participating sites to initiate study implementation. This is referred to as the "Site-Specific Study Activation Checklist." Sites are encouraged to complete all study activation requirements in a timely manner, with the overall goal of completing the activation process as soon as possible after the study is opened to accrual.

For all studies, sites must obtain required approvals and successfully complete the DAIDS protocol registration process as described in Sections 11.2.1 and 11.2.2 prior to study activation. Sites are also required to complete a study-specific delegation of duties (DoD) log, as described in Section 11.2.3, prior to study activation.

Additional study activation requirements are further described in the sections below.

Additional study-specific requirements may be specified and tailored to the needs of the study as determined by the protocol team to ensure site readiness for study implementation. Other requirements may include the following:

- Availability of specialized personnel
- Availability and confirmed operability of specialized equipment or supplies on site (e.g., study-specific electrocardiography [ECG] or dual x-ray absorptiometry [DXA] machines)
- Availability of required concomitant medications on site
- Availability of translated study implementation materials
- On-site review of study-specific documentation (e.g., study product investigator's brochure or package insert, study-specific MOP, study-specific LPC)

The CRM is responsible for coordinating the development and review of a study-specific template checklist in close collaboration with the protocol chair(s) and other protocol team members, some of whom are typically assigned responsibilities for confirming elements of activation for each site, as outlined in the generic, template activation checklist, posted on the IMPAACT website. Sign-off of all sections of the study-specific template checklist is required from one protocol chair and one DAIDS MO; sign-off on applicable sections is required from the protocol data manager, LC representative, and

protocol pharmacist (these representatives also actively participate in the activation process with sites and the CRM).

The CRM will distribute the activation checklist to participating sites, communicate with sites and other protocol team members as needed to confirm completion of the activation requirements, and maintain documentation of completion for each site as specified in the study activation checklist. Other team members typically involved in the process include the protocol data manager, LC representative, and protocol pharmacist. The CRM will follow up with sites in an iterative process to confirm when each requirement has been met, with the aim of confirming completion of all requirements as rapidly as possible and ideally by the time that the DAIDS protocol registration process has been completed. Requirements for laboratory-related activation requirements are determined by the LC in consultation with the DAIDS Clinical Laboratory Operations Team (DCLOT), as described in Section 11.2.8.

If significant updates are required to the study-specific template checklist (e.g., a new requirement is added for all sites to confirm), the CRM will update the template and circulate for sign-off from one protocol chair and one DAIDS MO; sign-off may also be required from the PDM, LC representative, and/or protocol pharmacist as applicable per the revisions.

Once all site activation requirements have been met, the CRM will grant site readiness approval through the DMC portal for the study-specific screening and enrollment screens in the SES or Stars. The CRM will also issue a site-specific study activation notice indicating that the site may initiate study implementation. *Sites may not conduct any study-specific screening or enrollment (on-study) procedures prior to receipt of their site-specific study activation notice*.

11.2.1 IRB/EC and Other Regulatory Approvals

Consistent with 45 US Code of Federal Regulations (CFR) 46 (and 21 CFR 56 for IND studies), all sites must obtain institutional review board (IRB)/ethics committee (EC) approval of IMPAACT study protocols. Approval must also be obtained from other regulatory and/or approving entities as described in the DAIDS Protocol Registration Manual. Sites located in the US rely upon approval by a single IRB (sIRB) for cooperative research. The sIRB reviews and approves each participating site's informed consent and assent forms; additional review may occur if required by the local IRB per their agreement with the sIRB; refer to Section 8 for further information on the sIRB. Each site should complete study-specific submissions to IRBs/ECs and other regulatory entities as soon as possible following distribution of the final study protocol and protocol amendments, if applicable. The site IoR is responsible for ensuring that all applicable review and approval requirements are met and adequately documented. It is recommended that sites request that IRB/EC and other regulatory entity approval letters reference the following:

- DAIDS Study ID and IMPAACT protocol number
- Full protocol title
- Protocol version number and date
- Version number and date of approved informed consent forms (and assent forms, if applicable)
- Risk/benefit category if research involves children or adolescents (this is required per the DAIDS Protocol Registration Manual)
- Effective date of approval
- Signature of the chair of the review body or designee
- Title of the person signing for the review body

It is also recommended, but not required, that the expiration date of the approval be included. If the date of expiration is not in the approval letter, it is assumed to be one year from the date of approval. If approval documentation is provided in a language other than English, the document must be translated into English.

11.2.2 DAIDS Protocol Registration

After obtaining approval from all required IRBs/ECs and regulatory entities, each site must complete the DAIDS protocol registration process as described in the DAIDS Protocol Registration Manual. The protocol registration process verifies that sites have obtained all required approvals to conduct a study and have submitted documentation pertaining to investigator qualifications, commitments, and responsibilities that are required by US regulations and DAIDS; this documentation includes the IoR's signed and dated protocol signature page (PSP) and a signed and dated Form FDA 1572 (for IND studies) or DAIDS Investigator of Record Form (for non-IND studies). The protocol registration process also verifies that site-specific informed consent and assent forms contain the necessary information to comply with US regulations.

In addition, the process verifies completion of the PSP by the site IoR. (Note: DAIDS does not require submission of the signed PSP to site IRBs/ECs or other regulatory entities, unless required by the regulatory entity.) The IoR at each site is responsible for completing the PSP and ensuring it is submitted to the DAIDS Protocol Registration Office (PRO). The completed PSP should also be filed on site with other study essential documents.

Upon successful completion of the protocol registration process, the site will receive a Registration Notification or a Registration with Required Corrections Notification, which is copied to the Operations Center, and subsequently noted by the CRM as constituting completion of this study activation requirement.

11.2.3 Study-Specific Delegation of Duties Log

DAIDS requires clinical research sites to maintain study-specific DoD logs using the DAIDS DoD log template or site-specific version. Sites should contact their OCSO Program Officer or Westat representative for further guidance as needed. Additional DAIDS guidance may be found in the Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at https://www.niaid.nih.gov/research/daids-score-manual.

Generally, the requirement for site-specific study activation for this element is that the site IoR or designee confirms to the Operations Center the completion of the study-specific DoD log.

11.2.4 Financial Disclosures

For studies conducted under an IND, all individuals listed on Form FDA 1572 must complete a study-specific financial disclosure form to fulfill 21 CFR 54 requirements. These forms must be completed prior to activation (at the time a site completes the Form FDA 1572) and kept up-to-date on site throughout the course of the study; additional details about this requirement are provided in Section 7 and on the DAIDS Regulatory Support Center website.

IMPAACT has developed a template financial disclosure form that may be used to record the required information. Alternatively, an equivalent form required by a pharmaceutical company may be used. The CRM will provide sites with the relevant form to be used for a given study.

To meet study activation requirements, at a minimum, the IoR or designee at each site must confirm when financial disclosure forms have been completed by all individuals listed on the Form FDA 1572. In some cases, the IoR will need to submit the completed forms to the Operations Center or to DAIDS. Completed forms must be available on site for review by site monitors and other sponsor, IMPAACT, FDA, and other regulatory entity representatives.

Note that the requirement to maintain financial disclosure documentation for a given study is separate and distinct from NIH requirements to identify conflicts of interest, which is done periodically through the Office of HIV/AIDS Network Coordination. While there may be some overlap in the information collected through these two mechanisms, financial disclosure documentation must be compiled and maintained on site for each IND study conducted at a site.

11.2.5 Clinical Trials Insurance

DAIDS requires verification of clinical trials insurance (CTI) prior to study activation for sites in countries where CTI is legally required, as listed on the DAIDS RSC website at https://rsc.niaid.nih.gov/networks-protocol-teams/clinical-trials-insurance.

The NIH will only provide funding for CTI for sites located in countries where CTI is required by DAIDS. Prior approval must be granted for a site to use grant funds to purchase CTI. To request approval for NIH funding for CTI, a site will submit an initial letter of request to JHU via IMPAACT-Subs@jhmi.edu. The initial letter of request must include the following information and documentation:

- Grant number and name of grantee organization
- Name of country
- Type of CTI coverage required
- Explanation of why the institution does not carry this insurance
- Explanation of how the required insurance premiums for other NIH-supported clinical trials have been paid by the institution, if applicable
- Explanation of selection process for determining which insurance company would be chosen
- Identification of person(s) responsible for making final decision for selection of insurance company
- Copy of country CTI regulations
- Completed US Department of Health and Human Services (DHHS) CTI Checklist and JHU CTI Checklist. Note: sites are required to obtain three insurance quotes or provide justification for why this is not possible in the DHHS CTI Checklist.
- Completed Vendor Selection Form

JHU will initially review the request and subsequently submit the letter of request and supporting documentation to the Grants Management Specialist (GMS) identified on the site Notice of Award (NoA) and DAIDS program officer for approval. If approval is granted, the site will be informed via email of this decision and the GMS will issue a revised NoA. Once the revised NoA is received by the site, the site may proceed with purchase of CTI.

Note*:* National Institute of Child Health and Human Development (NICHD)-funded sites that need CTI should contact their Westat Contract Administrator for assistance.

For each IMPAACT study, prior to study activation and as applicable, CTI will be verified by the Operations Center following review of the site's insurance certificate relative to the DAIDS Clinical Trials Insurance Certificate Checklist. Insurance certificates must be maintained in the site's essential document files and be available for inspection upon request. Site IoRs are responsible for maintaining

insurance coverage in good standing throughout the relevant coverage period for each study, consistent with DAIDS requirements.

11.2.6 Pharmacy Requirements

Completion of pharmacy-related activation requirements is generally confirmed by the DAIDS protocol pharmacist, who notifies the CRM when requirements have been met.

Before study products can be provided to a study site, the DAIDS protocol registration process described in Section 11.2.2 must be completed. For non-US sites, the site's Pharmacist of Record (PoR) must also communicate with the CRPMC and provide any documentation needed to permit import of study product. The site IoR and PoR are responsible for understanding the local requirements and obtaining the necessary approvals, including those that may provide waivers of import fees. To aid sites in obtaining local approvals, the CRPMC will provide a pro forma invoice upon request, detailing the quantity, lot numbers, expiration dates (when available), value, and other details of all products and related materials to be shipped to the site for use in the study. Sample product labels may also be provided by the DAIDS PAB upon request for use in obtaining local approvals, if necessary. PoRs are encouraged to provide information to the CRPMC that may be helpful in shipping products to the study site, including suggestions for preferred couriers and specific wording to be used on the shipping documents to avoid unnecessary customs delays or fees.

For studies involving drugs or biologics that are not conducted under an IND, export approval from the US FDA may also be required before study product can be shipped to certain countries. This approval may be sought by either the product manufacturer or the local drug authority and can take a significant amount of time to obtain; therefore, the process to obtain approval should be initiated as early as possible in the pre-implementation phase of the study.

Generally, study products are required to be on site prior to activation. However, depending on the length of the study screening process and other study product considerations, such as shelf-life, the protocol team may determine that this requirement can be waived. Other pharmacy requirements may include availability of required pharmacy infrastructure or equipment, availability of concomitant medications and supplies for study drug administration on site, availability of ancillary supplies (e.g., pharmacy vials, pill splitters, dosing cups, or oral syringes), and completion of specialized pharmacist training, when applicable.

11.2.7 Data Management Requirements

Completion of data management activation requirements is generally confirmed by the PDM, who notifies the CRM when requirements have been met. The following requirements are generally applicable for all studies:

- Creation of DMC portal accounts for relevant site staff with level 2 access and study enrollment privileges
- Creation of accounts in Medidata Rave for relevant site staff
- Completion of required Medidata Rave eLearning courses by at least one staff member
- Participation in study enrollment training by at least one staff member

The protocol team may require translation and back-translation of study-specific data collection instruments as an activation requirement. If so, translated instruments must be independently back-translated into English for review and approval by the DMC.

Other data management requirements for activation may include completion of training applicable to the study, such as for Medidata Rave and the SES/Stars, and availability of relevant materials and equipment on site for study implementation.

11.2.8 Laboratory Requirements

Laboratory-related activation requirements for each study are established by the LC representative (for NIAID-sites) and Westat (for NICHD sites) and should follow the same review processes as described for the study-specific activation checklist described in Section 11.2. Requirements are outlined on a study-specific template laboratory activation checklist for each study. Studies with US and non-US sites will have separate checklists for each site. Template laboratory activation checklists developed by the LC/Westat with DCLOT, are modified per protocol in a standard fashion, and are distributed following finalization of protocol Version 1.0.

Confirmation of relevant local laboratory certifications and/or approvals is typically required prior to activation. Completion of laboratory-related activation requirements is generally confirmed following DCLOT approval by the protocol LC representative (for NIAID sites) or by Westat (for NICHD sites), who notifies the CRM when requirements have been met (see Section 17). Completed laboratory activation checklists are maintained by the LC or Westat, with only the final date of completion documented on the overall study activation checklist.

Initiation or completion of specimen or material transfer agreements (STAs or MTAs) may also be required prior to activation to ensure that samples may be shipped in a timely manner as applicable for the study. As described further in Section 17, STAs or MTAs are between the testing/end user laboratory, repositories, and the clinical research site and are the responsibility of the site. In most cases, the LC or Westat will confirm to the Operations Center when a site has met the agreement requirements to be documented on the overall study activation checklist.

11.2.9 Study-Specific Standard Operating Procedures

The protocol team will consider the operational requirements to implement a study to identify study-specific SOPs that should be in place at each site prior to study activation. The protocol team may also require team review of draft SOPs and submission of the final version for activation. Requirements will be outlined in the study-specific activation checklist and are generally confirmed by the CRM.

11.2.10 Site-Specific Standard Operating Procedures

The Division of AIDS (DAIDS) requires that all sites have standard operating procedures established to guide site activities. See further information in the DAIDS SCORE Manual. These SOPs may be applicable across studies conducted at a given site, and therefore may not be study-specific. Template SOPs that may be adapted for use at each site and SOP review checklists are available from DAIDS.

As part of site-specific study activation, the IMPAACT Operations Center will require confirmation of SOP availability as below.

11.2.10.1 Regulatory Inspection Readiness

Sites participating in IND studies must be adequately prepared for regulatory inspection visits and/or audits. The activation requirements for IND studies include a site SOP for regulatory inspection readiness that describes the roles, responsibilities, and procedures for preparing for and participating in regulatory

inspection visits. For activation of each IND study, the site IoR or designee is required to confirm that this SOP is available at the site.

11.2.10.2 Age and Identify Verification

To maintain participant safety and study data integrity, DAIDS requires age and identity verification of clinical trial participants at all CRSs. The activation requirements for all IMPAACT studies include a site SOP for age and identity verification that describes the roles, responsibilities, and procedures for determining potential participants' age and establish identity before taking part in an IMPAACT study and to verify the participant's identity at each visit for the duration of the study before any study-specific procedures take plan. For activation of each IMPAACT study, the site IoR or designee is required to confirm that this SOP is available at the site.

11.2.11 Study-Specific Training

For each IMPAACT study, the protocol team agrees on a study-specific training plan that is tailored to the needs of the study and the participating sites, as further described in Section 16. The site IoR is responsible for ensuring that site staff are appropriately qualified and trained to carry out their delegated duties and that all training is adequately documented.

11.2.12 Local Language Translation of Study Documents

Site IoRs are responsible for ensuring that site staff and participants are provided all required study-related information in a language they understand. Site IoRs are responsible for notifying the protocol team whether protocol documents and other study implementation materials require translation into local languages. At most sites outside the US, sites translate site-specific informed consent and assent forms (if applicable) into local language(s); to facilitate development of the study-specific forms, the CRM shares Word versions of the sample informed consent and/or assent forms, as provided in the protocol, to sites following distribution of Protocol Version 1.0 and any subsequent full version protocol amendments.

Protocol team members may also identify translation needs; for example, interviewer-administered or participant-completed data collection instruments must be translated into local languages. For other types of documents, it is generally expected that site staff will translate the materials into applicable local languages and arrange for an independent translation certification or back-translation. In some situations, the Operations Center or the NICHD coordinating center may be able to assist with the translations. As applicable, the NICHD coordinating center will coordinate the translation of protocols into Portuguese for sites in Brazil; these documents are also posted to the study webpage.

When translated materials are required for study implementation, this will be reflected in the study activation checklist. In some circumstances, sites may be activated to initiate a study with only English language materials available, if this is appropriate for the study population at the site. In these situations, only English-speaking participants may be screened and enrolled in the study until the required local language materials are available. This will be stated in the initial site-specific study activation notice, and an updated notice will be issued once all required translated materials are available.

12 STUDY IMPLEMENTATION

This section provides guidance on key components of study implementation, including participant accrual and follow-up, data collection and documentation, and study communications.

Upon receipt of the Site-Specific Study Activation Notice, sites may begin study implementation and screening procedures. All study procedures are directed by the version of the protocol currently approved at the site, with operational guidance from the supplementary materials provided by the protocol team (e.g., Laboratory Processing Chart [LPC], study-specific manual of procedures [MOP]); in case of any discrepancies between the protocol and the supplementary materials, the protocol takes precedence.

12.1 Participant Accrual

12.1.1 Accrual Projections

As part of protocol development and the site selection process, overall study and site-specific participant accrual targets are established. Overall targets are specified in the study protocol based on the scientific objectives and statistical considerations. Site-specific targets are specified in the site selection and accrual plan developed by the protocol team and approved by the IMPAACT Management Oversight Group (MOG, see Section 10). Throughout the course of the study, the protocol team may survey study sites for updated accrual projections to assist with decisions related to study implementation (e.g., following the issuance of a full version protocol amendment or to determine the need for study expansion to other sites).

Site-specified accrual targets should reflect protocol specifications for distribution of participants (e.g., within specific geographical areas, age groups, etc.); enrollment caps for sites may be specified in the protocol or in the MOG-approved accrual plan, depending on the needs of the study. Otherwise, enrollment targets may be shifted across sites in response to actual accrual and/or other aspects of site performance. Protocol teams should consider whether to specify a maximum number of participants to be

enrolled for any site to ensure that one or more sites or populations from a given area are not inappropriately over-represented.

Some IMPAACT protocols specify an estimated total number of participants to be enrolled to reach a target number who are fully evaluable as defined in the protocol; in such cases, guidelines for adding participants are typically specified in the protocol. The protocol chair and statistician lead the protocol team in making these determinations and work with the protocol data manager (PDM), clinical research manager (CRM), and other team members to ensure that procedures are in place to operationalize accrual targets and restrictions as needed. Note that over-enrollment is not permitted as a means to make up for participant loss-to-follow-up unless the protocol wording permits over-enrollment.

Enrollment into each IMPAACT study is open to all sites that are selected to conduct the study. However, some sites may not be able to enroll any participants into studies for which they are selected. For example, sites may not be able identify participants who meet the study eligibility criteria. In addition, sites with protracted timelines for obtaining ethical and regulatory approval of the study protocols or completion of other study activation requirements may not be able to initiate screening and enrollment activities before the study enrollment target has been met.

Enrollment in IMPAACT studies is competitive across sites to encourage rapid completion of accrual, unless otherwise specified. Sites should inform their Institutional Review Boards/Ethics Committees (IRBs/ECs) of increases or decreases in their enrollment projections in accordance with IRB/EC requirements and revise their informed consent forms to reflect changes as needed.

The Statistical and Data Management Center (SDMC) generates routine study screening, enrollment, and retention reports – for each IMPAACT study overall and by site – for review by the MOG; the reports for each study are shared with the protocol team, typically on a monthly basis. Up to date accrual and retention information is also available via an interactive dashboard on the Data Management Center (DMC) Portal. When applicable, reports are also generated by cohort or other relevant study-specific groupings. Protocol teams are responsible for closely monitoring accrual and retention on an ongoing basis and taking appropriate action as necessary to ensure that targets are met, in consultation with the MOG as needed.

12.1.2 Screening and Enrollment

For each IMPAACT study, screening and enrollment visit procedures are described in detail in the study protocol and, if applicable, the study-specific MOP. Information pertinent to participant screening and enrollment that is applicable to all IMPAACT studies is provided in the remainder of this section. A study is considered to have met the Division of AIDS (DAIDS) status of "enrolling" on the date that the first participant is enrolled. The PDM notifies the protocol team, and the Operations Center notifies DAIDS of this change in status.

Unless otherwise specified, the study-specific enrollment period begins on the day the first participant enrolled at any participating study site; site-specific enrollment periods are considered to begin on the day that the first participant enrolled at that site. For many studies, the time from the first day of participant screening through the end of participant accrual is also tracked and reported.

Written informed consent must be obtained from all IMPAACT study participants or their legal guardians prior to the performance of any protocol-specified screening or enrollment procedures. See Section 8 for additional information on the informed consent process.

Unless determined otherwise in consultation with Network leadership, screening for each study is tracked using the DMC Study Enrollment System (SES) or Stars, and reasons for screening failures are entered on Screening Failure electronic case report forms (eCRFs). When relevant, protocol teams should also implement mechanisms to track recruitment and pre-screening activity. Screening data are monitored closely by the protocol team to identify specific barriers to enrollment (based on reasons for exclusion) and to monitor the pipeline of potential participants at participating sites, both of which inform study feasibility.

For each study, the DMC provides participating sites with a list of participant identification numbers (PIDs) to be assigned to study participants for purposes of study data management. A PID is assigned to a potential study participant at time of screening for their first IMPAACT study. This same PID is used if the participant enrolls to any future network study as well. Detailed information on the structure and format of PIDs, and instructions for assigning them to individual study participants, are available on the DMC portal under Site Support in the Computing Manual: Participant Enrollment Procedures.

From both a statistical and operational perspective, it is important to define when participants are considered enrolled in a study. For IMPAACT studies, participants are considered enrolled upon successful entry of required eligibility data into the SES or Stars. Successful entry into the system generates a study identification number (SID) and, when applicable, the participant's random assignment and/or prescribing information.

The DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual requires study sites to document IMPAACT study screening and enrollment activities on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. The SCORE Manual further specifies that participant initials be recorded on screening and enrollment logs, in addition to PIDs. For IMPAACT studies, in agreement with DAIDS, participant initials need not be recorded on screening and enrollment logs if doing so presents a potential threat to participant confidentiality. However, in such cases, a separate document must be available to document the link between a participant's name and PID.

12.2 Follow-Up Visits

For each IMPAACT study, the expected duration of participant follow-up, as well as the number and type of follow-up study visits or contacts scheduled to take place during the course of the study, are specified in the study protocol. In addition to specifying target visit dates, the protocol also specifies allowable visit windows for certain follow-up visits. Visit windows are defined as the period of time around the target date during which the visit procedures must be performed. In addition to allowable visit windows, narrower target visit windows within which the visit is expected to be performed may also be defined and used when reporting participant retention and the number of visits conducted early or late. Sites are encouraged to conduct visits as close to the target visit date as possible, and within the allowable visit window.

Interim visits are those that are not scheduled per protocol and are in addition to regular study visits. Interim visits or contacts may take place for a variety of reasons (e.g., a participant may be sick, need additional study product, additional laboratory tests, etc.). The interim visit must be documented in the participant's study record; unless immediate reporting is specified (e.g., an adverse event that meets the criteria for expedited reporting), data are entered on case report forms (CRFs) at the next scheduled study visit, or as instructed by the protocol team and PDM.

When necessary and unless otherwise specified in the study protocol, sites may conduct "split" visits in which the evaluations required for a given study visit are conducted over a period of more than one visit to the clinic.

12.2.1 Participant Transfer between IMPAACT Sites

During the course of IMPAACT studies, participants may leave the geographic area where they were enrolled and relocate to another area where the same study is taking place. To maximize retention, participants who relocate from one study area to another may be encouraged to continue their participation in their new location, unless otherwise directed by the study protocol. To accomplish this, study staff at both the originating site and the receiving site complete the process of a participant transfer.

All transfers should be performed using the Participant Transfer Request utility on the DMC portal. To complete a transfer using this utility, both sites must have completed the protocol registration process with the DAIDS Protocol Registration Office and have been issued a site-specific study activation notice from the Operations Center.

Key considerations are as follows:

- Care should be taken by both the originating site and the receiving site to protect participant privacy and confidentiality throughout the transfer process.
- The originating site is responsible for initiating each transfer using the Participant Transfer Request utility.
- The originating site is responsible for all aspects of study-related documentation and data management for study visits occurring before the transfer, including completion of eCRFs and resolution of data queries for visits occurring before the transfer. Should additional data queries for pre-transfer visits arise after the transfer has been completed, the originating and receiving sites should work together as needed to resolve the queries.
- After all documentation has been completed and all data queries have been resolved, the originating site is responsible for preparing copies of the participant's study records (source documents and any paper-based CRFs):
  - Original source documents — including original CRFs that serve as source documents — are retained at the originating site; certified copies are provided to the receiving site.
  - Original paper-based CRFs (excluding those that serve as source documents) are provided to the receiving site; certified copies are retained at the originating site.
  - eCRFs must be signed off by the originating site Investigator of Record (IoR) in Medidata Rave prior to the participant transfer; the DMC will work with the originating and receiving sites to make the eCRFs available to the receiving site.
- The originating site is responsible for providing participant-specific contact details and participant-specific pharmacy details to the receiving site.
- The participant must provide written informed consent to continue study participation at the receiving site; receiving site staff are responsible for conducting and documenting the informed consent process per site standard operating procedures (SOPs), using the informed consent form currently approved by the receiving site IRBs/ECs.
  - Note: exceptions to this requirement may be applicable when the same informed consent form is approved for use at both the originating site and the receiving site.
- The receiving site is responsible for completing the transfer using the Participant Transfer Request utility. The receiving site is then responsible for all aspects of study-related documentation and data management for the transferred participant.

- The PDM is copied on all correspondence generated by the Participant Transfer Request utility. When the receiving site completes the transfer through the utility, the PDM updates the clinical database to recognize that the transfer has been completed and the receiving site has taken full responsibility for the participant and study data going forward.
- If the study participant is on more than one study, this process needs to be completed for each study for which they are transferring study follow-up.
- The originating site should consult with the protocol team regarding the handling of specimens (e.g., when and where to ship specimens).

Due to concerns regarding confidentiality, documentation, and other factors, temporary transfers (when a participant will be away from their originating site and potentially followed at another participating site for a short period of time) are typically not allowed.

12.2.2 Investigator-Initiated Early Termination of Participants

IMPAACT study participants (or their parent or legal guardian) may withdraw their consent to participate in IMPAACT studies at any time, for any reason. Investigator-initiated termination of an individual's IMPAACT study participation prior to the protocol-specified completion of follow-up should occur only under extraordinary circumstances. For instance, termination may be considered if there is potential for harm to the participant or study staff, or significant disruption of study operations.

Reasons for investigator-initiated early termination and expectations for communication with the protocol team should be outlined in the study protocol, and these specifications should be followed. Site staff must always record reasons for termination in participant study records.

12.2.3 Participant Unblinding During Study Implementation

Protocol teams should indicate unblinding procedures in the protocol, including guidelines to determine if and when unblinding for individual participant management is appropriate. Any deviation from the guidelines included in Appendix I, Unblinding Procedures, must be explicitly stated in the protocol; such "non-standard" unblinding procedures are reviewed and approved by the SDMC and the IMPAACT Multidisciplinary Protocol Review Group prior to protocol finalization. Additional details describing the background on blinding, procedures for unblinding during study conduct for safety or per protocol, and procedures for unblinding following study closure can be found in Appendix I.

12.2.4 Closing to Accrual

IMPAACT studies will be considered to have met the DAIDS status of "closed to accrual" on the date when the last participant is enrolled in the study; the PDM notifies the protocol team, and the Operations Center notifies DAIDS of this change in status. Participant follow-up (including assessments, data collection, etc.) typically continues past the closed to accrual date. The closed to accrual date may occur once the protocol-specific accrual targets have been met or when the Study Monitoring Committee (SMC) or Data and Safety Monitoring Board (DSMB) recommends, and the MOG or DAIDS, respectively, accepts the decision that the study should discontinue enrollment.

For studies that are projected to close to accrual per protocol, the protocol team should begin planning for study closing to accrual approximately three months prior to the anticipated date. For studies that are closed to accrual following an SMC or DSMB review, such planning may not be possible.

Planning activities may include determining requirements for laboratory sample shipments, communicating with sites on accrual trends, communicating with site stakeholders, communicating with potential participants during the informed consent process about their potential to enroll, and/or planning for potential participants in the screening process when the protocol-specific accrual target is met.

As needed, the SDMC will provide the protocol team with information on the projected primary completion date for the study, which is the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure. In studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. The SDMC will also provide information on the projected date for closing to follow-up (i.e., the projected study completion date), and the date range during which the final follow-up study visits should occur. Initial projections are typically updated upon completion of accrual into the study. Thereafter, projections are updated as needed depending on the study design and planned duration of participant follow-up.

Upon confirmation of last enrollment:

- Notify protocol team and sites of last enrollment – PDM
- Notify the DAIDS Regulatory Support Center Clinical Study Information Office (RSC CSIO) of study status change to closed to accrual – DMC

12.3 Data Collection

The DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual specifies the essential documents that study sites must maintain for DAIDS-sponsored studies.

DAIDS requires study sites to establish an SOP for maintaining essential documents. All study sites must comply with this requirement and follow their SOP for maintaining essential documents for the studies. Site staff should also ensure that essential documents are subject to quality control (QC)/quality assurance (QA) procedures. Additional information is available in the DAIDS SCORE Manual, which is available at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

12.3.1 Participant Research Records

The United States Code of Federal Regulations and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance requires study site staff to maintain adequate and accurate participant "case history records" containing all information pertinent to the study for each IMPAACT study participant.

12.3.1.1 Participant Research Record Contents

Participant research records should contain all of the following elements:

- Basic participant identifiers such as PIDs or initials (Note that initials or other participant identifiers other than PID number should never be entered on a CRF or submitted to the DMC or study clinical database.)
- Documentation that the participant (or parent or legal guardian) provided written informed consent to participate in the study prior to the conduct of any study procedures
- Documentation that the participant met the study's eligibility criteria
- A record of the participant's random assignment (if applicable)

- A record of the participant's exposure to investigational products (if applicable)
- A record of all contacts, and attempted contacts, with the participant including all clinic visits, off-site visits (e.g., at home or work), and all verbal and written contacts
- A record of all procedures performed by study staff during the study
- Complete source documents
- All CRFs and other study data collected from the onset of screening through end of participation
- Study-related information on the participant's condition before, during, and at the conclusion of study participation, including:
  - Data obtained directly from the participant (e.g., interview responses)
  - Objective data ascertained by study staff (e.g., exam and laboratory findings)
  - Objective data obtained from non-study sources (e.g., medical records)

In addition to the above, all protocol deviations involving participants should be documented in participants' study records, along with reasons for the deviation and attempts to prevent or correct the deviations, if applicable. More information regarding DAIDS requirements can be found in the SCORE Manual. See Section 12.5 regarding IMPAACT requirements for reporting protocol deviations.

12.3.1.2 Concept of Source Data and Source Documentation

The ICH/GCP guidance defines source data and source documentation as follows:

- The term "source data" refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- The term "source documents" refers to original documents, data and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification as being accurate and complete; microfiche; photographic negatives; microfilm or magnetic media; x-rays; participant files; and records kept at the pharmacy, the laboratories, and medico-technical departments involved in the trial).

Source documents are commonly referred to as the documents — paper-based or electronic — upon which source data are first recorded.

IMPAACT study sites must adhere to the standards of source documentation specified in the DAIDS SCORE Manual and the DAIDS policy on Electronic Information Systems. In cases where DAIDS guidance contains both requirements and recommendations, study sites must comply with all requirements and are advised, but not required, to comply with all recommendations. Source documentation includes original documents and certified copies that include documentation pertaining to a participant while on study.

For each IMPAACT study, participant case history records typically consist of some or all of the following:

- Narrative chart notes
- Visit checklists or flow sheets
- Laboratory reports
- Medical records or clinic charts
- CRFs
- Randomization log or other documentation (when applicable)
- Investigational product dispensing and accountability records (when applicable)
- Other source documents and non-CRF data collection tools or questionnaires

As a condition for study activation, each site must have an established SOP for source documentation that specifies the use of these documents as source documents (see Section 11).

Supplemental information on use of chart notes, visit checklists, and CRFs as source documents is provided below. Also provided below is information related to investigational product dispensing and accountability records, document organization, and record retention requirements.

The DAIDS SOP for source documentation requires that a site must document which CRFs, if any, will be used as source documents. Study staff must follow the specifications of this SOP consistently for all study participants throughout the study. In the event that study staff are not able to record source data directly onto data collection instruments designated as source documents, the following procedures should be undertaken:

- Recording the data onto an alternate source document
- Entering the alternate source document into the participant's study chart
- Transcribing the data from the alternate source document onto the appropriate CRF
- Recording a chart note stating the reason why an alternate source document was used

12.3.1.3 Chart Notes

Chart notes must be used to document the following:

- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents

All chart notes or other tools used as source documentation must document the PID of the study participant to whom they pertain, the identity of the study staff member who entered information, and the date of the entry. Study sites are strongly encouraged to adopt a common format — such as the Subjective-Objective-Assessment-Plan (SOAP) format for all chart notes — to help ensure adequacy and consistency of note content and maximize adherence to GCP standards. Alternative standardized formats are acceptable and may be adopted by study sites.

12.3.1.4 Visit Checklists

In some studies, visit checklists may be a convenient tool for study staff to fulfill the requirement of documenting all procedures performed with each study participant. Note that checklists alone often are not sufficient for documenting all procedures. For example, chart notes may be required to document

procedures performed at unscheduled study visits, to explain why procedures, in addition to those specified on a checklist, may have been performed, or why procedures specified on a checklist were not performed. Chart notes also may be required to document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

Visit checklists that are used as source documentation for study procedures must contain the PID, the initials or signature of the authorized study staff member completing each of the procedures, and the date the procedure was completed. Individual study staff members must initial only those procedures that they complete. In addition, if procedures listed on a single checklist are completed across multiple dates, the date upon which each procedure is completed must be clearly noted. Additional detailed guidance related to proper use of visit checklists may be provided in each study-specific MOP.

12.3.2 Case Report Form Distribution, Completion, and Data Entry

The DMC makes the following materials available for use for the study.

- CRF completion guide: PDF guide containing blank versions of the eCRFs with instructions and help text for completion as well as data collection forms schedules, which may be downloaded by site personnel from the DMC portal
- Print matrix: PDF containing blank versions of the eCRFs as they appear in Medidata Rave, which may be downloaded by site personnel from the DMC portal
- Annotated print matrix: PDF containing blank versions of the eCRFs as they appear in the Medidata Rave, with field annotations that may be used to assist with data retrieval, which may be downloaded by site personnel from the DMC portal
- eCRFs for Participant Interviews or Questionnaires: blank PDF versions of these CRFs are available to sites within the Forms Management Utility on the DMC portal and sites are responsible for printing them

Study staff may use these tools to develop documentation for collection of participant data for entry into Medidata Rave.

Aspects of eCRF completion and data entry vary depending on the data standards in use for the study (either CDISC or legacy format). All IMPAACT studies will utilize Medidata Rave.

12.3.2.1 Data Management Procedures

Data entry into Medidata Rave is completed by designated study staff. Site staff should perform quality checks of the data prior to and while entering the data, as well as after saving the data in Medidata Rave. Site staff should utilize reports within Medidata Rave to resolve queries and address overdue data. Reports for quality review of participant data, productivity, and administrative reports are available to sites on the DMC portal and in Medidata Rave.

Site staff should use completion guides developed and made available by the DMC. These guides provide the framework for collecting the necessary study data based on the schedules of evaluation in the study protocol and aid in scheduling participant visits and specimen collection.

Sites use the SES or Stars on the DMC portal for submission of screening checklists and eligibility checklists for both new and subsequent steps for participant enrollments. Requests for participant transfers to new sites and unblinding requests are managed through the appropriate utilities on the DMC

portal. Requests for eligibility corrections are managed by issuing site to DM queries in Medidata Rave. Any questions on available reports should be sent to the PDM.

Site staff should utilize reports provided by the DMC and in Medidata Rave for error resolution, resolving data delinquencies, and responding to data queries. Select web utilities on the DMC portal provide additional data QA/QC reports site staff may utilize to review participant data.

The PDMs and other DMC staff answer questions about data management and system issues. If the PDM is unavailable, sites should contact the Chief Data Manager or Coordinating Data Manager, who have overall responsibility for central data management in IMPAACT.

Hardware and software computing requirements as well as procedures for enrolling participants, submitting participant data, and other areas of central DMC requirements can be obtained by contacting Frontier Science User Support and from the Computing Manual, accessible on the DMC Portal. Information regarding DMC training programs is also available on the DMC Portal.

12.4 Study Team Communications

After initial release of a study protocol, several types of study-related communications may be used to report on study progress or provide further clarification of protocol-specified procedures and study documentation requirements. Such communications may include but are not limited to those listed in Table 12-1. Unless otherwise specified in a study protocol, quorum and sign-off requirements included in Table 12-1 should be considered minimum standards; protocol teams may specify additional requirements, beyond those specified in the table, if applicable. Further guidance on expectations and procedures for meeting quorum requirements is provided below the table.

Table 12-1. Study Team Communications

Communication Type	Description
Conference calls and meetings	Protocol teams (including site representatives), and designated subgroups (e.g., Clinical Management Committee [CMC]), take part in routine meetings and conference calls throughout the period of study implementation. Summaries of these meetings and conference calls are typically prepared and distributed by the protocol CRM. Refer to Table 12-2 and Figure 12-1 for requirements related to quorum and for alternative procedures to be followed for study-specific groups that function — in whole or in part — independent of the protocol team (e.g., safety or endpoint review groups). Meeting and conference call summaries will list all participants and state whether relevant quorum requirements were met. CRMs may use their discretion when documenting calls with large numbers of site representatives; in these cases, overall site representation may be indicated, without individual names. When protocol-specified or other important study implementation decisions require review and/or recommendations from a SMC or DSMB, these will be documented per the procedures described in Section 13.

Table 12-1. Study Team Communications

Communication Type	Description
All-site email messages	Protocol teams typically provide key study-related updates to site representatives via email. For example, updates on participant accrual and achievement of study milestones (e.g., completion of accrual, closure to follow-up) are often provided by email.
Memorandum of Operational Instruction and other memoranda	When protocol-specified or other important study implementation decisions require communication to sites (e.g., study drug dose-finding or cohort progression decisions), these are communicated in a memorandum that is reviewed by the protocol team or designated subgroup and then distributed to all sites via email. Prior to distribution of any such memorandum, sign-off must be obtained from one protocol chair (chair or vice chair), one protocol statistician, one PDM, and one DAIDS medical officer (MO); when a memorandum involves pharmacokinetic (PK) considerations, sign-off must also be obtained from one protocol pharmacologist. The process of preparing, obtaining review and sign-off, and distributing this type of memorandum is coordinated by the protocol CRM.
Communications to Network leadership (e.g., MOG and SLG)	Protocol teams may need to provide study-related communications to IMPAACT leadership. For example, teams may need to provide study-related updates or request consultation on study design or study implementation issues. When this type of communication is needed, relevant team members will prepare a memorandum or other applicable document for review by the protocol team or designated subgroup. Prior to distribution to the Network leadership or oversight group, sign-off must be obtained from one protocol chair (chair, or vice chair), one protocol statistician, one PDM, and one DAIDS MO; when the document involves PK considerations, sign-off must also be obtained from one protocol pharmacologist. The process of preparing, obtaining review and sign-off, and distributing this type of memorandum is coordinated by the protocol CRM.
Protocol clarification memoranda, letters of amendment, and full amendments with an attendant summary of changes	These documents are developed and issued as described in Section 9. Development of these documents is coordinated by the protocol CRM, and final versions are distributed to all protocol team members and study sites. Final versions are also posted on the IMPAACT website.
Study reports	Data reports on study progress, protocol adherence, data quality, etc., are developed and issued by the SDMC in accordance with the study progress, data, and safety monitoring plan (SPDSMP, see Section 11).
Study implementation questions	These questions may be related to protocol interpretation as well as administrative, ethical, regulatory, clinical, counseling, data, and laboratory operations. Any such questions that are not answered by the protocol or other operational guidance documents should be emailed to the protocol team or designated subgroup (e.g., study-specific CMC), as indicated in the protocol or study-specific MOP. As described in Section 12.5, reportable protocol deviations are submitted to the protocol deviation email list (IMPAACT.deviation@fstrf.org).

Table 12-1. Study Team Communications

Communication Type	Description
Site-specific conference calls and refresher training sessions	Refresher trainings and conference calls for IoRs, study coordinators, and other site staff with members of the protocol team are held as needed, and for some studies on a routine basis. These sessions provide a forum for discussion of study implementation challenges, clarification of operational aspects, review of protocol updates (i.e., associated with amendments and clarification memoranda), and other topics suggested by site staff.

The quorum requirements specified in Table 12-2 should routinely be met through active real-time participation in meetings and conference calls. Quorum members should proactively identify any meetings or conference calls for which they are not available and provide written review comments or other required input in advance of the meeting or call; receipt of such input in advance will be considered sufficient to meet quorum requirements.

When quorum requirements are not met, the decision to be made or the review to be performed should be deferred to a later date while still meeting protocol requirements for timeliness and frequency of review; in particular, safety data reviews should occur within protocol-specified timelines. When it is not possible to re-schedule in a timely manner, the following procedures may be followed to complete the required decision-making or perform the required review:

- All available team members will take part in the scheduled call or meeting; the CRM will prepare a summary of the call or meeting, listing all participants and stating that quorum requirements were not met.
- A protocol chair will provide a summary of the relevant discussion to the absent quorum member via email (copied to the CRM) and request that the absent member reply via email to confirm their review and indicate whether they concur with the discussion that took place in their absence (copied to the CRM).
- If the absent quorum member does not concur, the protocol chair will determine next steps (e.g., further email communication, convening an *ad hoc* conference call, deferral to the next scheduled conference call).
- Once consensus is achieved, the CRM will document the discussion and inform all relevant team members of the outcome (e.g., updates or an addendum to a call summary, capturing in the subsequent call summary, or issuing a separate memorandum).

Use of the above-listed procedures is expected to be infrequent within a given protocol team or sub-group. Should any team or sub-group identify that quorum requirements are frequently not being met, action should be taken by the team to address this; when resolution cannot be achieved within the team, action may be taken by the IMPAACT MOG.

Table 12-2. Quorum Requirements

Quorum Type	Required Members to Meet Quorum
When **protocol-specified or other important study implementation decisions** are made via conference call, the following team members, who comprise the quorum for decision-making, must take part in the call:	• One protocol chair (chair, or vice chair) • One protocol statistician • One PDM • One CRM • One DAIDS MO or designee* • When decisions involve PK considerations, the quorum also includes one protocol pharmacologist.
When reviews of study data for purposes of **monitoring participant safety** are conducted via conference call, the following team or subgroup members, who comprise the quorum for this type of review, must take part in the call:	• One protocol chair (chair, or vice chair) • One protocol statistician • One PDM • One CRM • One DAIDS MO or designee* • When reviews involve PK data and/or considerations for individual study drug dosing, the quorum also includes one protocol pharmacologist.
When reviews of study data for purposes of **monitoring study progress and/or the quality of study conduct** are conducted via conference call, the following team or subgroup members who comprise the quorum for this type of review, must take part in the call:	• One protocol chair (chair, or vice chair) • One protocol statistician • One PDM • One CRM • One DAIDS MO or designee*
*At least one assigned DAIDS MO should ideally take part in all reviews and decisions. If no assigned DAIDS MO is available, an assigned NICHD MO or an alternate DAIDS representative designated by an assigned DAIDS MO may take part in the place of an assigned DAIDS MO(s).	

The above-listed procedures generally apply to decisions made or reviews performed via meeting or conference call. In some cases, decisions may be made and reviews may be performed via email. In such cases, all protocol team or subgroup members should ideally provide input via email and an email response must be obtained from the applicable quorum members (as listed in Table 12-2). A protocol chair will coordinate with the CRM to confirm the outcome of the decision or the review and, if consensus is not reached, to determine next steps. Once consensus is achieved, the CRM will inform all relevant team members of the outcome.

Figure 12-1. Alternative procedures to be followed for study-specific groups that function independent of protocol teams

For some IMPAACT studies, groups designated to fulfill key responsibilities may function — in whole or in part — independently of the protocol team (e.g., safety or endpoint review groups). In some cases, protocol team members (e.g., protocol chair, MO) are members of the group. In most cases, PDMs and/or statisticians work directly with the group (e.g., by providing data reports to be reviewed by the group and documenting review outcomes). For any such group, the requirements of this MOP section are generally expected to apply, and the following should be described in the SPDSMP:

- Quorum requirements for the group's key functions must be defined. Group members may or may not choose to designate a chair of the group, but regardless of this designation, a quorum must be defined.
- An individual must be designated to fulfill the documentation requirements specified in this section. This individual may be a protocol chair, chair of the group, PDM, protocol statistician, or other designee.

See Section 4 for additional details related to study-specific groups.

12.4.1 Confidentiality of Study Data

Unless otherwise specified in the study protocol, sharing and/or discussion of post-entry study data during an ongoing study should be limited to designated committees (e.g., DSMB) to avoid bias in study conduct and/or interpretation of data. Discussion within the team should be limited to the functions described in the SPDSMP.

12.4.2 Clinical Management Committee (CMC)

Note: This section describes CMC responsibilities in support of participant management. CMCs may also be involved in study data reviews and decision-making; refer to Table 12-1 for more information on those topics. Typically, the CMC consists of the protocol chair(s), MOs, statisticians, PDMs and LDMs, CRMs, and Laboratory Center representatives; the pharmacologist(s) should also be included for PK studies and other specialists (e.g., immunologist, virologist) may be added as applicable. Other study investigators/clinicians may be added to the CMC, dependent on the protocol design and safety considerations, and membership should be defined in each IMPAACT protocol. For studies with collaborating pharmaceutical companies, 1-3 representatives per company may be added to the CMC. Any pharmaceutical representatives should have organizational roles consistent with a medical monitor (primary and back-up); a company pharmacologist may be included, if applicable, as part of the total representatives. Within the CMC, company representatives will have an advisory role only.

Each IMPAACT protocol will specify if a CMC or analogous group composed of appropriate protocol team members is designated to provide support to site investigators and clinicians regarding clinical management of participants and any adverse events, management of study drug regimens, and other clinical considerations. The CMC may also respond to site requests for guidance related to eligibility and co-enrollment in IMPAACT and other studies. Separate from information that may be provided to the CMC as part of notifications or queries from sites, distribution of study data to the CMC (or not) is

directed by protocol specifications and the study monitoring plan(s). For comparative studies, treatment assignment information should not be provided to the CMC unless necessary for participant safety.

Site personnel should submit queries directly to the CMC based on the template included in the study-specific MOP (if available), or other standardized guidance, to ensure complete background information is provided. Queries should, at a minimum, include site number/contact, study number, PID, duration of time on study, and case description. The study number and PID should be included in the subject line of the email for ease of tracking. Attachments should only be included if necessary, and site personnel should include relevant clinical information from the attachment(s) in the case description to provide a detailed summary. Care should be taken to ensure that no confidential participant information is shared via email.

In general, designated members of the CMC are clinicians on the protocol team, as decided by the protocol chair(s), and are responsible for responding to queries received from sites as soon as possible and ideally within 24 hours of receipt. When a complete response cannot be provided within 24 hours, a reply will be emailed to the site confirming receipt and indicating that a full response is in process.

When fielding site queries, designated CMC members are encouraged, but not required, to seek input from other CMC members before responding to the site to confirm the accuracy and completeness of a proposed response. However, internal CMC consultation should be done routinely in the first few months of study implementation to establish consensus among CMC members. The designated CMC member may also seek input from members of the protocol team who are not on the CMC when their expertise may be needed to guide the appropriate response (for example, the protocol pharmacist may be consulted for queries involving study product supply). When the CMC discusses a site query within the committee, the site personnel must be removed from the email messages. This will minimize confusion and/or potential misunderstanding at the site.

The designated CMC member should respond to the site, copying the CMC email group (generally, IMPAACT.####CMC@fstrf.org), and all site personnel included on the original query. The protocol team and site representative email groups (generally, IMPAACT.TEAM####@fstrf.org; IMPAACT.PROT####@fstrf.org) should not be copied (even if copied by the site in error). Responses should indicate when follow-up action and/or additional information is needed from the site and when a query or consultation is considered resolved or completed. Follow-up communications from the site and the CMC should be sent as replies to the original email message and "final response" should be included in the body of the CMC's final email response to the site. The site will be instructed to file a copy of the final response (email exchange) in the participant's study chart. For some studies, the CMC response may be archived with the DMC and available upon request.

Designated CMC members are permitted to respond to queries from the site with which they are affiliated, unless otherwise specified by the protocol or other operational guidance, such as the study-specific MOP. This should be done following the same process described above, with the CMC email group copied.

If an incomplete or incorrect response is inadvertently sent to a site, a correction or additional relevant guidance should be sent to the site as soon as possible. Sites should file any additional correspondence from the CMC in the participant's chart along with the original response.

The protocol CRMs, who are members of the CMC, will support the query response process by prompting for responses within 24 hours and by providing references to protocol and MOP sections that are relevant to a query. Upon request, the CRMs may also send responses on behalf of the designated CMC member. However, designated CMC members should generally plan to send all responses over

weekend and holiday periods. When responding to queries, the CMC is encouraged to review relevant prior correspondence, for example, to provide background information from a prior query for the same participant or provide a reminder of how similar queries were handled in the past.

Query responses must provide guidance to site staff that is consistent with protocol specifications. Responses cannot authorize or approve protocol deviations. In the event that a protocol deviation is identified in CMC communications with a site, the deviation should be acknowledged, and the site should be reminded to fully document the deviation, the reason why it occurred, and corrective and preventive actions taken, in accordance with DAIDS policies and GCP guidelines. The CRMs can provide template wording when this type of response is necessary. The CRMs can also follow-up with sites as needed when deviations meeting IMPAACT criteria for network-level reporting are identified (see Section 12.5).

12.4.3 DMC Queries and QC Reports

The PDM and designated DMC staff (e.g., LDMs, medical coders) review eCRF data and laboratory data submitted to the DMC; items requiring verification or further clarification are sent as queries to the site data management staff or laboratory staff.

Reports to review queries, overdue data, and other quality assurance reports are available within Medidata Rave and may be run as needed by sites. Data management staff at the sites should routinely review the reports and task dashboards and correct or clarify the data items in question. Site staff should routinely check within Medidata Rave to ensure QC issues, such as overdue data or queries, are addressed. Laboratory staff should routinely review open queries within the Query System on the DMC Portal.

Queries may also be sent in preparation for interim analyses, and these should be addressed as soon as possible. If the site has questions about any queried items that show up repeatedly on QC reports, they should contact the PDM for further explanation. Any issues should be addressed as soon as possible, generally within seven to ten working days of receipt.

12.4.4 Data Management Quality Summary Reports

The SDMC routinely generates reports on site-specific and protocol-specific data management performance.

The reports include:
- Data completeness
- Timeliness of submitted data
- Query responsiveness
- Error responsiveness
- Regulatory (Serious Adverse Event timeliness)

The site laboratory reports include:
- Query responsiveness
- Peripheral blood mononuclear cells (PBMC) shipping storage compliance
- Shipping evaluation score

If there are concerns about a site's data management quality, the PDM and protocol team will work with the site to help develop strategies for improving performance.

12.5 Protocol Deviations

This section outlines the process by which protocol deviations are defined, classified, reported, and documented for IMPAACT studies. These guidelines apply to all IMPAACT studies and may be augmented by additional sponsor requirements or any protocol specifications.

IoRs and, by delegation, all study staff, are responsible for conducting IMPAACT studies in compliance with the IRB-approved protocol; applicable US laws and regulations; ICH Guidelines on GCP; applicable local laws, regulations, and guidelines; and standards of professional conduct and practice. Any non-compliance with the IRB-approved protocol is a protocol deviation. Deviations may be incurred by study participants, protocol team members, IoRs, sub-investigators, coordinators, physicians, nurses, counselors, data managers, pharmacy staff, laboratory staff, and/or additional supervisory, oversight, or support staff.

Note: throughout this section, reference is made to the "IRB-approved protocol." This terminology refers to the study protocol that has been approved by DAIDS, site IRBs, ECs, drug regulatory authorities, and all other applicable regulatory entities.

12.5.1 Applicable Regulatory Requirements and Guidance

United States Code of Federal Regulations (US CFR)

- **21 CFR 312.60:** states that "an investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and the applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation…"
- **21 CFR 56.108:** states that investigators must "(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval."
- **45 CFR 46.113:** authorizes the IRB to "suspend or terminate approval of research that is not being conducted in accordance with IRB's requirements or that has been associated with unexpected or serious harm to subjects."
- **45 CFR 46.108(a)(3)(iii) and (4)(i):** states that institutions must have written procedures (which investigators must follow) for ensuring the prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
- **45 CFR 46.103(b)(5):** states that institutions must have written procedures (which investigators must follow) for prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval.

The full US CFR may be found at www.ecfr.gov/.

International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- **ICH Guideline 4.5.2:** states that the investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

- **ICH 4.5.3:** states that the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The full ICH guidelines may be found at https://www.ich.org/page/ich-guidelines.

United States Food and Drug Administration (US FDA)

Guidance, compliance, and regulatory information from the US Food and Drug Administration (FDA) may be found at http://www.fda.gov/drugs/default.htm. The FDA considers protocol deviations as acts contrary to the written protocol.

Further insight into the FDA's perspective on protocol deviations can be found at http://www.fda.gov. The website contains copies of warning letters issued by the FDA, as made available under the 1996 amended Freedom of Information Act. Examples of warning letters including protocol non-compliance issues include:

- Letter to JM Isner; 28 April 2000 (St. Elizabeth's Medical Center; Boston, Massachusetts): *Subject was enrolled into study VEGF2-CAD-001 (cardiac arterial disease study); however, the subject met the protocol exclusion criteria.*
- Letter to EJ Kopp; 21 June 2000 (CARE Center, Raleigh, NC): *Two of 14 subjects did not meet protocol criteria regarding duration of _____.*

United States Health and Human Services

Regulations from the US HHS may be found at http://www.hhs.gov/ohrp/.

12.5.2 Definitions Applicable to IMPAACT Research

Table 12-3. Definitions

Term	Definition
Protocol deviations	Any change, divergence, or departure from the study design or procedures defined in the DAIDS-approved, GCP-compliant protocol (ICH E3). Noncompliance may be on the part of the participant, the investigator, the study staff, or a combination of these groups. This includes but is not limited to the following: • Administrative inconsistencies or minor errors in the implementation of the protocol (e.g., visit outside the window, laboratory evaluation assessed off schedule, violation of inclusion/exclusion criteria) • Departure from specified treatment, examination, or data collection procedures in a study protocol Protocol deviations may or may not render a participant ineligible to participate in a study and may be considered significant or serious when they increase potential risk to participants or affect the integrity of study data. An isolated deviation may not be significant by itself, but significance may increase with numerous deviations of the same nature. The term "protocol deviation" is often used interchangeably with "protocol violation." "Protocol deviation" is the term preferred by ICH.
Reportable protocol deviation	IMPAACT Network studies will follow the definition and processes for reportable deviations as described in the Cross-Network Protocol Deviation Reporting Guide, available here: https://www.hanc.info/resources/sops-guidelines-resources/daids.html
Corrective action	Action taken to correct (when possible) or otherwise address a protocol deviation. Corrective actions are commonly specified in consultation with the relevant protocol team and/or IMPAACT leadership. In all cases, corrective action must include documentation of the deviation. All protocol departures/deviations/violations must be recorded in the participant's research record and, if pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation. Examples of corrective actions include (but are not limited to) notifying the affected participant(s), protocol team, and/or IRB; re-consenting the participant(s); completing missed procedures; repeating laboratory tests; completing additional participant monitoring or management procedures; and/or destroying specimens collected in error.
Preventive action	Action taken to prevent recurrence of a deviation. Preventive actions are commonly specified in consultation with the relevant protocol team and/or IMPAACT leadership. In all cases, preventive action must include documentation of the deviation. All protocol departures/deviations/violations must be recorded in the participant's research record and, if pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation.

Table 12-3. Definitions

Term	Definition
	Examples of preventive actions include (but are not limited to) discussion of the deviation with relevant study staff, refresher training of study staff; review and/or revision of SOPs or other study implementation materials; development of new study implementation materials; implementation of additional communication, QC/QA, or oversight/supervisory procedures; changes in day-to-day workflow; and/or changes in general participant management or laboratory procedures.

NIAID and NICHD Clinical Site Monitors may identify protocol deviations in their monitoring reports and some of these may meet the definition of a reportable protocol deviation. In the event that deviations identified by Clinical Site Monitors meet these definitions, the IoR or designee must report the deviation as described in Section 12.5.3. Likewise, other network partners such as representatives of the Operations Center, DMC, or LC may identify reportable protocol deviations; these persons should notify the IoR as soon as possible (within three days of awareness) so that the IoR can then report the deviation.

Note that there is not a one-to-one correspondence between events reported by the Clinical Site Monitor and those to be reported through the protocol deviation reporting system. The Clinical Site Monitor may report protocol non-adherence events and violations that encompass every infraction of the protocol. For example, if a blood specimen is drawn for ALT, but is not processed by the laboratory, it is a non-adherence event according to the Clinical Site Monitor. This would not be a reportable protocol deviation because it is one missed collection and does not represent a systemic issue that would affect study data. If, however, an ALT is to be drawn at each participant visit and is not being done at all, this would be a reportable protocol deviation.

Section 12.5.3 describes procedures for reportable protocol deviations.

12.5.3 Procedures for Reportable Protocol Deviations

All reportable protocol deviations must be reported by site investigators within five reporting days of site awareness (unless a shorter timeframe is otherwise specified in the protocol). Note that reporting days are defined in the Cross-Network Protocol Deviation Reporting Guide, available on the HIV/AIDS Network Coordination website (https://www.hanc.info/resources/sops-guidelines-resources/daids.html) and are consistent with EAE reporting requirements. If needed, consultation with the Operations Center, SDMC, LC, or respective protocol team is available. Of note, based on protocol-specific directions, protocol deviations may be communicated to protocol teams (for example, through consultation with the study-specific CMC) ahead of submission of the protocol deviation to the study database.

Based on the reporting timeframes specified in the Cross-Network Protocol Deviation Reporting Guide, it is understood that the corrective and/or preventive actions (CAPA) may not be fully developed at the time a deviation is reported; because of this and because of the potential for inconsistencies between eCRF and source documents, the protocol deviation eCRF no longer includes collection of CAPA details. Sites should continue to document CAPA information per their site-specific requirements and processes; CAPA documents may be requested for review by protocol teams, Network leadership reviewers, and/or DAIDS. The final plans for management of the current deviation and the prevention of future occurrences must be documented.

Reporting procedures require that protocol deviations be entered either via eCRF or into the Protocol Deviation Reporting System (PDRS) on the DMC portal — so that the deviation is recorded in the study

database — and that a copy of the deviation report be distributed to members of IMPAACT leadership and the respective protocol team, as listed below.

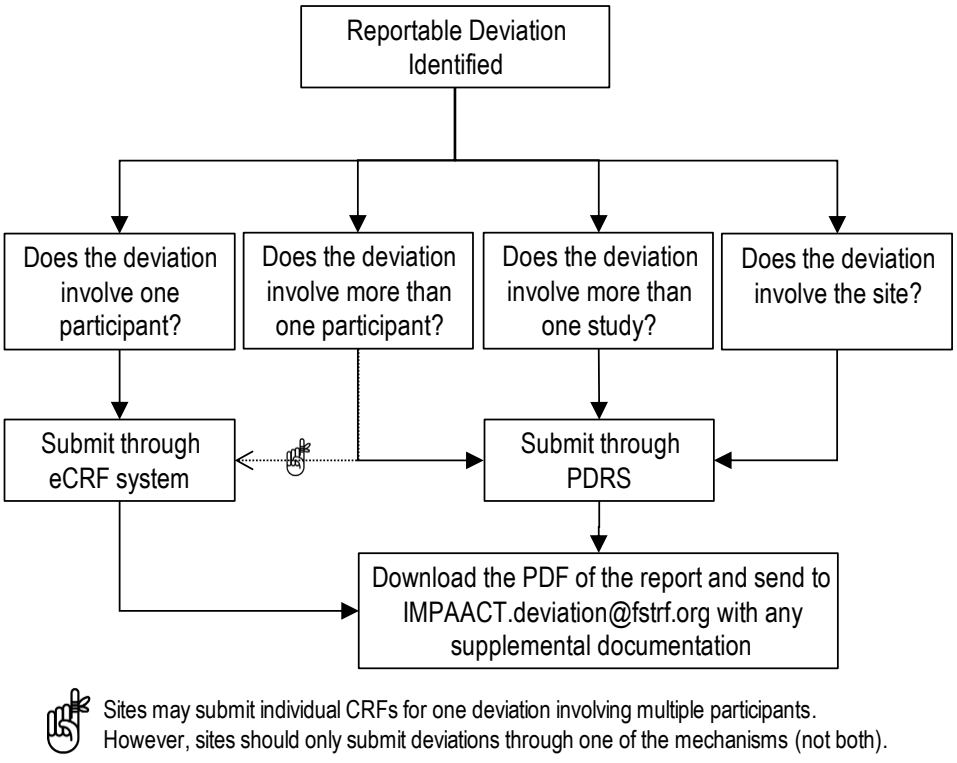
Protocol deviations that involve only one participant should generally be reported using the study protocol deviation eCRF. Sites may also choose to report deviations involving more than one participant using the study protocol deviation eCRF; however, in that case, one protocol deviation CRF should be completed for each impacted participant.

Protocol deviations that occurred at the study or site level (i.e., those that do not involve specific participants) should be reported using the PDRS. Sites may also choose to report deviations involving more than one participant using the PDRS; in that case, one submission documenting all impacted participants may be entered (i.e., individual submissions by participant need not be entered).

Sites should complete and enter the eCRF or PDRS record per usual data management procedures, save a PDF version of the eCRF or PDRS record, and email the PDF with any additional supplemental documents (e.g., IRB correspondence) to IMPAACT.Deviation@fstrf.org. If the deviation occurred over a period of time, the range of dates over which the deviation occurred should be indicated in the submission.

See Figure 12-2 for a visual representation of the protocol deviation reporting process.

Figure 12-2. Protocol Deviation Reporting Process



The Operations Center will review the emailed report(s) for completeness (e.g., all fields are completed, all pages are provided), comprehensiveness (e.g., the deviation is clearly described), and legibility (e.g., all fields are readable, pages and text are not cut off). In addition, if the reported deviation is unclear or incomplete, the Operations Center representative may consult with the protocol-specific CRM to work on next steps. Once any issues involving completeness, comprehensiveness, and legibility are resolved, the emailed report (completed deviation report and any supplementary materials) is sent to the following distribution list typically within five working days by the Operations Center:

- Protocol chair(s)
- Protocol MO(s)
- Protocol CRM(s)
- IMPAACT leadership (Network chair and vice chairs, as well as NIH and operational component representatives, including leadership of the SDMC, LC, and Operations Center)
- IMPAACT program officer(s)
- Site OCSO program officer (NIAID sites only) or Westat site contact (NICHD sites only)
- Protocol pharmacist (if the deviation involves study product or prescribing issues)
- Protocol Laboratory Center representative (if the deviation involves laboratory issues)

If revisions are incorporated following submission of the report into the database, the original protocol deviation eCRF or PDRS record should be updated in the study database; if requested, the updated PDF version of the revised eCRF or PDRS record should be emailed to IMPAACT.Deviation@fstrf.org.

13 STUDY OVERSIGHT

Oversight of IMPAACT studies occurs at many levels, consistent with US and international regulations, policies, and guidelines applicable to human subjects research funded by the National Institutes of Health (NIH):

- At each clinical research site (CRS), the Investigator of Record (IoR) and delegated study staff are responsible for continuous monitoring of participant safety. The IoR and delegated staff are also responsible for continuous monitoring of the quality of study conduct and study data.
- The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development (NICHD) contract with clinical site monitors to conduct site monitoring activities and have established procedures to ensure that monitoring findings are addressed as needed at each site.
- For each study, the protocol chair, DAIDS Medical Officer (MO), NICHD Medical Officer, and other team members routinely monitor study progress and the quality of study conduct; any emerging issues identified through this monitoring are addressed with study sites and elevated to IMPAACT Network leadership, as needed.
- The IMPAACT Network leadership has established oversight procedures that are continuously carried out for all studies by the Management Oversight Group (MOG).
- An independent IMPAACT Study Monitoring Committee (SMC) or NIAID Data and Safety Monitoring Board (DSMB) also provides oversight of IMPAACT studies when applicable.

Each of these levels of oversight is further described in this section.

13.1 On-Site Clinical Quality Management

Per the Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual, all sites conducting or participating in DAIDS-supported and/or DAIDS-sponsored clinical research must develop and implement a clinical quality management plan (CQMP). The CQMP must describe the

quality assurance (QA) and quality control (QC) activities that will be performed at the site for each study and describe the types of tools and checklists that will be used in the QA and QC processes. The CQMP must also state the frequency with which QA and QC activities will be performed. Further details can be found in the DAIDS SCORE Manual at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

13.2 Clinical Site Monitoring

As the sponsor of IMPAACT studies, the NIH has a regulatory responsibility for oversight of IMPAACT studies per the US Code of Federal Regulations (CFR; Title 45, Parts 46, 160, and 164; Title 21, Parts 11, 50, 54, 56, and 312) and per the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). As part of fulfilling these responsibilities, NIAID and NICHD contract with clinical site monitors to conduct site monitoring activities. Contracted monitors inspect study site facilities and review participant study records – including informed consent forms, paper-based case report forms (CRFs, if used), electronic case report forms (eCRFs), laboratory records, and pharmacy records – to ensure protection of study participants, compliance with IRB/EC approved protocols, and accuracy and completeness of study records. Site investigators will make study facilities and documents available for inspection by monitors.

Remote monitoring may be performed to supplement or reduce the frequency and extent of on-site monitoring. Site investigators must make study documents available for remote monitoring utilizing a secure platform that is 21 CFR Part 11 compliant and HIPAA compliant (for sites in the US). The DMC has configured Medidata Remote Source Review (RSR) to be available to all sites. If Medidata RSR is not utilized, other secure platforms that are 21 CFR Part 11 compliant and HIPAA compliant (for sites in the US) may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.

All sites are monitored at least once annually. The extent and frequency of monitoring will depend on the size, risk, and complexity of studies conducted at the site and may change over time depending on study status and performance of the site. Monitoring reports are prepared following each visit and provided to the sponsor (NIAID or NICHD) and the site. Sites are required to respond to monitoring findings in a timely manner and in accordance with sponsor-specific (NIAID or NICHD) procedures.

13.3 Protocol Team Monitoring

IMPAACT protocol teams are responsible for actively monitoring both participant safety and the quality of study conduct, and for working with sites to address any issues or concerns that may arise. Quality indicators monitored by protocol teams typically include participant accrual and retention, compliance with the study protocol, adherence to the study intervention, endpoint evaluability, data and specimen availability, and data quality and completeness.

Monitoring by the protocol team is typically accomplished through review of study-specific reports generated by the Statistical and Data Management Center (SDMC) per the Study Progress, Data, and Safety Monitoring Plan (SPDSMP); additional monitoring plans may also be developed as needed for individual studies (e.g., pharmacology data management plans or qualitative monitoring plans). The protocol chair and protocol team members from the Operations Center, Data Management Center (DMC), and Laboratory Center (LC) may visit sites or hold virtual meetings to assess study implementation and/or provide training and other technical assistance to site staff.

Designated protocol team members are responsible for monitoring participant safety. Specific roles and responsibilities are specified in the SPDSMP. These roles and responsibilities may differ based on the phase of the study and whether the study involves comparative groups. Team members are generally

expected to review safety data at least monthly; more frequent reviews may occur if specified by the study protocol or at the discretion of the team. For some studies, again depending on protocol specifications, team members are also responsible for identifying when criteria for pausing a study or convening a safety review have been met. If at any time a safety issue or concern is identified, designated protocol team members are responsible for taking appropriate action to address the issue or concern. Such actions may include requesting additional review of study data by the SMC or DSMB, modifying the dosing of study agents, or modifying other protocol specifications. The protocol team is also responsible for informing study sites in the event that any changes in study conduct are required.

The data upon which protocol team and other study oversight reviews are based are generated at the site level, based on evaluations performed by site clinicians and other study site staff. Site staff are responsible for monitoring the safety of each study participant and entering clinical and laboratory data into eCRFs in a timely manner, so that current data are available for review by the protocol team and other oversight bodies. Site staff are also responsible for alerting designated protocol team members to any safety-related issues or concerns that may arise; all protocol specifications for notification or consultation with the team must be followed.

SDMC staff also play a key role in monitoring participant safety, through their roles in reviewing and coding safety data, querying sites as needed to ensure that accurate and complete data are available for review, generating safety data reports for review, generating interim analysis reports for SMC or DSMB review, and identifying when study pause or stopping rules have been met.

Designated protocol team members typically review study monitoring reports during conference calls, although reviews may also take place during in-person meetings or by email; refer to Section 12 for detailed information on quorum requirements for these reviews. When team member assessments are required for the study database, these are recorded by the protocol data manager following standard DMC procedures. Otherwise, reviews are documented in the form of conference call or meeting summaries. Documentation of these reviews is not typically provided to study sites. However, sites are notified of any issues that may necessitate a change in study conduct; such notifications also provide instructions to sites regarding notification of Institutional Review Boards/Ethics Committees (IRBs/ECs) and other applicable review bodies. Similar notifications may also be provided following safety reviews in studies with multiple sequential cohorts of participants. Should a study site require a safety-related summary in order to meet IRB/EC requirements for continuing review, this may be requested from the protocol team, with the request emailed to the clinical research manager (CRM). During the ongoing conduct of a study, available information will be limited.

13.4 IMPAACT Leadership Oversight

The IMPAACT MOG monitors network studies with regard to protocol development, study implementation, analysis, and reporting.

Routine MOG oversight includes evaluation of study progress with respect to key milestones; the MOG also monitors resource allocation and use across studies. In support of the MOG's oversight function, a Study Operations Report is generated each month by the Operations Center with updates on the status of each study and any study implementation issues and problems; similar information is included in the report for protocols in development. Other data reports are generated for the MOG by the SDMC as needed. Members of the MOG who represent the SDMC, LC, and Operations Center may also bring issues to the attention of the MOG. The MOG reviews proposals from protocol teams to modify protocols and/or study implementations plans (e.g., to expand to additional sites) as needed (see Sections 9 and 10). MOG discussion and decision-making is documented in conference call and meeting summaries, and decisions and recommendations are formally communicated to protocol teams when applicable. Also,

when applicable, the MOG coordinates with NIH to assess and respond to needs for additional resources, for example, because of unexpected costs associated with planned study procedures or to support additional sites or ancillary studies.

The MOG is supported in its oversight role by independent SMC reviews of selected studies, as described in Section 13.5.

13.5 IMPAACT Study Monitoring Committee Review

In support of the management and oversight functions of the MOG, for designated studies, an IMPAACT SMC monitors participant safety and the progress and quality of IMPAACT study conduct. Based on its reviews, the SMC makes recommendations related to study continuation, including cohort progression and dose selection, when applicable. The scope of SMC reviews varies across studies, depending on protocol specifications. The policies and procedures included in this section are followed for all IMPAACT studies subject to SMC oversight, in lieu of study-specific SMC charters; these procedures may be supplemented or amended if needed for individual studies, consistent with protocol specifications.

13.5.1 SMC Membership

For each study that is subject to SMC oversight, SMC membership includes:

- SMC chair
- IMPAACT Network chair or vice chair
- IMPAACT Scientific Committee (SC) representative
- IMPAACT Operations Center representative
- IMPAACT Statistical and Data Analysis Center (SDAC) representative
- IMPAACT Laboratory Center (LC) representative
- DAIDS representative
- NICHD representative

In addition to the above, other relevant content area reviewers (e.g., pharmacology reviewer) may be added as needed. When applicable, SMC members may fill multiple roles; for example, when the SMC chair is a member of the relevant SC, they may serve as both the SMC chair and SC representative. While SMC membership may vary across studies, every effort is made to maintain consistent composition for each study over time.

The SMC chair and an alternate chair are appointed by the MOG; other SMC members are designated by the organization they represent. The appointed chair serves in this role unless they are conflicted due to study involvement (see below) or other potential conflicts of interest (see Section 7). When the appointed chair has a conflict, the appointed alternate serves as chair. Given conflict of interest and quorum requirements (described below), the Operations Center, LC, and SDAC may designate two representatives to the SMC; if this is done, the two members provide consensus input to SMC recommendations. For regulatory purposes, all SMC members must provide updates of their resumes to the Operations Center approximately every three years.

SMC members are independent of each study under review. They may not be members of the protocol team or directly involved in the conduct of the study at a study site. If affiliated with a study site, SMC members should have no expected involvement in study or participant management at the site. In addition, all SMC members must comply with the financial disclosure requirements and responsibilities described in Section 7.

The following SMC members comprise the quorum for SMC decision-making: SMC chair (or alternate chair), DAIDS representative, and one representative each from the Operations Center and SDAC. These members must take part in each review. For reviews that take place via conference call, these members must attend the call or provide written review comments in advance if they cannot attend the call. In the latter scenario, an alternate representative of the IMPAACT Operations Center, SDAC, and DAIDS may be designated to attend the call (written review comments must still be provided in advance by the SMC member). Alternatively, the NICHD representative may serve in place of the DAIDS representative. In the event the SMC chair cannot attend the call, another SMC member may be designated to serve as chair during the call; the SMC chair must provide written review comments in advance. If quorum requirements are not met, the review will be postponed.

13.5.2 SMC Review Process

SMC reviews typically take place via conference call; in-person or email reviews may also occur. Convened conference call reviews typically include open and closed review sessions and may include executive sessions as described in Sections 13.5.2.1–13.5.2.3. The Operations Center schedules and coordinates all reviews. In the event that an SMC member is not available to take part in a review, they may provide written review comments in advance of the review (see Section 13.5.1 for quorum requirements).

Protocol team members, including the protocol chair(s), protocol pharmacologist(s) (as applicable), NIH medical and program officers, and CRMs generally attend open review sessions. Protocol statisticians attend both open and closed sessions. Other team members who are designated in the SPDSMP to receive SMC data reports may attend open sessions at the discretion of the protocol chair.

The scheduling of SMC reviews is coordinated by the Operations Center. SMC review requirements are noted in the Study Operations Reports generated each month and these notations may serve as a guide for when reviews are required. Protocol teams are responsible for awareness of when reviews are expected to take place and proactively planning for all scheduled reviews. Protocol statisticians should lead planning efforts within the team, including but not limited to establishing timelines for drafting and finalizing data reports and other materials for review, and should coordinate with the Operations Center to identify potential review dates and timelines for distributing materials to the SMC. Materials prepared for SMC review must adhere to good documentation practices and are distributed using secure methods when individual participant data or analysis results are included.

A summary of roles, responsibilities, and timelines associated with SMC reviews is provided in Table 13-1, with additional description below. For each study, roles, responsibilities, and the scope of SMC oversight are directed by the protocol and the SPDSMP. The SMC typically monitors the quality of study conduct, participant safety, and other key issues through review of indicators such as participant accrual, participant retention, compliance with/deviations from the study protocol, adherence to the study intervention, data quality, data completeness, specimen availability, endpoint evaluability, and adverse events as indicated in the SPDSMP; pharmacokinetics (PK) findings and other study outcome measures may also be reviewed if specified in the protocol and/or SPDSMP. Reviews may evaluate the safety, efficacy, and/or feasibility of the study as designed and determine whether modification may be required to minimize risks to study participants or meet study objectives.

Table 13-1. Summary of SMC Roles and Responsibilities

Person Responsible	Role/Responsibility	Timeline
SMC chair	• Review data reports and other submitted materials	• Prior to each review
	• Request clarification of materials submitted for review via email (copying other SMC members)	• Prior to each review (as needed)
	• Lead all review sessions, ensuring input and discussion as needed from all SMC members	• During each review
	• Ensure that findings, recommendations, action items, and next steps are agreed upon prior to the close of each review	• During each review
	• Coordinate with Operations Center representative to draft summary review reports for review by SMC members and then finalize these reports	• Ideally within 3-5 working days after each review
	• Coordinate with Operations Center representative to receive and review protocol team responses to review reports	• Following each review (as applicable)
	• Coordinate with Operations Center representative to finalize a memorandum documenting the review for study sites	• Ideally within 7 working days after the final outcome of each review
	• Liaise with the IMPAACT MOG regarding SMC operations, review findings, and recommendations	• As needed
SMC members	• Review data reports and other submitted materials	• Prior to each review
	• Request clarification of materials submitted for review via email (copying other SMC members)	• Prior to each review (as needed)
	• Provide review comments and recommendations	• During each review
	• Optionally review and provide feedback on draft summary review reports	• Typically within 2 working days after receipt of draft review report
Operations Center representative to the SMC (in addition to other SMC member roles and responsibilities)	• Coordinate with protocol statistician and CRM to schedule SMC reviews	• Ongoing based on study-specific needs
	• Coordinate review conference calls; distribute administrative information in support of each review	• Approximately 2-4 weeks prior to each review
	• Coordinate with SMC chair to draft summary review reports for review by SMC members and then finalize these reports	• Following each review
	• Distribute final summary review reports to protocol teams	• Ideally within 3-5 working days after each review
	• Coordinate with SMC chair to receive and review protocol team responses to summary review reports	• Following each review (as applicable)
	• Coordinate with SMC chair to prepare a memorandum documenting the review for study sites and coordinate with the CRM to distribute the memorandum to participating sites	• Ideally within 7 working days after the final outcome of each review
	• Coordinate with the CRM to include relevant information in Study Operations Reports	• Monthly when applicable

Table 13-1. Summary of SMC Roles and Responsibilities

Person Responsible	Role/Responsibility	Timeline
Protocol statistician	• Coordinate with the Operations Center and the protocol pharmacologist when applicable to schedule SMC reviews • Prepare and distribute draft open data reports for selected protocol team member review • Finalize and distribute data reports and other materials for SMC review*** • Take part in open and closed review sessions; provide an overview of the data report during review sessions; respond to SMC questions	• Ongoing based on study-specific review needs • At least 9 working days prior to each review* • At least 4 working days prior to each review** • During each review (open and closed sessions)
Protocol Data Manager	• Notify sites of upcoming SMC review and timelines for data keying and query responses, noting critical data for review • Review targeted data for SMC and issue queries, as needed • Generate reports and/or datasets for protocol statistician per the SPDSMP	• Prior to each review • Prior to each review • Prior to each review*
Laboratory Data Manager	• Review targeted data for SMC and issue queries, as needed • Generate reports and/or datasets for protocol statistician per the SPDSMP	• Prior to each review • Prior to each review*
Protocol chair	• Review draft data reports and other materials to be submitted for SMC review • Take part in open review sessions; during these sessions, provide a brief synopsis of study status, key issues and problems (if any), and strategies undertaken or planned to address these; identify issues that the protocol team would like to bring to the SMC's attention for consultation and feedback; respond to SMC questions	• 7-9 working days prior to each review • During open review sessions
Protocol pharmacologist (as needed for SMC reviews of pharmacology data)	• Coordinate with the protocol statistician and Operations Center to schedule SMC reviews • Prepare and distribute draft data reports for protocol team member review • Coordinate with protocol statisticians to finalize and distribute data reports and other materials for SMC review*** • Take part in open review sessions; provide an overview of the pharmacology data report during review sessions; respond to SMC questions	• Ongoing based on study-specific review needs • At least 9 working days prior to each review* • At least 4 working days prior to each review** • During open review sessions
Medical Officers	• Review draft data reports prepared by the protocol statistician and other materials to be submitted for review when applicable • Take part in open review sessions; respond to SMC questions when applicable	• 7-9 days working days prior to each review • During open review sessions

Table 13-1. Summary of SMC Roles and Responsibilities

Person Responsible	Role/Responsibility	Timeline
Other protocol team members, as applicable based upon the content of the review	• Review draft data reports prepared by the protocol statistician and other materials to be submitted for review when applicable • Take part in open review sessions; respond to SMC questions when applicable	• 7-9 days working days prior to each review • During open review sessions

*Sufficient time should be allowed for applicable team members to review data reports and other materials to enable distribution of final materials to the SMC at least three working days prior to each review. If timeline is unlikely to be met, SDAC will inform the protocol team.
**For example, for SMC reviews scheduled on a Friday, materials should be distributed to the SMC on the preceding Monday.
***All materials submitted for SMC review must comply with good documentation practices.

13.5.2.1 Open Review Sessions

SMC reviews typically include an open session to provide an opportunity for the protocol chair and other protocol team members, if applicable, to discuss the study with the SMC. For such sessions, the SMC and designated protocol team members are provided with an open report containing relevant monitoring data as defined in the SPDSMP. For reviews that include separate data reports for open and closed sessions, the data contained in open and closed reports are based on the same dataset, but open reports present data pooled across study arms.

During open review sessions, protocol chairs are not expected to provide a formal presentation to the SMC but should provide a brief synopsis of study status, key issues and problems (if any) with respect to study implementation, and strategies undertaken or planned to address these. With respect to safety and PK data (when applicable), the protocol chair may summarize the team's overall assessment of currently available data. The protocol chair may also identify issues the protocol team would like to bring to the SMC's attention for targeted consultation and feedback. In addition to the protocol chair's synopsis, the protocol statistician will provide an overview of the data report that serves as the basis for the review; the protocol pharmacologist may likewise provide an overview of any PK reports provided for review. The protocol statistician is generally expected to present the report on screen, displaying the key data highlighted in their overview. Slide presentations are not expected unless requested by the SMC. These overviews and presentations are expected to be brief and typically no longer 20 minutes. SMC members may ask questions of the protocol chair, statistician, and other team members, requesting their insights into data presented in open reports and further clarifying issues, problems, and strategies to address these.

For non-comparative studies, SMC members may provide assessments of the quality of study conduct, participant safety, and other key issues during open sessions or they may choose to further discuss these assessments in closed review sessions before providing consensus findings and recommendations to the protocol team.

13.5.2.2 Closed Review Sessions

SMC reviews typically include a closed session in which SMC members assess the quality of study conduct, participant safety, and other key issues and agree upon consensus findings and recommendations. For comparative studies, closed sessions may include review of closed reports with data presented by study arm. Study arms are typically coded to avoid unnecessary unblinding, but coding keys are provided in the event the SMC determines that unblinding is necessary to protect participant

safety or evaluate study integrity. If an SMC member wishes to discuss results by unblinded study arm, the SMC chair must first confirm that all members of the SMC agree to being unblinded.

Participation in closed review sessions is limited to SMC members and the protocol statisticians unless exceptions are requested by the SMC or specified in the SPDSMP. Closed data reports are considered confidential, to be distributed only to designated SMC members. However, distribution to others may be permitted on a case-by-case basis in consultation with the SMC chair and the MOG.

13.5.2.3 Executive Review Sessions

SMC reviews may include an optional executive session, attended only by SMC members, to review selected data or otherwise take part in discussions that are limited to SMC members only. These sessions differ from closed sessions in that the protocol statisticians are not included.

13.5.3 Types of SMC Review

13.5.3.1 Initial Review

Studies subject to SMC review undergo an initial SMC review in which a draft SPDSMP is reviewed, along with the draft protocol (unless already finalized and posted on the study website), and discussed in detail with the protocol chair, statistician, CRM, MOs, and other team members. CRMs, in close coordination with statisticians, will coordinate scheduling of the initial SMC review. Typically, the protocol statistician distributes the draft SPDSMP and any other documents (e.g., draft Pharmacology Data Management Plan), which are expected to describe key aspects of study monitoring or are otherwise referenced in the SPDSMP, to the SMC no later than four working days prior to the review date (for example, for SMC reviews scheduled on a Friday, materials should be distributed to the SMC on the preceding Monday). Protocol team members should not be copied on submissions to the SMC; however, they may be notified once submission is complete.

This initial review should ideally take place in the late stages of protocol development to enable the SPDSMP and other relevant documents to be finalized prior to opening the study to accrual. The purpose of this review is to orient SMC members to the study protocol, agree upon key specifications of the SPDSMP, the required frequency of SMC reviews for the study, criteria for triggered SMC reviews, if applicable, and the data to be presented in reports prepared for SMC review. The SPDSMP and any other applicable documents are finalized after the initial SMC review takes place and SMC review comments are addressed.

The protocol chair should work with the protocol statistician and other team members as needed to prepare a presentation for the initial review. The protocol chair or protocol statistician distributes the presentation to the SMC, no later than the day prior to the scheduled review. During the open review session, the protocol chair should present a brief overview of the study, focusing on the rationale, objectives, and design. The protocol chair may also highlight key issues the protocol team would like to emphasize for consideration by the SMC. This presentation should be completed in no more than ten minutes. Following this introduction, the protocol statistician may briefly highlight the statistical design of the study and present key aspects of the SPDSMP, including an overview of the types of monitoring data reports that will be provided to the study team and to the SMC. Any protocol-specified triggers for *ad hoc* SMC reviews should also be noted. This presentation should be completed in no more than 15 minutes.

Following the presentations, the SMC will discuss the SPDSMP and other materials submitted for review. A written report documenting the review discussion and delineating SMC feedback on the team's materials will be provided following the review (see Section 13.5.4). It is generally expected that the protocol team will be asked to revise the SPDSMP and other materials submitted for review based on SMC feedback; the statisticians will then submit the revised documents to the SMC for additional review. A response document is not typically required; however, in some cases, the SMC may ask for specific responses or clarifications from the protocol team. The process of preparing and submitting the response is typically coordinated by the CRM. Protocol teams should review and provide feedback on the response, though sign-off is not required. The SMC will provide a final memorandum to the protocol team, documenting any further comments, or to confirm no further comments. Unless otherwise specified, this additional review is expected to be completed via email.

13.5.3.2 Reviews During Study Implementation

If memoranda are prepared by the protocol team during study implementation for routine, event-driven, or interim analysis reviews, either in response to prior reviews or in advance of an upcoming review, the CRM coordinates preparation, review, sign-off (see Section 13.5.5), and submission. Scheduling and other administrative questions and clarifications, regardless of format, do not require sign-off. Due to their urgent nature, materials shared with the SMC in advance of triggered or emergent safety reviews do not require sign-off. Data reports developed and finalized by the SDMC or protocol pharmacologists must be reviewed following the processes above (see Section 13.5.2) but do not require sign-off.

Routine Reviews

For most studies, the primary purpose of SMC reviews is to routinely assess whether the study is proceeding as expected with respect to participant safety and the timeliness and quality of study conduct. Routine reviews should occur at least annually. More frequent reviews may be conducted per protocol or as requested by the SMC or MOG.

Event-Driven and Interim Analysis Reviews

For some studies, the protocol and SPDSMP may require SMC review of interim analyses or when certain pre-specified criteria are met (e.g., when sufficient data have been accumulated to support decision-making on cohort progression or dose confirmation or comparing data across arms). The timing of these reviews may be periodic, event-driven, or upon request by the protocol team, SMC, or MOG.

Triggered or Emergent Safety Reviews

Protocols may also specify SMC review when certain safety triggers are met. Emergent safety issues not otherwise specified in a study protocol may also require SMC review. For triggered or emergent safety reviews, timelines for scheduling, preparation and distribution of data reports, and documentation of review findings and recommendations may be truncated.

13.5.4 Documentation and Response to SMC Reviews

As part of each review, the SMC will agree upon consensus findings, recommendations, action items, and next steps. With respect to ongoing conduct of the study, recommendations will typically be made within the following categories:

(A) Continue as currently designed
(B) Continue with recommended modifications
(C) Discontinue study implementation

Review findings, recommendations, action items, and next steps will be documented in a summary review report drafted by the Operations Center and reviewed by the SMC chair prior to distribution. Other SMC members who took part in the review will be provided an opportunity to review the draft report prior to finalization; however, review by all SMC members is not required prior to finalization. Every effort will be made to finalize and distribute the review report to protocol team members within three to five working days after the review; the final report will also be provided to all SMC members. The MOG will be informed of review outcomes and recommendations at the time of their next scheduled call or meeting unless a more immediate notification is required (e.g., when recommendations involve significant protocol modifications or discontinuation of study implementation). Memoranda documenting SMC reviews that occur during study implementation will also be provided to participating study sites by the Operations Center for submission to IRBs/ECs and other applicable review bodies within approximately one week after the final summary to the team. Summary review reports, memoranda, and other communications from the SMC will adhere to good documentation practices.

When requested by the SMC, protocol teams will respond to SMC findings and recommendations. Responses will be reviewed for adequacy and completeness by the SMC chair, with support from the Operations Center and other SMC members as needed. In the event that the SMC chair assesses that the team's response is not adequate or complete, communication with the team will continue until satisfactory resolution. Completion of this process will be documented in a memorandum to the protocol team and in the monthly Study Operations Report.

13.5.5 Protocol Team Review and Sign-Off

Protocol team members are expected to review materials for submission to the SMC within agreed-upon timelines. For materials other than data reports prepared by the SDMC or pharmacologist and when sign-off is required, the CRM requests sign-off from one protocol chair (chair, co-chair, or vice chair), one statistician/epidemiologist, one PDM, and one DAIDS MO; when the materials involve PK considerations, sign-off must also be obtained from one protocol pharmacologist.

13.6 Sponsor Oversight

As sponsor of IMPAACT studies, the NIH has regulatory responsibility for oversight and monitoring of IMPAACT studies. As part of fulfilling these responsibilities, NIAID requires IMPAACT sites to develop and implement a CQMP, and NIAID and NICHD contract with clinical site monitors to perform on-site monitoring at the IMPAACT-affiliated sites that they fund, as described in Sections 13.1 and 13.2. NIAID and NICHD staff (or their contractors) work with study sites as needed to address monitoring findings and other study implementation issues or problems. When issues or problems necessitate suspension of study implementation at a site, procedures described in Section 13.7 are followed.

NIH medical and program officers are also active in overseeing study implementation as part of protocol teams and as members of the IMPAACT leadership (see Sections 13.3 and 13.4).

For some IMPAACT studies, NIAID convenes DSMB reviews as part of its study oversight responsibilities, as described in Section 13.8.

13.7 IMPAACT Network Issue Escalation

13.7.1 Overview

Issues or problems identified by any protocol team member or Network entity (including other central resource members or site and laboratory staff) during review of study-specific reports, site visits, or other means, should be raised for discussion to the protocol team. The protocol team will determine follow-up and requested corrective actions, as needed. If any issues arise during the study that are site-specific, the relevant IoR should also be informed, and the site's issue-escalation procedures should be followed.

The Network leadership (including the chair and content-specific leadership members [e.g., LC PI or SDMC PIs]) should be notified by the protocol chair and/or relevant protocol team members, as appropriate, if any issues arise during a study that could:

- Significantly compromise study outcomes or integrity
- Require additional time or Network/sponsor resources to investigate and resolve
- Affect other Network studies, and/or
- Require specific communications with pharmaceutical collaborators

Such matters may be referred to the MOG for further review, guidance, and decision-making.

13.7.2 Site Suspension Process

Serious and/or persistent non-compliance with protocol, regulatory, or grant requirements may result in temporary or permanent suspension of study-specific activities, network-specific activities, or all DAIDS-sponsored research being conducted at a site. Concerns with site conduct may be identified at multiple levels, including by the sponsor, clinical site monitors, protocol teams, and IMPAACT Network central resources (i.e., Operations Center, LC, SDMC).

If any of these individuals become aware of significant concerns about a site's implementation of a study, they should ensure that the organization escalation pathways are followed; these generally should include ensuring that the protocol chair(s), MOs, site IoR, and other site leadership are aware of emerging concerns. This may include site team consultation with the study protocol team and/or Clinical Management Committee. It is also generally expected that the IoR will ensure that the CRS leaders, Clinical Trials Unit (CTU) leaders, and other relevant site staff are aware as per site escalation procedures.

The concerns should also be shared with IMPAACT leadership through communication to the MOG. The MOG, in close consultation with DAIDS and NICHD representatives on the MOG, makes a determination on whether a suspension (e.g., enrollment pause) should be recommended and whether study-specific nuances should be specified. The OCSO Network Liaison, OCSO Program Officer (PO), or Westat manager should be informed of this recommendation.

Regardless of who identifies the concern, the site suspension communications and process will be managed by the DAIDS OCSO for NIAID-funded sites and by Westat for NICHD-funded sites, unless an urgent safety concern is identified requiring immediate notification (e.g., of a pause in enrollment) by the Network.

13.7.3 Communication of Site Suspensions and Resolution

The OCSO PO (or Westat manager) and relevant stakeholders will review concerns and make a determination on whether a suspension should be enacted. The OCSO PO (or Westat manager) notifies the site leadership, including the CRS leader, CRS coordinator, and (if applicable) CTU leaders, as well as IMPAACT.SiteActions@fstrf.org, which includes the Network Chairs and key contacts within Operations Center, SDMC, and LC. The IMPAACT Operations Center will also notify the relevant protocol chair(s) and team members. The relevant Network central resource group representatives on the MOG will further circulate the suspension notification to relevant central resource group members, as needed.

In rare but urgent cases when it may not be possible to notify OCSO or Westat manager in advance, such as an immediate safety concern, the MOG may issue a site suspension notification to the site directly, copying the OCSO PO and OCSO Network Liaison or the Westat manager.

At the time of site notification of the suspension, Network members will complete any necessary follow-up actions (e.g., closing enrollment screens by the DMC). The site will complete corrective and preventive actions (CAPA) and forward responses to OCSO or Westat, IMPAACT leadership, and applicable central resource group members. IMPAACT leadership and central resource group members will work with OCSO/Westat to review the CAPA and determine when the suspension should be lifted. Once concerns are resolved and OCSO/Westat, in consultation with the MOG, agrees that the suspension can be lifted, the OCSO PO/Westat communicates the decision to the site.

13.8 Data and Safety Monitoring Board Reviews

DSMB reviews are most commonly convened for large, randomized studies; however, other types of IMPAACT studies may be subject to DSMB review. NIAID decides which studies require DSMB review and coordinates all DSMB activities; for studies that are subject to DSMB review, reviews are conducted at least annually and in accordance with relevant NIAID standard operating procedures, which can be found at https://www.niaid.nih.gov/research/data-and-safety-monitoring-boards. DSMB members are independent of the studies they review, with no financial interest in the outcomes of the studies they review. Members include experts in the fields of HIV/AIDS, biostatistics, and medical ethics. Appointments to the DSMB are made by NIAID.

13.8.1 Preparation for and Participation in Reviews

The SDMC prepares data reports for DSMB review; other materials (e.g., memorandums, slide presentations) may also be prepared by the protocol team. Protocol team members designated in the SPDSMP to receive DSMB data reports are provided an opportunity to review draft reports and other materials planned to be discussed with the DSMB.

Representatives of the protocol team — including protocol chairs, statisticians, CRMs, and MOs — attend DSMB reviews in person or virtually. Similar to procedures described for SMC reviews, team members designated in the SPDSMP to receive open DSMB data reports typically attend open review sessions to discuss study progress, present blinded data (pooled across randomization arms), and respond

to questions from the DSMB. Statisticians also attend closed review sessions to present data by coded randomization arm and respond to questions from the DSMB.

Prior to each review, the Operations Center coordinates with the DAIDS Maternal, Adolescent and Pediatric Research Branch (MAPRB) Chief to schedule a conference call with IMPAACT leadership soon after the review date (typically within two days) to discuss any significant DSMB recommendations. If, based on the review findings and recommendations, the call is not required, it will be canceled. If the call is required, participants include:

- IMPAACT Network chair and vice chairs
- Relevant SC chair
- Protocol chair(s)
- Operations Center Director and protocol CRM
- SDMC principal investigator (PI) and protocol statistician
- LC principal investigator
- DAIDS Prevention Science Program Director
- DAIDS MAPRB Chief
- Protocol NIH medical and program officers
- Others as required

13.8.2 Review Findings and Recommendations

At the close of each review, the DSMB's findings and recommendations may be provided to team members who attended the review, depending on the nature of the recommendations (see Section 13.7.3). The findings and recommendations are communicated within DAIDS/NIAID and NIAID leadership has ultimate responsibility for determining whether to accept the recommendations. Recommendations may involve continuing a study as currently designed or modifying or stopping a study, for the following types of reasons:

- The study question has been answered
- The study question will not be answered
- The study question is no longer relevant
- Unacceptable risk to participant safety
- New information from other research is now available

Within approximately two weeks after each review, a summary of the review is distributed to the protocol team and participating study sites by DAIDS and its contractors. If requested in the summary report, the protocol team will submit a written response to the DSMB (with sign-off per Section 13.5.5); otherwise, the team response will be included in the data reports for the next DSMB review. Study sites must submit the summary of the review to their IRBs/ECs and other applicable review bodies; protocol teams may provide supplemental materials to sites for submission along with the summary.

13.8.3 Response to Significant Recommendations

If the DSMB recommends significant modifications of a study (e.g., early termination, closure of one or more randomized groups), this information will be immediately communicated to DAIDS/NIAID leadership, and NIAID leadership will determine whether to accept the recommendations. IMPAACT leadership and protocol team members will be informed of the recommendations and the NIAID decision during the conference call (described in Section 13.7.1) scheduled to take place soon after the review. During this call, immediate next steps, action items, and timelines will be agreed upon. Subsequent

communications among the protocol team and with study sites will be coordinated by the Operations Center in close collaboration with the protocol chair(s) and NIH medical and program officers; NIAID will assume primary responsibility for any public statements or press release associated with the DSMB recommendations.

In the event that a press release is planned, DSMB review findings and recommendations should remain confidential prior to the public release. Nonetheless, site investigators will be informed of the findings and recommendations with adequate advance notice to inform their IRBs/ECs and other review bodies in a timely and appropriate manner. In addition, priority will be given to informing study participants and other community stakeholders as soon as possible. To facilitate timely and appropriate communication, protocol teams should establish tentative communications plans (roles, responsibilities, timelines) in advance of DSMB reviews. See Section 12 for additional information on protocol team communications that may be applicable in this context.

14 SITE STUDY-SPECIFIC CLOSE-OUT

14.1 Overview, Key Principles, and Definitions

The term "close-out" refers to procedures undertaken to fulfill protocol, administrative, regulatory, and human participant requirements after all participant follow-up in an IMPAACT study has been completed. These procedures may include protocol-specified laboratory testing, data cleaning, locking the study database, and ensuring appropriate final disposition of study products and stored specimens. These activities and the use of the term "close-out" are independent of study closure with each study site's Institutional Review Boards/Ethics Committees (IRBs/ECs) and other regulatory entities.

Some of the procedures outlined below may require modification for a study that closes earlier than planned according to the study design. For example, early study closure may be recommended by a Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC) at an interim analysis review or due to the inability to meet accrual goals (see Section 13).

The timeline and procedures described in this section are overlapping but distinct from timelines and procedures for analysis, manuscript development, and publication procedures. Refer to Section 19 for more information on analysis, ClinicalTrials.gov results entry, manuscript development, publication procedures, and concluding a study.

Table 14-1 provides definitions of terms used when describing activities related to study close-out. Some of these terms are Network-specific; the sources of others are National Institute of Allergy and Infectious Diseases/Division of AIDS (NIAID/DAIDS) or ClinicalTrials.gov.

Table 14-1. Definitions of Terms

Term	Definition
Closed to Follow-up *[DAIDS Study Status]*	The study has been permanently closed to accrual, all participants have completed study agents/products and all follow-up visits have been completed. Last participant has completed the last study visit (may also be referred to as LPLV) and all participants are "off study." Equivalent to "Study Completion Date" in ClinicalTrials.gov.
Data Entry Termination Date	Date by which sites enter all new case report form (electronic CRF [eCRF]) data.
Participant Unblinding	"Unblinding a study" may refer to: (1) informing participants of their blinded treatment codes, (2) informing the sites of the blinding codes for their participants, or (3) informing protocol chair(s) or other medical investigators of the study results or treatment codes. See Appendix I for a full description of unblinding in IMPAACT studies.
Primary Completion Date (PCD)	Date that the final participant was examined or received an intervention for the purpose of the final collection of data for the primary outcome measures. May or may not be the same as the closed to follow-up date, depending on the study design.
Rave Database Lock/Primary Laboratory Data Complete	The eCRF data and the primary laboratory data are complete so the final analysis can be completed. The Rave database is locked, and routine queries and edits have ceased; non-eCRF laboratory data that are to be included in the primary publication have been finalized and made available to the party conducting the analysis.

14.2 Timeline for Study Close-Out

The timeline for study close-out is in relation to the closed to follow-up date for the study. The protocol team will begin planning for study close-out approximately four to six months prior to the anticipated closed to follow-up date. The protocol statistician(s) and the protocol data manager (PDM) – in consultation with the protocol clinical research manager (CRM) – will provide the protocol team with information on the projected primary completion date (PCD) and the projected date or date range for closed to follow-up for the study, respectively. Initial projections are typically updated upon completion of accrual into the study. Thereafter, projections are updated as needed depending on the study design and planned duration of participant follow-up.

Depending on the study design, the closed to follow-up date may be the same or different than the PCD. See Section 19 for further details on the PCD. The Statistical and Data Management Center (SDMC) will work with other team members to generate a timeline for completion of data entry, resolution of data queries, shipping of specimens, testing of specimens, and locking the study eCRF database to comply with the recommended study analysis timelines provided in Section 19 and the requirements for data entry per ClinicalTrials.gov provided in Section 7.

The protocol statisticians and PDM are responsible for notifying the protocol team of the anticipated and actual PCD and closed to follow-up dates, respectively. The DAIDS Monitoring Operations Branch (MOB) will also be included on these notifications, and the CRM will invite MOB representatives to participate in team calls and discussions that involve study closure timelines using the DAIDS MOB email alias, ocsomob@mail.nih.gov.

Procedures for data entry and clean-up, resolution of data queries, and database lock, if applicable, for all data should be initiated upon confirmation of the PCD and/or closed to follow-up date. The PDM notifies

the protocol team and the study sites of the closed to follow-up date. The Operations Center is responsible for informing DAIDS Regulatory Support Center (RSC) Clinical Study Information Office (CSIO).

The typical close-out timeline is shown in Table 14-2; however, this may be condensed or modified for studies that have a short duration of follow-up, studies with accrual targets based on determination of evaluability, studies preparing for a regulatory submission, and/or those that are closed early (e.g., at the recommendation of the DSMB or SMC).

Table 14-2. Timeline for Study Close-Out Procedures

Event	Timeline *(time from closed to follow-up date)*	Procedures	Responsibilities
Prior to Closed to Follow-Up Date			
Protocol Team Planning for Closed to Follow-Up	Approximately 6 months (26 weeks) prior	• Notify protocol team and DAIDS MOB of upcoming closed to follow-up date • Facilitate discussion of close-out preparations (through pre-closure conference call or standing agenda item on team calls, including DAIDS MOB representatives) • Begin work on close-out and analysis timeline and consideration of study-specific issues related to study close-out, including: – Prepare Site Considerations for Study Close-Out memorandum – Prepare specimen shipping and testing plan for laboratory specimens – Confirm that Material Transfer Agreements (MTAs), export/import permits, and/or Specimen Transfer Agreements (STAs) are in place/updated as needed to facilitate specimen shipments – Confirm Data Transfer Agreements (DTAs)	PDM CRM Protocol team CRM Laboratory Data Manager (LDM) Laboratory Center (LC) LDM
Site Considerations for Study Close-Out Memorandum	Approximately 2-3 months (8-12 weeks) prior	• Finalize memorandum to sites • Distribute Site Considerations for Study Close-Out memorandum to sites	CRM with protocol team CRM
Site Implementation of Study-Specific Close-Out Procedures	Approximately 2-3 months (8-12 weeks) prior	• Develop operational and staffing plans for completion of all required study close-out procedures as listed in the Site Considerations for Study Close-Out memorandum	Sites
Following Closed to Follow-Up Date			
Final Closed to Follow-up Notification	Approximately 1 week after	• Notify protocol team, DAIDS MOB, and sites of closed to follow-up completion • Notify the DAIDS RSC CSIO of study status change to closed to follow-up	PDM Operations Center
Final Visit Data Entry	2 weeks after	• Enter all participant visit data by this date	Sites

Table 14-2. Timeline for Study Close-Out Procedures

Event	Timeline *(time from closed to follow-up date)*	Procedures	Responsibilities
Specimen Shipment Request Lists Distributed	2 weeks after	• Distribute specimen shipment request lists to sites/laboratories, as applicable to primary outcome evaluation (and secondary or other outcomes, as needed)	LDM
Entry of all Remaining Data and Distribution of Data Queries	4 weeks after	• Ensure data completeness (collection and verification of all available study outcome data) • Distribute queries (e.g., data and laboratory) to sites and laboratories to resolve data discrepancies	PDM PDM, LDM
Notification of Upcoming Rave Database Freeze and Lock	10 weeks after (4 weeks prior to Rave database lock date)	• Notify sites of the upcoming Rave database freeze and lock dates	PDM
Submission of Laboratory Data to DMC	12 weeks after	• Submit laboratory data to DMC • Confirm laboratory data received by DMC	Testing Laboratories LDM
Monitoring Complete	Prior to database freeze	• Notify DMC that all monitoring, including verification of the Rave data, is complete	DAIDS OCSO MOB or Westat (if applicable) representatives
Rave Database Freeze	15 weeks after	• Complete Rave database freeze • Request site Investigator of Record (IoR) signatures • Sign off on eCRFs	PDM PDM IoRs
Rave Database Lock/Primary Laboratory Data Complete	21 weeks after	• Complete Rave database lock • Confirm primary laboratory data are complete • Notify protocol team and sites when the Rave database is locked, and the primary laboratory data are complete	PDM PDM, LDM PDM
Note: For more information on analysis, manuscript development, and publication procedures, refer to Section 19. For more information on specimen storage for future use and distribution of specimen destruction instructions, refer to Section 17.			

14.3 Study Close-Out Communications and Considerations for Sites

The protocol team is responsible for addressing all unresolved issues related to study closure (e.g., confirming procedure for reporting adverse events, unblinding), defining study-specific close-out milestones and requirements, and developing appropriate study-specific close-out communications for sites regarding study closure and data analysis (refer to Table 14-2 for details on procedural timelines and responsibilities). Protocol teams will develop a Site Considerations for Study Close-Out memorandum to be distributed to all participating sites along with additional communications as described below.

The PDM(s) – in collaboration with the study sponsor, CRM(s), statistician(s), LDM(s), and LC representative(s) – will help study sites complete required study close-out data management procedures, distribute appropriate communications regarding Rave database lock and data analysis, and distribute queries to sites to resolve data discrepancies; for laboratory-related queries, the LDM(s) distribute communications and queries.

Sites are responsible for completing required study close-out procedures according to the timelines provided by the protocol team. The study-specific IoR is ultimately responsible for ensuring all site requirements are met. Sites will develop operational and staffing plans for completion of all required study close-out procedures as listed in the Site Considerations Study Close-Out memorandum.

Study close-out communications will be developed by the protocol team, with instructions and considerations tailored to study-specific needs and protocol requirements, as described below:

- Site Considerations for Study Close-Out memorandum (*approximately two to three months prior to the anticipated closed to follow-up date*): detailed considerations for study close-out are distributed to participating sites. The memorandum generally addresses:

  - Reason for closure as well as the anticipated closed to follow-up date
  - Any study-specific guidance related to final participant visits and participant transition plans
  - Guidance on informing participants, parents/guardians, community advisory boards, and other key stakeholders of forthcoming study close-out status, participant transition plans (as appropriate), and plans for disseminating study results (if known; see Section 19)
  - IRB/EC and other regulatory entity communications
  - Guidance on protocol deregistration
  - Laboratory considerations (e.g., specimen storage, shipping timelines, destruction)
  - Pharmacy considerations (e.g., study product storage, post-study access, disposition)
  - Data management considerations (e.g., timelines for completion of data entry, resolution of data queries, locking the study database, and eCRF IoR signature requirement)
  - Unblinding considerations (if applicable)
  - Regulatory and other essential document considerations, including any study-specific record retention requirements

  The CRM, in collaboration with the protocol team, is responsible for preparing the draft memorandum and coordinating the development, review, and distribution of this memorandum. The protocol team is responsible for contributing to and reviewing the draft memorandum. Sign-off is required from one protocol chair (chair, or vice chair), one CRM, one DAIDS Medical Officer (MO), and one PDM; if laboratory considerations are included, sign-off from one LDM and one LC representative is required; if pharmacy considerations are included, sign-off from one protocol pharmacist is also required. Sign-off requirements must be completed before the memorandum is distributed to participating sites.

- Final Closed to Follow-up Notification (*approximately one week following the closed to follow-up date)*: a final confirmation notification is distributed to participating sites. This notification includes the closed to follow-up date as well as any additional details or clarifications, as needed. This notice is generally distributed to sites by the PDM.

- Notification of Upcoming Rave Database Freeze and Lock *(approximately ten weeks following the closed to follow-up date and approximately four weeks prior to the anticipated Study Database Closure date)*: an initial notification of the forthcoming Rave database freeze and lock dates is distributed to participating sites by the PDM.

- Notification of Rave Database Lock/Primary Laboratory Data Complete *(approximately 21 weeks following the closed to follow-up date)*: a confirmation notification distributed to participating sites. This notice is generally distributed to sites by the PDM and includes:
  - Confirmation that the Rave database for the study is locked and the primary laboratory data are complete
  - Indication that no additional queries to which sites would need to respond are anticipated

14.3.1 IRB/EC and Other Regulatory Entity Communications

Sites are responsible for notifying their IRBs/ECs, including the single IRB (sIRB) if applicable, and other regulatory entities that the follow-up of participants has been completed according to their IRBs'/ECs' and other regulatory entities' procedures. Sites should continue routine communication with these review bodies (e.g., for continuing review, or for submission of other relevant documentation) as needed per IRB/EC policies and procedures.

The PDM will provide technical assistance as needed to study site staff who need to access data maintained at the SDMC to fulfill IRB/EC study close-out reporting requirements. The Operations Center will provide assistance with sIRB close-out, as needed.

14.3.2 DAIDS Protocol Deregistration

Consistent with the DAIDS Protocol Registration Manual, sites may deregister from a protocol in the following circumstances:

- The clinical research site (CRS) no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional participants.
- If no participants were ever enrolled at the CRS and the study has closed to accrual.

Deregistration is not automatic when a study is completed. The deregistration process is independent of a site's closure of a study with its IRBs/ECs; however, site IRB/EC policies should be reviewed prior to deregistration to help ensure that all IRB/EC requirements are met. For example, if an IRB/EC requires continued submission of safety information while data cleaning, analysis, and manuscript preparation are ongoing, deregistration may need to be deferred. NIAID sites may contact their DAIDS Site Office of Clinical Site Oversight program officer for additional guidance. National Institute of Child Health and Human Development (NICHD) sites may contact Westat for additional guidance.

Refer to the current version of the DAIDS Protocol Registration Manual for complete deregistration details: https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual.

14.3.3 Review of Financial Disclosure Forms

Consistent with guidance provided in Section 7 , sites should perform a comprehensive review of financial disclosure forms when closing studies conducted under an Investigational New Drug (IND) Application. Sites should ensure that all applicable forms for all study staff listed on Form FDA 1572 are reviewed and/or updated, as needed. The study-specific form is available on the study-specific webpage.

Refer also as needed to DAIDS guidance: https://rsc.niaid.nih.gov/clinical-research-sites/financial-disclosure-forms.

14.3.4 Informing Participants and Community Advisory Boards

Participants, parents/guardians, community advisory board members, and other key local stakeholders should be informed of study follow-up completion, consistent with usual site practices and standard operating procedures.

Study results may also be available for dissemination close to or after study close to follow-up. Refer to Section 19 for details describing study result dissemination.

14.3.5 Laboratory Specimen Storage and Shipping

Prior to study closure, the protocol team determines if additional laboratory testing is needed to complete the protocol-specified primary and secondary analyses, consistent with the protocol and statistical analysis plan(s). Each protocol should minimally provide an indication of when stored specimens are planned to be tested; details regarding specimen processing, storage, shipping, and testing are specified in the Laboratory Processing Chart. Some specimens may be stored at sites until after the study is closed to follow-up and/or they are requested to be shipped by the protocol team. To assist the team in prioritizing and determining specimens to be shipped for final study testing, the LDM will prepare a Status of Batched Laboratory Assays report prior to the anticipated closed to follow-up date.

In preparation for final laboratory testing, all study sites and testing laboratories should initiate efforts well in advance to fully execute all MTAs/STAs, export permits, and import permits needed to permit specimen shipping and testing. The LDM will communicate with study sites, testing laboratories, and repositories to request specimens to be shipped within specified timelines. Sites, testing laboratories, and repositories are responsible for preparing shipments within the timelines specified in the Specimen Shipment Request Letter from the LDM. Testing laboratories are responsible for completing testing and transmitting test results to the DMC within the specified timeline and following the format and transmission method defined in the Data Transfer Agreement (DTA). Site- and laboratory-specific specimen inventory quality assurance/quality control (QA/QC) procedures should be performed to ensure complete and accurate records. Any laboratory data queries and discrepancies should be resolved as soon as possible and within two weeks. These processes will help ensure that all required specimens have been shipped, tested, and reported appropriately to complete the study analyses.

14.3.6 Future Use Specimen Storage and Destruction

Specimens remaining after all protocol-specified laboratory testing has been performed may be stored in on-site storage or at NIAID or NICHD repositories. For some studies, participants (or their parents/guardians) are asked to provide written informed consent for continued storage and future research of these specimens. If such consent has been provided, the specimens may be retained when approved by the IMPAACT Management Oversight Group (MOG). If such consent has not been

provided, the specimens will be destroyed. See Section 17 for further details on specimen storage and destruction at the end of a study.

14.3.7 Study Product and Pharmacy

Post-Study Access to Study Product

Plans for post-study access to study product are typically addressed in the study protocol. The protocol team should provide any information necessary to facilitate transition of study participants to non-study sources of care and non-study provided treatment, as needed. For studies that close early, the protocol team may need to rapidly address issues related to access to study product as final study visits are conducted.

Final Disposition of Study Product

Directions for final disposition of study drug are typically addressed in the study protocol. If applicable, the DAIDS protocol pharmacist will develop written instructions for final disposition of study product and associated documentation to provide to sites as part of the Site Considerations for Study Close-Out memorandum referenced above. Guidance will generally follow procedures as outlined in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* available here: https://www.niaid.nih.gov/research/daids-clinical-research-pharmacy-and-study-products-management.

14.3.8 Data Management

The PDM is responsible for informing the protocol team and sites of the date the final participant completed the final study visit and is off-study (i.e., the closed to follow-up date), ensuring clinical data completeness (collection and QC of all available study outcome data), distributing queries to sites to resolve data discrepancies, and distributing appropriate communications to all sites indicating the final data submission/QC/query timelines and planned/final Rave database freeze and lock dates, as well as requesting IoR signatures on eCRFs. The LDM is responsible for ensuring non-eCRF laboratory data completeness and distributing queries to laboratories to resolve discrepancies.

Sites are expected to enter all study data within approximately two weeks following the closed to follow-up date and resolve all pending data queries within approximately two weeks of receipt of the query. Exceptions may be made to this timeline for large databases or for laboratory data that may require additional time after the closed to follow-up date. Data queries, including queries to testing laboratories, may be generated as a result of the data cleaning process, and additional queries may be generated later as data analysis proceeds. All sites should continue data management activities, as required, through the period of data analysis. Site-specific QA/QC procedures should be completed in coordination with Rave database freeze and lock expectations provided by the DMC, and data queries and delinquencies should be resolved as rapidly as possible. Study site staff are responsible for contacting the study PDMs with any questions, issues, or problems.

14.3.9 Unblinding Procedures

If applicable, unblinding of all participant treatment assignments will occur once all primary outcome data (i.e., clinical, virologic, or laboratory-based) and safety data for each participant have been entered and cleaned, all outstanding data queries resolved, and any clinical outcomes are reviewed as specified by the protocol.

As appropriate per Appendix I, the statistician and PDM collaborate with the protocol team to confirm plans for unblinding participants. The PDM provides unblinding memoranda to the protocol team for review, and the DMC/IMPAACT Chief Data Manager (or designee) prepares the unblinding listings for each site and distributes the listings to each site along with the unblinding memorandum. Sites should inform participants (or their parents/guardians) of their treatment assignments.

Refer to Appendix I for a full description of definitions, roles and responsibilities, and procedures related to unblinding.

14.3.10 Regulatory and Other Essential Documents

Refer as needed to the DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, which is available at the following website: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

All study-specific essential documents will need to be prepared and organized for long-term storage. Unless other site-specific organizational systems are in place, essential documents should be organized and categorized, to the extent possible, according to International Conference for Harmonisation Good Clinical Practice guidelines (ICH E6, Section 8.4).

14.3.11 Record Retention Requirements

All sites are encouraged to begin planning for long-term storage of participant study records, including source documents and eCRFs, early in the study close-out process. Site staff (e.g., coordinators and data managers) are encouraged to work with site quality management officers to develop operational plans and timelines for final QA/QC and organization of all files.

Sites should refer to the DAIDS Policy on Storage and Retention of Research Records, which is available at the following website: https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent. This policy defines minimum requirements for retaining study records to ensure compliance with applicable regulations, laws, and policies. Requirements differ for IND versus non-IND studies. **In all cases, sites should contact the study sponsor for approval before destroying any clinical study records.**

For studies that are DAIDS-supported and/or sponsored, the institution or designee must maintain adequate documentation of all IRB/EC records and clinical research records for at least three years or as designated after the completion of research. The three-year time period begins when all of the following are completed:

- All research-related interventions or interactions with participants (e.g., when all participants are off study)
- All protocol-required data collection and analysis of identifiable private information described in the IRB/EC-approved research plan
- Primary analysis of either identifiable private or de-identified information

For studies conducted under an IND, the same guidelines apply with the addition that the investigator or designee must retain clinical research records for two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the US Food and Drug Administration is notified.

US Department of Health and Human Services regulations require that records be maintained for at least three years after the study is completed.

No study records are permitted to be destroyed before the study to which the records relate is included on one of the lists entitled "List of Protocols having CRF/Pharmacy Records that will not be stored by DAIDS." There is one list for IND protocols and one list for non-IND protocols. These are studies for which DAIDS no longer has any regulatory obligation. This information can be found on the DAIDS RSC webpage for eCRF management: https://rsc.niaid.nih.gov/clinical-research-sites/case-report-form-management.

Most importantly, site investigators must retain records in accordance with the most stringent regulation, institutional policy, or local law that applies to the study being conducted.

15 ANCILLARY STUDIES, INVESTIGATIONS, AND ACCESS TO STUDY DATA

15.1 Scope and Definitions

This section describes the requirements for the development, submission, review, approval, and conduct of Data Requests (DRs), Data Analysis Concept Sheets (DACSs), and New Works Concept Sheets (NWCSs). The requirements for completion of Specimen and Data Usage Agreements (SDUAs) are also included.

The procedures apply to IMPAACT and non-IMPAACT investigators.

Information on available biological specimens for approved IMPAACT and Pediatric AIDS Clinical Trials Group (PACTG) studies can be accessed on the interactive Specimen Repository website at http://www.specimenrepository.org. IMPAACT protocol documents and study completion statuses may be found on the IMPAACT website (http://impaactnetwork.org) or requested from the Operations Center at IMPAACT.OperationsCenter@fstrf.org. Operations Center support for the development of DRs, DACSs, or NWCSs is not provided unless otherwise directed by the IMPAACT Management Oversight Group (MOG). The procedures outlined below may vary on a case-by-case basis.

For some ancillary studies, investigators may submit requests for funding or support to external groups; if letters of support are required from the Network to support these applications and requests, processes for letters are outlined in Section 7.

Table 15-1. Definitions

Data Analysis Concept Sheet (DACS)	A proposed investigation involving analysis of existing data from an IMPAACT (or PACTG) study to be undertaken by the Statistical and Data Analysis Center (SDAC) with IMPAACT funding. If the IMPAACT Network has not designated the study as concluded or openly available for use by investigators outside of the protocol team, the objectives of the proposed investigation should not overlap with the objectives stated in the study protocol or with secondary analyses defined by the protocol team after receipt of the final analysis report. The objectives should also not overlap with those specified in an approved IMPAACT DACS or NWCS that is not yet completed.
Data Request (DR)	A proposed investigation for which existing data from an IMPAACT (or PACTG) study are being requested for analyses to be performed without IMPAACT funding. (Note that an SDAC statistician may be among the proposing investigators but would not be seeking IMPAACT support for the work.) If the IMPAACT Network has not designated the IMPAACT study as concluded or openly available for use by investigators outside of the protocol team, the objectives of the proposed investigation should not overlap with the objectives stated in the study protocol or with secondary analyses defined by the protocol team after receipt of the final analysis report. The objectives should also not overlap with those specified in an approved IMPAACT DACS or NWCS that is not yet completed. The statistical design of the research project and associated data analyses must be undertaken by the proposing investigators without IMPAACT funding.
New Works Concept Sheet (NWCS)	A proposed investigation involving use of existing biological specimens and data from an IMPAACT (or PACTG) study that may or may not require IMPAACT funding and may or may not involve analysis work by SDAC. If the IMPAACT Network has not designated the study as concluded or openly available for use by investigators outside of the protocol team, the objectives of the proposed investigation should not overlap with the objectives stated in the study protocol or with secondary analyses defined by the protocol team after receipt of the final analysis report. The objectives should also not overlap with those specified in an approved IMPAACT NWCS that is not yet completed.
Specimen and Data Use Agreement (SDUA)	A formal agreement describing the receipt and specific use of IMPAACT (or PACTG) study specimens and/or IMPAACT (or PACTG) study data to be exported to external investigators. Parties to the agreement are the IMPAACT Network and the recipient(s) of the specimens and/or the data.
Public Use Dataset	Data from an IMPAACT (or PACTG) study in a format that does not require an SDUA for receipt of the file.
Relevant studies	IMPAACT (or PACTG) protocols, DACSs, or NWCSs that provide data or specimens to be analyzed in a proposed DR, DACS, or NWCS.

15.2 Responsibilities and Procedures for Development and Review of Ancillary Studies

15.2.1 Development and Submission

Proposing investigators should review their proposal in the context of the overall IMPAACT research agenda; this agenda is shared on the IMPAACT Network website: https://impaactnetwork.org. Investigators should also consult with the protocol chair and relevant Scientific Committee (SC) for input regarding potential overlap of a proposed research project with approved IMPAACT research prior to developing a proposal; this early consultation is particularly important for DACSs and NWCSs which need significant Statistical and Data Management Center (SDMC) resources.

Prior to submitting a proposal, proposing investigators should consider the following:

- **For DRs:** Confirm that the data required are not available in public use datasets, if available, for the IMPAACT study of interest. Guidance on available public use datasets may be obtained by contacting the SDAC at sdac.data@sdac.harvard.edu.

- **For NWCSs:** Utilize the interactive Specimen Repository website (http://www.specimenrepository.org) to determine availability of specimens.

Following this background research and preparation, investigators should develop and submit the proposal using the appropriate form available on the IMPAACT website adhering to the specified page limit. Completed proposals should be submitted by the proposing investigator(s) to the Operations Center via the following email address: impaact.capsubmissions@fstrf.org. The proposal is then assigned an identification number for tracking purposes, and the tracking number is communicated to SDAC at cbar.qb@sdac.harvard.edu.

Upon receipt of a proposal, the Operations Center proposal coordinator reviews the proposed ancillary study to ensure that all required elements are included. If the document is missing information, the proposal is returned to the investigators for completion; the Operations Center proposal coordinator may also provide initial questions for the proposing investigators' response to help facilitate the review process. Following this initial review, the Operations Center will forward the proposal as described in Sections 15.2.2 – 15.2.4.

For NWCSs: The Operations Center proposal coordinator also reviews the language in the relevant protocol(s), sample informed consent forms (ICFs), and site-specific ICFs (approved by the IRBs/ECs and submitted to DAIDS PRO), if available. If restrictions concerning the shipment or use of samples for other research are identified for any clinical research sites, the Operations Center proposal coordinator shares this information with the proposing investigator. The proposing investigator should work with the relevant study sites to confirm if the site-specific ICFs and Institutional Review Board/Ethics Committee (IRB/EC)-approval documents require that the site IRBs/ECs approve the shipment or use of samples for other research investigations. Prior to requesting specimens for new laboratory testing, investigators must also ensure compliance with relevant sites' Material Transfer Agreements (MTAs). This review will also identify any restrictions on use of specimens for a particular research area that would need to match the scope of the NWCS. The proposing investigator may contact the Operations Center for site contact information, as needed.

Note: There is no IMPAACT-funded SDAC statistical support for the design and development of DRs, other than guidance on availability of public use datasets noted above.

15.2.2 Protocol Chairs and/or Potentially Overlapping DACS or NWCS Lead Investigators Review

For proposals requesting data from an IMPAACT study that is not yet concluded, the Operations Center shares the proposed ancillary study with the relevant protocol chairs or designee for review and comments. If the objectives of the proposal may overlap with those specified in an approved IMPAACT DACS or NWCS that is not yet completed, the Operations Center shares the proposed ancillary study with the lead investigators of the approved DACS or NWCS.

The relevant protocol chairs or designees and/or relevant approved DACS or NWCS lead investigators review the proposed ancillary study with respect to potential overlap with study objectives or approved analyses and send comments to the Operations Center within seven days of receipt. If they do not comment within the seven-day period, they forfeit the right to comment on the proposal. If the relevant protocol chair is listed as an investigator on the DACS or NWCS, their review may not be requested, and the proposal will proceed directly to SC review (see Section 15.2.3).

The relevant protocol chairs or designees should ensure the following in their review of the proposed ancillary study:

- The proposed ancillary study will not jeopardize the completion of the relevant protocol(s) or the publication of the primary results.
- The proposed ancillary study does not compete or overlap with objectives of the protocol(s) or with other ancillary studies.

The relevant approved DACS or NWCS lead investigators should comment on whether the objectives of the proposed ancillary study compete or overlap with the objectives of their approved DACS or NWCS.

A proposed ancillary study may be deferred if further information is required from the investigators to address potential issues concerning overlap or appropriateness of using data from IMPAACT studies to address the proposed study objectives. In this scenario, the Operations Center will inform the proposing investigators and request the specific information needed.

If a proposal is deferred, unless otherwise directed, investigators may submit a revised proposal that addresses the overlap or concerns raised by the protocol chairs, SC, or Network leadership for re-review.

If the proposal is disapproved, the Operations Center notifies the proposing investigators and informs SDAC (cbar.qb@sdac.harvard.edu) and the Data Management Center (DMC) (fstrf.nwcs@fstrf.org).

If the proposal is approved, the proposal is shared for relevant SC review, as below.

15.2.3 Scientific Committee (SC) Review

Following protocol chair or designee review (and/or review by potentially overlapping approved DACS or NWCS lead investigators, if applicable), the relevant Operations Center SC representative shares the proposed ancillary study with the relevant SC chair, vice chair, and SDAC SC representatives.

As part of their review, the SC chair, vice chair, and SDAC SC representatives determine if there is a need for review by the full SC or if they will review and approve the proposed ancillary study on behalf of the SC. They may also determine that additional information is needed from the proposing investigators before any decisions can be made.

The relevant SC reviews the scientific merit and feasibility of the proposed ancillary study and decides whether to approve it for submission to the Network Leadership for review, approval, disapproval, or deferral. The SC should account for the following in their review of the proposal:

- The proposal uses data from the IMPAACT studies appropriately to address the proposed objectives (taking into account any comments from the protocol chairs and/or relevant DACS/NWCS lead investigators about competing or overlapping objectives).
- The proposal aligns with IMPAACT Network research goals and objectives.
- The SC may provide feedback on the scientific merit of the research project, including any significant limitations that might arise in addressing the proposed objectives in using data from IMPAACT studies.
- **For DRs:** As part of the SC review, the SDAC SC representatives (after consulting with the protocol statisticians and data managers, as needed) should comment on availability of the requested data items and overlap with ongoing or planned analyses. If the DR requires data customization, the SDAC SC representatives should provide an estimate of approximate SDMC staff time needed.
- **For DACSs and NWCSs:** SDAC SC representatives should also coordinate internal review of the proposal for SDMC estimated time and resources required for completion of work; these estimates should be added if none are included.
- **For NWCSs:** If specimens from an IMPAACT study that has other ongoing NWCSs are being requested, the SC may request that the DMC review the proposal for specimen availability.

A proposed ancillary study may be deferred if further information is required from the investigators to address potential issues concerning overlap or appropriateness of using data from IMPAACT studies to address the proposed study objectives. In this scenario, the Operations Center proposal coordinator will inform the proposing investigators and request the specific information needed.

If the proposal is disapproved, the Operations Center proposal coordinator notifies the proposing investigators and informs SDAC (cbar.qb@sdac.harvard.edu) and the DMC (fstrf.nwcs@fstrf.org). At the discretion of the SC chair and vice chair, the notification may specify the reasons for disapproval and include comments.

If the proposal is approved, the proposal is shared for Network leadership review, as below.

15.2.4 IMPAACT Network Leadership Review

Following SC review, the relevant Operations Center SC representative shares the outcome of the review with the Operations Center proposal coordinator to share with relevant Network leadership representatives:

- **For DRs and DACSs:** Applicable proposals are shared with the Network chair and SDAC principal investigator (PI) for discussion of resources required and determination of the need for review by the full MOG or SLG. As part of their review, the Network chair and SDAC PI determine if there is a need for review by the full MOG or SLG or if they will review and approve or disapprove the proposed ancillary study on behalf of the Network. Generally, the Network chair and SDAC PI review and approve or disapprove ancillary studies on behalf of the Network.

- **For NWCSs:** Applicable proposals are shared with the Laboratory Center (LC) PI and SDAC PI for discussion of resources required and determination of the need for review by the full MOG or SLG. In some cases, the Network chair may review on behalf of the LC, e.g., if there is a conflict of interest. As part of their review, the LC PI and SDAC PI determine if there is a need for review by the

full MOG or SLG or if they will review and approve or disapprove the proposed ancillary study on behalf of the Network. Generally, the LC PI and SDAC PI review and approve or disapprove ancillary studies on behalf of the Network.

Network leadership representatives may determine that additional information is needed from the proposing investigators before any decisions can be made.

Full MOG or SLG review may be required for some ancillary studies if significant SDMC or other Network resources are required for data preparation or as otherwise determined by the Network chair, LC PI, and SDAC PI. If additional leadership review is required, the Operations Center will request that the MOG or SLG review the proposed ancillary study and render a decision (approve, disapprove, or defer).

A proposed ancillary study may be deferred if further information is required from the investigators to address potential issues concerning overlap or appropriateness of using data from IMPAACT studies to address the proposed study objectives. In this scenario, the Operations Center proposal coordinator will inform the proposing investigators and request the specific information needed.

If the proposal is disapproved, the Operations Center proposal coordinator notifies the proposing investigators and informs SDAC (cbar.qb@sdac.harvard.edu and sdac.peds.coord@sdac.harvard.edu) and the DMC (fstrf.nwcs@fstrf.org). At the discretion of the Network chair, LC PI, and/or SDAC PI, the notification may specify the reasons for disapproval and include comments.

If the proposal is approved, the Operations Center proposal coordinator notifies the proposing investigators and informs SDAC (cbar.qb@sdac.harvard.edu and sdac.peds.coord@sdac.harvard.edu). For DRs and NWCSs, the DMC is also notified (fstrf.nwcs@fstrf.org). This communication includes a copy of the approved proposal along with instructions to the proposing investigators regarding the need for completion of an SDUA (see Section 15.4), if applicable. The DMC will assign an LDM to approved NWCSs and notify SDAC (cbar.qb@sdac.harvard.edu and sdac.peds.coord@sdac.harvard.edu) and the Operations Center (impaact.capsubmissions@fstrf.org). SDAC will contact the proposing investigators (for NWCSs, the assigned LDM is copied) to confirm receipt of the specimen or data transfer request and establish a timeline for undertaking the transfer.

15.3 Special Considerations for Proposals Requiring Genetic Analyses

An ancillary study proposal that involves use of existing IMPAACT human genetic data must be clearly linked to the protocol and/or NWCS(s) under which the human genetic data were created and should also specify:

(A) the frequency and expected range of individual polymorphisms
(B) the rationale for studying the polymorphisms, including evidence of association with outcome

Investigators who will be performing human genetic testing on IMPAACT specimens must clearly specify this in their NWCS proposal. Only specimens from participants who consented to non-protocol human genetic testing will be available for NWCS human genetic testing.

Investigators who receive IMPAACT genome-wide association studies (GWAS) data under a proposed IMPAACT ancillary study should not submit these data to a National Institutes of Health (NIH) GWAS data repository. In compliance with the NIH Genomic Data Sharing Policy (NOT-OD-07-088), for sharing of data obtained in NIH-supported or -conducted GWAS, the SDMC will have already submitted to the NIH GWAS data repository (named the “database of Genotypes and Phenotypes”, or “dbGaP”)

GWAS data that were generated with IMPAACT funding, and only from participants who have consented to dbGaP submission.

Investigators who produce new GWAS data under a NWCS using IMPAACT specimens may submit these datasets to an NIH GWAS data repository (such as dbGaP). This requirement must be clearly stated in the NWCS proposal and, if approved by IMPAACT leadership, must only be done for those participants who have consented to dbGaP submission.

15.4 Specimen and Data Usage Agreements

SDUAs are required for ancillary studies when data are to be exported from SDAC or the DMC for analysis, and for ancillary studies requiring use of biological specimens. The SDUA forms are issued by the Operations Center proposal coordinator to proposing investigators and, in accordance with the ancillary study review process, following approval from the Network. The following sections provide additional information on the projects that require an SDUA and the procedures for completing and submitting an SDUA.

The completed SDUA must be submitted to the Operations Center by the proposing investigator(s) and any other collaborating investigators who will receive and be responsible for the data (and specimens, for NWCSs) before the data (and specimens, for NWCSs) are released. SDAC and the DMC will be notified upon receipt of the completed SDUA via the specified email aliases (fstrf.nwcs@fstrf.org, cbar.qb@sdac.harvard.edu, sdac.sdua@sdac.harvard.edu).

Data and/or specimens for projects requiring an SDUA will not be released or shipped until the SDMC has confirmation that the Operations Center has received a signed SDUA.

15.4.1 Projects that Require an SDUA

In general, an SDUA is required for any ancillary study for which data are to be exported from the SDAC or the DMC and/or for which biological specimens are to be used. An SDUA is typically required for all NWCSs.

More specifically, an SDUA is typically required for the following:

- All NWCSs
- Any DR or DACS for which data are to be exported
- Any export of human genomic data
- Shipment of specimens and/or datasets for an approved IMPAACT protocol if the activity has not been described in the protocol or Division of Acquired Immunodeficiency Syndrome (DAIDS) Clinical Trials Agreement (CTA)
- Export of data from multiple studies for a meta-analysis or other grouped analysis, even if not developed as a formal DR or DACS

15.4.2 Projects that do not Require an SDUA

Under the following conditions, an SDUA may not be required:

- The use of data that have been moved to a public repository or de-identified per requirements for public use datasets.

- Shipment of specimens and/or data if the send-out has been described in an approved IMPAACT protocol and, therefore, did not require a DR, DACS, or NWCS.
- Shipment of specimens and/or data to pharmaceutical companies when covered by DAIDS CTAs.
- Shipment of specimens and/or data for the purposes of quality assurance.
- Shipment of specimens to an IMPAACT funded site, laboratory, or repository for the purpose of long-term storage.
- Any DR or DACS, for which SDAC statisticians are among the proposing investigators or will perform the analyses and no data will be exported to other investigators.

15.5 Responsibilities and Procedures for Completion of Ancillary Studies

To support approved ancillary studies, representatives from the SDMC will be assigned as noted below:

- **For DRs:** An SDAC statistician or epidemiologist is assigned to work with proposing investigators and the DMC to facilitate the transfer of data. This coordinator also serves as the contact person for any data-related questions. The SDMC will inform the proposing investigators of any costs associated with providing data in formats other than those in which they already exist (these costs will need to be covered by the proposing investigators).

- **For DACSs:** An SDAC statistician or epidemiologist is assigned (or confirmed) to work with the proposing investigators to complete and publish the proposed analyses.

- **For NWCSs:**
  - If SDAC is performing associated data analyses, an SDAC statistician is assigned (or confirmed) to work with the proposing investigators to complete and publish the proposed analyses.
  - If the proposing investigators are performing associated data analyses, an SDAC statistician or epidemiologist is assigned to work with the proposing investigators and the DMC to facilitate the transfer of specimens and, if applicable, associated clinical data. This coordinator also serves as the contact person for any data-related questions.
  - A laboratory data manager (LDM) from the DMC is assigned to each approved NWCS. The LDM assists the proposing investigators (and SDAC coordinator) by coordinating the shipment of specimens to the testing laboratories. The following should be considered:
    - Specimens from sites that require MTAs with the receiving NWCS investigator or other types of site approvals will not be shipped until the NWCS investigator confirms those agreements or approvals are in place.
    - Specimens from participants who did not consent to non-protocol testing of their specimens will not be shipped for NWCS testing.
    - If the last aliquot (defined below) is potentially going to be used for a NWCS, the assigned LDM or DMC designee will request the following additional approvals:
      - If the study is not yet concluded (i.e., still has ongoing analyses), the protocol chair must approve the use.
      - If the study is concluded, Network leadership must approve the use. Network leadership includes the Network chair, LC PI, SDAC PI, SDAC Associate Director, Operations Center Director, and the DMC Laboratory Data Division Chief. In some cases, it will also be sent to the IMPAACT SLG for review and approval.
    - The last aliquot is defined as the last aliquot available from a specific participant, visit, or specimen type if the specimen is from a baseline (Week 0) time point OR the specimen is from a perinatal study and is the last specimen at any visit for a parental participant or their infant with HIV.

- Data or specimens will not be shared until the SDMC has received confirmation from the Operations Center that the SDUA process is complete.
- Proposing investigators must submit to the DMC any data generated from assays performed on IMPAACT specimens. The LDM works with the testing laboratory to transfer assay results back to the DMC regardless of whether an SDAC statistician is performing the data analysis.

15.6 Publications Resulting from Data Requests

It is the responsibility of the investigator/author to ensure that development of manuscript results from the proposed ancillary study follow the procedures specified in Section 19, including timelines, authorship, Network review, and citations. Any publications associated with the proposal should include acknowledgement of IMPAACT.

15.7 Procedures for Access to Study Data During Trial Conduct and After Trial Completion

The central database for the majority of IMPAACT studies resides at the SDMC. This includes case report form (CRF) data, results of protocol-specified laboratory analyses, ancillary study data, and analysis datasets. This section describes the policy for site, Network investigator, and non-Network investigator access to study data during conduct of a trial and after study closure and database lock.

IMPAACT is a rich source of data that should, in many instances, be accessible to members and others outside of IMPAACT. Special reports and analyses beyond routine approved activities are often required or desired for specific applications by IMPAACT members outside of a protocol, DACS, or NWCS team. The Network must balance the importance of making appropriate data available as quickly as possible with the need to conserve resources and, most importantly, preserve the integrity of ongoing studies.

The simple request method outlined below will ensure that protocol chairs are aware and approve of the requests for access to data from their studies. In addition, by using this procedure, the SDAC PI, in consultation with the SLG, ensures that the requests are appropriate (i.e., do not release confidential information to unauthorized persons), clearly specified, prioritized, and fulfilled on a timely basis. Finally, this centralized procedure allows IMPAACT to have a record of what data were requested from which studies, and for what purpose.

There are several types of data access requests that are not covered by this set of procedures, as follows:

1. Requests to access data for which any kind of proposal (protocol, DACS, NWCS, or DR) would be appropriate. IMPAACT investigators, including SDAC or DAIDS staff, or external investigators who wish to publish or present results involving IMPAACT data, must submit a proposal for Network leadership approval; refer to Section 15.2.
2. Requests from sites for summary data that have previously been made available in some form to the IMPAACT membership at large. The SDMC will provide that data in a reasonable amount of time without requiring approval through the formal request process.
3. Requests by SDAC staff: SDAC staff frequently require access to data for purposes of conducting internal IMPAACT business. Results of these analyses are not intended for publication or presentation and are kept confidential. Examples of such needs are: (1) analyses which are necessary to plan successor studies and (2) analysis of virology calibration data. Only the approval of the senior statistician is necessary for within-SDAC access for sample size calculations, etc. If a protocol will reference information from ongoing study(ies), the standard data request procedure outlined below must be followed, wherein the study chair(s) of the ongoing study(ies) would be consulted.

4. Data and Safety Monitoring Board (DSMB) Requests: Requests for special analyses made by the DSMB are considered confidential. Generally, the DSMB would contact the SDAC statistician assigned to the study in question or to the SDAC liaison to the DSMB.

15.7.1 General Guidelines Regarding Data Access

The fundamental principles guiding the approval process for requests for data or analysis are as follows:

- The fulfillment of requests must not jeopardize the completion of the study(ies) or the publication of the primary manuscript(s) and must be compatible with the sample ICFs in the protocol(s).
- The right to access or receive IMPAACT data does not imply the right to disseminate them: these are two clearly distinct concepts. IMPAACT as a group determines who is authorized to disseminate its data in any form.
- Patient confidentiality must be respected and protected. The minimum amount of data necessary to achieve a stated purpose should be distributed, particularly data which could conceivably be used to identify a patient through cross-linking of other information. For example, patient birth dates should not be released unless there is compelling reason to do so.
- Site confidentiality must be respected and protected. Data should not be associated with a given site unless there is compelling reason to do so.
- In general, SDAC (and the study pharmacologist, if applicable) will conduct all team-initiated analyses.
- Sites have access to data from their site.

15.7.2 Procedures for Data Access Requests

The requestor must send the request by electronic mail to SDAC.DATA@fstrf.org, either directly or routed through the statistician, data manager, or other members of the DMC. Requests to SDAC.DATA must be highly specific, including at a minimum the following information: who is asking for the data, the specific data they need and when they need it, the purpose of the request, how the data will be used, and who else will be given access to it. SDAC.DATA will log the request and forward it to the appropriate individuals, including the statistician(s), the protocol chair, and the SDAC PI, asking for approval/disapproval or comment.

The SDAC PI acts for the SLG and thus will seek guidance from the SLG if the appropriateness of the request is unclear.

The final decision will be communicated by email back to the initiator of the request. If the data request is approved, the SDMC will fulfill it after the requestor agrees in writing to the following stipulations:

- The data will only be used for the purpose described in the original data request;
- Any other use of the data would require prior IMPAACT approval (by sending a follow-up request to SDAC.DATA or by submission of a DACS, NWCS, or DR, as appropriate); and
- The data will not be provided to anyone or disseminated in any way other than as specified in the original data request, unless prior IMPAACT approval is granted.

Appeals Procedure: Decisions to deny data access may be appealed in writing to the SLG.

15.7.3 Specific Examples of Data Access Requests

The following are examples of required requests for data access using this process.

1. Requests by DAIDS Staff, Protocol Chairs, IMPAACT Scientific Committee Chairs, the SLG Chair, or the Operations Center

   DAIDS staff may require information for reports to the National Institute of Allergy and Infectious Diseases (NIAID), Congress, constituency groups, or the media. All DAIDS staff requests should only come through the DAIDS Program Officer for SDMC or their designee. Requests from study chairs, SC chairs, or the SLG chair often involve information needed to monitor study/IMPAACT progress (such as data completeness by a clinical site or reasons for dropout). These requests are normally made through the study statistician or SDAC SC representative, who would consult with the SDAC PI if the issues were unclear. The Operations Center will occasionally need to initiate the fulfillment of a supplemental contract with a pharmaceutical company by requesting information or data access per the contract. This request will come from the Operations Center to SDAC.DATA. SDAC must have copies of the appropriate sections of these contracts on file.

2. Requests from the Regulatory Affairs Section of DAIDS

   Requests from the Regulatory Affairs Section of the Pharmaceutical and Regulatory Affairs Branch of DAIDS may originate when an adverse event report (AER) indicates a severe toxicity in a study participant and further investigation of the case history is required to resolve safety concerns. The US Food and Drug Administration (FDA) requires a 10-day turnaround for this information, beginning at the time the adverse event is reported to DAIDS. Such requests should be channeled to the SDAC PI through the DAIDS Program Officer.

3. Pharmaceutical Protocol Team Member Requests

   Pharmaceutical companies participate in CTAs with DAIDS and in supplementary contracts with IMPAACT. They also often require data access or analysis beyond what is in the CTA for FDA review of a New Drug Application (NDA) or to determine future drug development. All requests for fulfillment of CTAs, supplementary contracts, or additional information should come through SDAC.DATA, who will review the requests for appropriateness.

4. Investigator/Site Requests

   An investigator requests clinical data from a particular study or studies for purposes other than publication or presentation (which would require a Concept Sheet or DR).

5. External (non-IMPAACT members) Data Requests

   Requests for IMPAACT data may originate from various parties outside of IMPAACT. These may include researchers, government agencies, pharmaceutical companies, and representatives of the media. The individual receiving the request should obtain the name of the requestor and the organization they represent, if any, and direct the requestor to follow the procedures described in Section 15.2. Information about the encounter should be sent to SDAC.DATA to give advance warning of the impending request.

16 TRAINING FOR SITE KEY PERSONNEL AND OTHER SITE AND LABORATORY STAFF

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network is committed to developing qualified, trained staff to conduct IMPAACT studies. For each IMPAACT study, the site Investigator of Record (IoR) is responsible for ensuring that study site staff are appropriately qualified and trained to carry out their delegated duties, and that all training is adequately documented. Clinical Trial Unit (CTU) leaders, Principal Investigators, and Clinical Research Site (CRS) leaders are responsible for ensuring that IoRs fulfill this responsibility. All sites must establish and follow standard operating procedures (SOPs) for personnel training and certification documentation; IoRs must maintain adequate training documentation, and make training documentation available to National Institute of Allergy and Infectious Diseases (NIAID) or National Institute of Child Health and Human Development (NICHD) Program Officers, site monitors, inspectors, and/or auditors acting on behalf of study sponsors, regulatory authorities, site institutional review boards/ethics committees (IRBs/ECs), and other applicable review bodies. Additional Division of AIDS (DAIDS) guidance can be found in the Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

Further training requirements related to Human Subjects Protection (HSP) training and Good Clinical Practice (GCP) training are presented in Section 16.1; related to laboratory specifications are presented in Section 16.2; related to data management specifications are presented in Section 16.3; and related to research ethics training for community representatives are presented in Section 16.4.

IMPAACT requires study-specific site training prior to study initiation (Section 16.5).

IMPAACT sites are also expected to provide training for new staff and continuing training for current staff. Sites are required to maintain up-to-date and accurate training records of all required Network and study-required trainings.

An overview of mandated training is found in Table 16-1 with further details in the following sections. When the term “key personnel” is referenced throughout the remainder of this section, this term generally includes individuals named on the Form FDA 1572 and/or DAIDS Investigator of Record (IoR) Form, and any CRS personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures or providing intervention) or more than minimal study

conduct-related contact with study participants or confidential study data records, or specimens, and any CRS personnel who are otherwise listed on the Delegation of Duties Log.

Table 16-1. IMPAACT Training Requirements

Training	Required Personnel	Timing/Frequency	Sources for Training
International Air Transportation Association (IATA) training	All staff who transport, ship, or receive infectious substances and diagnostic specimens	Prior to handling infectious substances and specimens as part of an IMPAACT study (certification of staff members required for study activation at the site); regulations reviewed annually and certification every two years thereafter	• Resources listed in Section 16.2.2
Laboratory Data Management System (LDMS) training	IMPAACT laboratory staff	At time of installation of LDMS and, as needed	• Frontier Science Foundation (FSTRF) training at Network meetings and regional meetings, on-site, online, or at FSTRF • Resources can be found on the LDMS website at: https://www.ldms.org/training/
Good Clinical Laboratory Practice (GCLP)	Laboratory Director, Laboratory Manager/ Supervisor and/or quality assurance/quality control (QA/QC) technologists	Prior to involvement in an IMPAACT study and then as needed	• GCLP courses provided by the DAIDS contractor (at annual and/or regional meetings) or online • Courses available from private training companies Note: these may not cover the appropriate DAIDS related regulations
Study-specific training	All site staff involved in the study	Prior to initiation of study (for new staff, prior to start dates on delegation of duties logs and performing study-specific tasks/duties without direct supervision) and then as needed	• Protocol clinical research managers (CRMs), data managers, Laboratory Center (LC) representative, and other protocol team members, as applicable and as described in Section 16.5 • IoR or designee for new staff

Table 16-1. IMPAACT Training Requirements

Training	Required Personnel	Timing/Frequency	Sources for Training
Data Management Center (DMC) Training	IMPAACT site staff	Prior to site activation, and as needed	• **Frontier Science Portal Training:** Complete new user training via Online Portal Training link • **DMC Introductory Training and eLearnings**: Complete self-guided courses for independent learning via DMC Virtual Learning Room • **Medidata Rave:** Required eLearning courses appear on iMedidata dashboard in the upper right-hand corner. Users must complete and pass these courses for further access to Medidata Rave. • **Study Enrollment System (SES):** Complete SES/Stars new user training • Contact dmc.training@fstrf.org for additional training options

16.1 Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training

HSP and GCP training of all IMPAACT site staff is encouraged. Requirements, sources, and options for HSP and GCP training are described in full in Section 8.

16.2 Laboratory Related Training

To ensure quality research and to safeguard study participants, DAIDS requires that all IMPAACT studies be conducted in accordance with GCLP. The LC also requires that key laboratory personnel receive GCLP training prior to involvement in an IMPAACT study. Training of all IMPAACT key laboratory staff is facilitated through the provision of regional GCLP training as well as through an online training program. Refer to Section 17 for further details on IMPAACT Network Laboratory requirements.

All IMPAACT studies rely heavily on the capacity of IMPAACT laboratories to handle, process, and ship participant specimens. The work of qualified and trained laboratory staff at the research sites is essential. The IMPAACT Network requires the training described in the remainder of this section for laboratory personnel.

16.2.1 Laboratory Data Management System (LDMS)

The LDMS is the laboratory software provided to each of the sites/laboratories to assist with specimen management, labeling, storage, and shipping. LDMS training is provided by FSTRF when the site/laboratory is provided access. If travel is required for training, this is a site/laboratory expense.

Opportunities for refresher training are provided as needed. At the request of the ILC, FSTRF may provide refresher training on the LDMS at annual meetings, regional meetings, protocol-specific trainings, or through web-based trainings. The ILC staff members are typically available at protocol-specific training sessions to provide laboratory information related to IMPAACT, and also to answer questions from site representatives. Site representatives are expected to share the information learned from training with other site staff.

In addition, there are numerous LDMS training resources available on the LDMS website (www.ldms.org), including training tutorial videos, training workbooks, exercises, and quizzes.

As part of study monitoring and oversight, the protocol team and Network leadership routinely review specimen testing, availability, as well as data quality and completeness; if any issues or concerns are identified during these reviews, additional training or other corrective actions may be required (see Section 13).

Sites, at their expense, if applicable, may also request additional training if needed; for example, when new laboratory personnel are hired.

16.2.2 International Air Transport Association (IATA)

IATA regulates the safe transportation of dangerous goods by air in accordance with the legal requirements of the International Civil Aviation Organization (see Section 17 for further details). IMPAACT, in accordance with IATA requirements, requires training and certification for all IMPAACT laboratory staff involved with the handling, transporting (by air and ground), receiving and shipping of infectious substances and diagnostic samples. Certification of all site staff members, who transport and/or ship dangerous goods, is required prior to study activation at a site.

Site personnel should review the IATA regulations annually as well as complete required training in hazardous materials (HAZMAT) regulations as they pertain to IATA shipping regulations.

Each site is responsible for training the pertinent staff members on IATA shipping regulations and is required to have a current IATA manual on site. Sites are required to provide documentation of IATA certification of personnel upon request by the LC or a DAIDS contractor. The site's Primary Network Laboratory (PNL) is responsible for ensuring that the laboratory has a current IATA Dangerous Goods Manual and appropriate training materials. See Section 17 for a complete listing of additional laboratory-specific training resources.

16.2.3 Biohazard and Containment Training

Clinical and laboratory personnel are expected to complete annual clinical safety training, including training on bloodborne pathogens and infection control. It is the responsibility of the site to provide the training to all clinical and laboratory staff using information and materials provided by their institutions as well as DAIDS contractors and cross-network training groups.

16.2.4 Other Requirements for Laboratory Personnel

Laboratory personnel are also expected to participate and complete training as specified in this section for site personnel; for key laboratory personnel, this includes HSP, GCP, GCLP, and study-specific training.

Sites will be notified of relevant laboratory issues and developments which may affect multiple IMPAACT protocols, or Network activities by the IMPAACT Operations Center, LC, and/or DMC. Such issues may also be discussed, with training opportunities, at the annual meetings or through other methods of communication.

16.3 Data Management Training

Site personnel are responsible for providing study data that are correct and of high quality to the DMC. Knowledge of data management systems, quality assurance tools, and reports is necessary to meet this requirement. Data management training is offered to site personnel through routine trainings at the DMC, regional trainings, trainings offered at annual Network meeting demonstration rooms, web-based trainings, and study-specific trainings. Training resources, including historical presentations and recorded trainings, may be found on the training pages of the DMC portal website at: http://www.frontierscience.org.

16.4 Research Ethics Training for Community Representatives

The FHI 360 Research Ethics Training Curriculum for Community Representatives is designed to train community representatives about their roles and responsibilities and inform community representatives, members of research teams, Community Advisory Boards (CABs), and research ECs about the general principles of research ethics. It also reviews the need for ECs, their importance, and the roles and responsibilities of community representatives in the research process. The curriculum includes easy-to-use materials such as slides, case studies, activities, facilitator notes, as well as an ethics training certificate. Community education staff, community advisors, and partners are encouraged to complete this training.

Additional details related to community participation and engagement in the IMPAACT Network is described in Section 5.

16.5 Study-Specific Training

Site IoRs are responsible for ensuring that site study staff members are adequately trained to perform their delegated study-specific functions. Designated members of IMPAACT protocol teams — including but not limited to Operations Center, Statistical and Data Management Center (SDMC), and LC staff — collaborate with IoRs to fulfill this responsibility in preparation for initiation of new IMPAACT studies by conducting study-specific training. Self-study of study-specific documents and/or training materials (alone) is not typically considered adequate training for IMPAACT studies. However, study-specific training may be provided in various formats and for various durations depending on the training needs of the site and the study. The IMPAACT staff mentioned above work closely with the protocol chair(s) and site IoRs to determine the optimal format and length of each training.

Each site IoR is responsible for ensuring that all training is documented. Protocol team members may assist with this, for example, by providing copies of signature sheets from an in-person training or by providing participant logs from an online training. Presented training materials will also be provided, typically by posting on the study-specific web page; if any materials are not suitable for public posting, copies will be provided directly to site representatives via email or other delivery methods. When key site staff are not available to attend study-specific training for any reason, or a staff member joins the study team after the study-specific training has already taken place, the site IoR is responsible for ensuring adequate and appropriate training of these staff, prior to their initiation of study activities. Documentation of all study staff training must be maintained in each site's Essential Document files.

Blinded studies should include review of the Network Manual of Procedures (MOP) Appendix I, Unblinding Procedures, as part of study-specific training.

16.5.1 Development of Study-Specific Training Plan

For each IMPAACT study, the protocol team agrees on a study-specific training plan that is tailored to the needs of the study and participating study sites. Discussion of training plans is generally initiated within the protocol team around the time of protocol finalization and plans are further developed as sites work on completing site-specific study activation requirements, as described further in Section 11. Input on training plans is also obtained from site representatives to ensure that all perceived training needs are considered. Once a study-specific training plan is finalized, the operational approach is communicated to the study sites, and training timelines and materials are developed. The Operations Center coordinates with the protocol chair, SDMC, and LC to lead these training efforts, with input from protocol pharmacists and medical officers, as needed. For studies involving specialized procedures and/or interventions, relevant content area experts are also consulted; these persons may be members of the protocol team or may be external to the team. Site input may be obtained in a variety of ways, including telephone and email communications and online surveys.

The objectives of study-specific training are to:

- Establish a common understanding of key aspects of the study, including the background and rationale, objectives and outcomes, design, intervention, and schedule of evaluations
- Ensure that site study staff are informed and familiar with:
  - Day-to-day study implementation requirements, in accordance with the protocol, study-specific MOP, LPC, electronic case report forms (eCRF) completion guide, other relevant study implementation materials, and relevant regulations, guidelines, policies and procedures
  - Study-specific communication procedures and operational resources and utilities available to support day-to-day study implementation
- Ensure standardization of study implementation across sites so that data can be combined for analysis

Study-specific training plans may include, but are not limited to, the following:

- Self-study of training materials developed by the protocol team
- Remote participation in live or recorded conference call and/or webinar training sessions
- In-person participation in centralized, regional, or site-specific training sessions
  - When centralized or regional in-person trainings are planned, a train-the-trainer approach is typically taken, with site staff who attend the trainings being responsible for training other study staff members at their site.
  - When site-specific in-person trainings are planned, it is expected that most if not all key site staff will attend the training.

Study-specific training plans should also:

- Identify members of the study-specific training team (i.e., protocol team members and others who will be involved in providing training).
- Specify the extent to which translation into languages other than English may be required and indicate whether translation may need to be arranged centrally or performed locally at one or more study sites.
- Specify minimum requirements for sites to be considered adequately trained as a condition for site-specific study activation. Although it is generally expected that the same training will be provided for all sites, when necessary, different approaches and requirements may be specified for different sites (e.g., less experienced sites may require additional training).

Initial draft training agendas are prepared as part of study-specific training plans. These should include, at minimum, a listing of training topics to be covered and a designation of persons responsible for each topic; other details may be specified later, as agendas are further developed and finalized. Key considerations for training agendas include the following:

- Consider the audience, which site personnel are required, what they need to know, and what is the most effective method to present the material.
- Address community-related as well as scientific and operational training needs.
- Involve site staff as well as training team members in presenting/leading training topics.
- Allow adequate time for each topic, including time for questions and answers and discussion.
- Consider the overall training time as well as the amount of time scheduled for each topic (shorter sessions with breaks in between are usually advantageous for learning).
- Include interactive sessions when possible and applicable.
- Incorporate time for cross-site interaction and problem-solving when possible.

If a study design is straightforward and the participating sites have experience with similar studies, the training plan may specify telephone or web-based training. In contrast, if the study design is unique or complex, or if sites are less experienced, an in-person training may be required. In-person training may also be required when training on specialized study procedures is needed. A combination approach can also be taken. For example, telephone and web-based training could be planned for experienced sites while in-person training would be offered to less experienced sites or for a targeted study-related purpose, such as reviewing specialized laboratory procedures. Cost-efficiency and training effectiveness are also key considerations in determining the best approach.

When in-person trainings are planned, options include regional trainings for study staff from multiple sites as well as individual on-site trainings. Study-specific trainings may include sessions for community educators and CAB members, focused on such topics as community education and outreach, participant recruitment and retention, human subjects and participant safety protections, community perceptions and potential misconceptions of the study.

16.5.2 Scheduling Study-Specific Site Training

The responsibility for scheduling study-specific training is shared among designated members of protocol teams in conjunction with site representatives.

Training is conducted as closely as possible to the time when one or more CRSs will have met all other site-specific study activation requirements, such that activation and initiation of the study will occur upon (or very soon after) completion of training. Generally, a study will be open to accrual or the majority of requirements to open a study to accrual will be met prior to training. One or more sites should have completed the DAIDS protocol registration process for the study and, if applicable, should have received supplies of the investigational study drug or product on-site. All other activation requirements should also be completed or nearly completed. For example, required site SOPs may be fully drafted prior to training with the expectation of finalization immediately following training (to incorporate information provided during the training). See Figure 16-1 for required and recommended study- and site-specific elements to be completed prior to training. Introductory overview sessions may be conducted prior to this timepoint, as webinars or at pre-convened meetings, like the Network annual meeting.

If site activation is delayed following training, site IoRs are responsible for conducting retraining (see Section 16.5.5).

Figure 16-1. Guidelines for Scheduling IMPAACT Study-Specific Training

To be completed prior to scheduling study-specific training (as applicable to the study; see Section 11 for details related to study-specific pre-implementation activities):
• Completion of US Food and Drug Administration (FDA) 30-day review period/safe to proceed notice • Signed Clinical Trials Agreement(s) (CTA) • Study product(s) available at the DAIDS Clinical Research Product Management Center (CRPMC) • Finalization of the study-specific MOP for use as a reference during training (Note: a draft version may be used for training purposes) • At least one site close to meeting all activation requirements, such that activation and initiation of the study will occur upon (or very soon after) completion of training
Note: sites that have made significant progress towards meeting study-specific site activation requirements, as outlined in Section 11, will be prioritized when scheduling study-specific training. However, other sites may be invited to participate in training sessions, as determined in the training plan.

16.5.3 Site Preparation for Training

In addition to completion of requirements for scheduling study training, site study staff will carry out other activities to prepare staff for study training and, ultimately, the conduct of the study. Under the supervision of the IoR, the following items are generally completed by sites as they prepare for study implementation:

- Hire staff (if needed)
- Designate site study staff team and assess local training needs
- Provide orientation and background training locally, as needed, including:
  - Local staffing and organizational plan (including roles and responsibilities)
  - Local site operations
  - Local role-specific training and certification
  - Other local requirements
- Complete "mock visits" using study implementation materials, ideally in clinic and laboratory facilities that will be used for the study
- Discuss and develop SOPs (as needed) and other local study implementation materials
- Review and become thoroughly familiar with the study protocol, informed consent documents, CRFs, training materials, other study implementation materials, and site SOPs
- Review and become familiar with the study-specific specimen management plan and the "chain of custody" for study samples
- Identify questions, issues, and problems requiring training team input

Depending on the training plan, expectations of site study staff prior to study-specific training include:

- Work with training team to plan training and finalize agenda
- Work with training team to identify and meet translation and interpreter needs
- Arrange staff backup for staff who will attend training sessions
- Arrange access to training rooms and any required equipment

16.5.4 Implementation of Study-Specific Training

Training team members are responsible for developing training agendas, developing training materials, and conducting training sessions. Topics to be covered for all IMPAACT studies are listed in Figure 16-2. Ideally, all site staff members who have been delegated duties or responsibilities for a study will take part in study-specific training; however, a train-the-trainer approach may also be considered for centralized or regional trainings, which all site staff may not be able to attend. The training plan will clearly identify required attendees.

During training sessions, site study staff are expected to:

- Present training topics (if specified in the training agenda)
- Present site-specific operational plans and/or SOPs (if specified in the training agenda)
- Attend all required training sessions (by study-specific role if applicable) per the study training plan
- Fully engage in the training (ask questions; identify issues requiring additional clarification; describe site-specific study implementation plans, materials, and tools; etc.)

Failure of study staff to attend required training sessions typically will delay site-specific study activation, as additional training will be required before study activation can occur. Therefore, every effort should be made to avoid absences from required sessions.

Figure 16-2. Minimum Topics to be Covered for IMPAACT Study-Specific Trainings

- Study Overview including Rationale and Objectives
- Study-Related Communications
- Informed Consent Considerations
- Eligibility Criteria
- Screening and Enrollment Process
- Study Procedures (covering protocol Section 6 and the Schedules of Evaluation)
- Pharmacy and Study Drug Considerations
- Data Management Considerations
- Laboratory Considerations
- Toxicity/Participant Management
- Adverse Event and Expedited Adverse Event Reporting
- If needed, Network structure and procedures overview (including protocol deviation reporting)
- Other study- or site-specific topics may be added

16.5.5 Continuing Study-Specific Training

Site IoRs are responsible for ensuring that new site study staff members are adequately trained to serve their delegated study-specific functions. Study-specific training teams typically do not provide training for newly hired site staff following the initial study training. However, team members will make every effort to be available to answer questions and provide technical assistance to new key personnel, as needed. Conference call discussions and/or targeted webinar trainings can be provided, if requested by the site.

Once a study is underway, designated protocol team members — typically the Operations Center, DMC, and LC staff — issue study-related communications, answers to frequently asked questions, and other similar documents to guide study implementation at each site (see Section 12). IoRs are responsible for ensuring that study sites have SOPs in place for receipt and filing of these communications, and for

ensuring that all relevant study staff are informed of and trained on these materials, as needed, and incorporating the content into day-to-day study operations.

When necessary, designated protocol team members will provide study-specific "refresher" training to site staff. This may be done via conference call or webinar, at in-person meetings (e.g., IMPAACT annual meeting) or during site visits. Recordings of prior training sessions may also be options for continuing training at study sites.

16.6 Documenting Training

Site IoRs are responsible for ensuring that study site staff members are appropriately qualified and trained to carry out their delegated duties and that all training is adequately documented. Per the DAIDS SCORE Manual, all sites must establish and follow SOPs for personnel training and certification documentation. Site SOPs may specify the use of training logs, training certificates, meeting summaries with participant lists, and/or other documents as applicable. All training documentation must be maintained in on-site Essential Document files.

The DAIDS SCORE manual includes training log templates that are trainee-specific and topic-specific. Sites may use the template logs provided in the DAIDS SCORE manual, or use their own institutional templates, but should ensure that the minimum information as described in the SCORE manual is present.

For study-specific trainings, as described in Section 16.5, the CRMs may help document completed training; for example, by providing the sign-in log from an in-person training and by providing training materials as posted files on the study-specific web page or via email to site representatives. The lists of participants in webinar trainings are not comprehensive; as such, virtual attendees must document their attendance in on-site training files following site-specific SOPs for personnel training and documentation. See Figures 16-3 and 16-4 for examples of a training documentation message and of a training log documenting attendance for study-specific webinars.

Figure 16-3. Example of Training Memorandum from CRM Documenting a Study-Specific Webinar

TO: IMPAACT 2060 Sites
FROM: Sarah Adams, IMPAACT 2060 Clinical Research Managers
CC: IMPAACT 2060 Protocol Team
SUBJECT: Documentation of IMPAACT 2060 Cohort 2 Training

This memorandum serves to document the study-specific training webinar conducted for IMPAACT 2060, Phase I/II Study of Drug X in Children, on 18 January 2022 for approximately one and a half hours.

The training, entitled "IMPAACT 2060 Cohort 1 Overview," was led by Emily Jones, Study Chair, and Sarah Adams, CRM. The training was intended primarily for Cohort 1 site staff; however, participation was not restricted, and other study site staff were welcome to attend.

The objective of this training was to establish a common understanding of the following:

- Study design, rationale, and objectives
- Cohort 1 eligibility criteria and study-specific procedures for recruitment, screening, and enrollment
- Cohort 1 procedures and evaluations

The training also provided an opportunity to address questions and to share key information, operational, tips, and reminders across sites.

The training materials presented as part of this webinar have been posted on the study-specific web page (http://impaactnetwork.org/studies/IMPAACT2060) and are available upon request from the IMPAACT Operations Center.

Study site Investigators of Record are responsible for ensuring that a copy of this message, the associated training materials, and site-specific attendance documentation are filed in on-site training files for IMPAACT 2060. As a reminder, per the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, all sites must establish and follow a standard operation procedure (SOP) for personnel training and certification documentation. **Each site is responsible for preparing attendance documentation for this webinar in accordance with this SOP.**

Thank you for your participation in the webinar; please contact the protocol team with any questions.

Page 1 of 1

Figure 16-4. Example of Training Documentation for Attendance at Study-Specific Webinar

IMPAACT 2040, Phase I/II Study of Drug X in Children
Cohort 1 Overview Webinar
16 August 2018

Training Led by: IMPAACT 2040 Protocol Team Members
Training Content: see attached slide set
Training Participants: as recorded below

Printed Name	Signature	Role on Study
Jane M. Doe	Jane M. Doe	Study Coordinator
Judy B. Taylor	Judy B. Taylor	Data Manager
Sarah Smith	Sarah Smith	Investigator of Record
Anna Brandon	Anna Brandon	Sub-Investigator
Samantha Ray	Samantha Ray	Lab tech
Clara White	Clara White	Research Nurse
James Nunn	James Nunn	Pharmacist of Record
		JMD 16 AUG 2018

Site Investigator: Sarah Smith

Site Number: 12345

Note: This is an example training log; any format consistent with site SOPs may be used.

17 LABORATORY CONSIDERATIONS

17.1 Network Laboratory Center

The Network Laboratory Center (NLC) consists of the IMPAACT Laboratory Center (ILC) and Westat. The ILC provides oversight to 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).

17.1.1 IMPAACT Laboratory Center

The 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 (QA)

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.

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 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. • Perform specimen processing, storage, and shipping activities for the site *(note: the ILC does not have oversight of processing facilities within sites)*
Network Laboratories Centers (NLCs)	• All DAIDS-sponsored clinical trials Networks are led by PIs whose personnel oversee the QA of the non-US laboratories participating in DAIDS-sponsored clinical trials • The NLC for IMPAACT consists of the ILC and Westat. 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.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 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.

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

Laboratory Types	Description
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 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 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 and focus 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. Site laboratory training and support will be coordinated with the Patient Safety Monitoring in International Laboratories (pSMILE), other external QA (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:

- Confirming that all laboratory testing in support of IMPAACT clinical trials meets the DAIDS requirements, including generating and overseeing study-specific Domestic Analyte Lists (DALs), Protocol Analyte Lists (PALs) for non-US laboratories, and DCLOT laboratory approval.

- Providing guidance to Network laboratories responsible for collection and oversight on 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 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 for all laboratories affiliated with NIAID CTUs sponsored by IMPAACT (e.g., Laboratory Director CV, CAP/CLIA or equivalent / accreditation certificates, and Laboratory Activation Checklist).
- 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.
- 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 Good Clinical Laboratory Practice (GCLP), will be brought to the IMPAACT Network Leadership, if applicable, as they are identified.

17.1.2 Westat

In collaboration with DCLOT, Westat provides support to 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 clinical trial results from biological specimens.
- Tracking of regulatory and QA documentation for all laboratories affiliated with NICHD CTUs sponsored by IMPAACT.
- Preparing international (non-US) NICHD laboratories to implement specific IMPAACT studies.
- Confirming that all laboratory testing in support of IMPAACT clinical trials meets the 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, will be 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 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 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 federal and international 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) protocol eligibility (e.g., pregnancy tests); 4) primary study endpoints or outcomes (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 Clinical Laboratory Improvement Amendments (CLIA) or state equivalent and certified by the College of American Pathologists (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, Virology Quality Assurance (VQA), Immunology Quality Assessment (IQA), Tuberculosis Quality Assessment Program (TBQA), and Clinical Pharmacology Quality Assurance (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 clinical trial. In some cases (e.g., novel bNAb testing), validation may not be available; appropriate requirements will be determined on a protocol-specific basis.

Laboratories must satisfy all Network-specific requirements **prior** to testing in the conduct of an IMPAACT clinical trial. 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 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 laboratory and assist in exploring options to ensure 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. The LPC outlines the specimen collection, processing, and shipping requirements for the study, as described in Section 11. The analytes required by the protocol are reflected in the study-specific LPC, PAL, and DAL. 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.

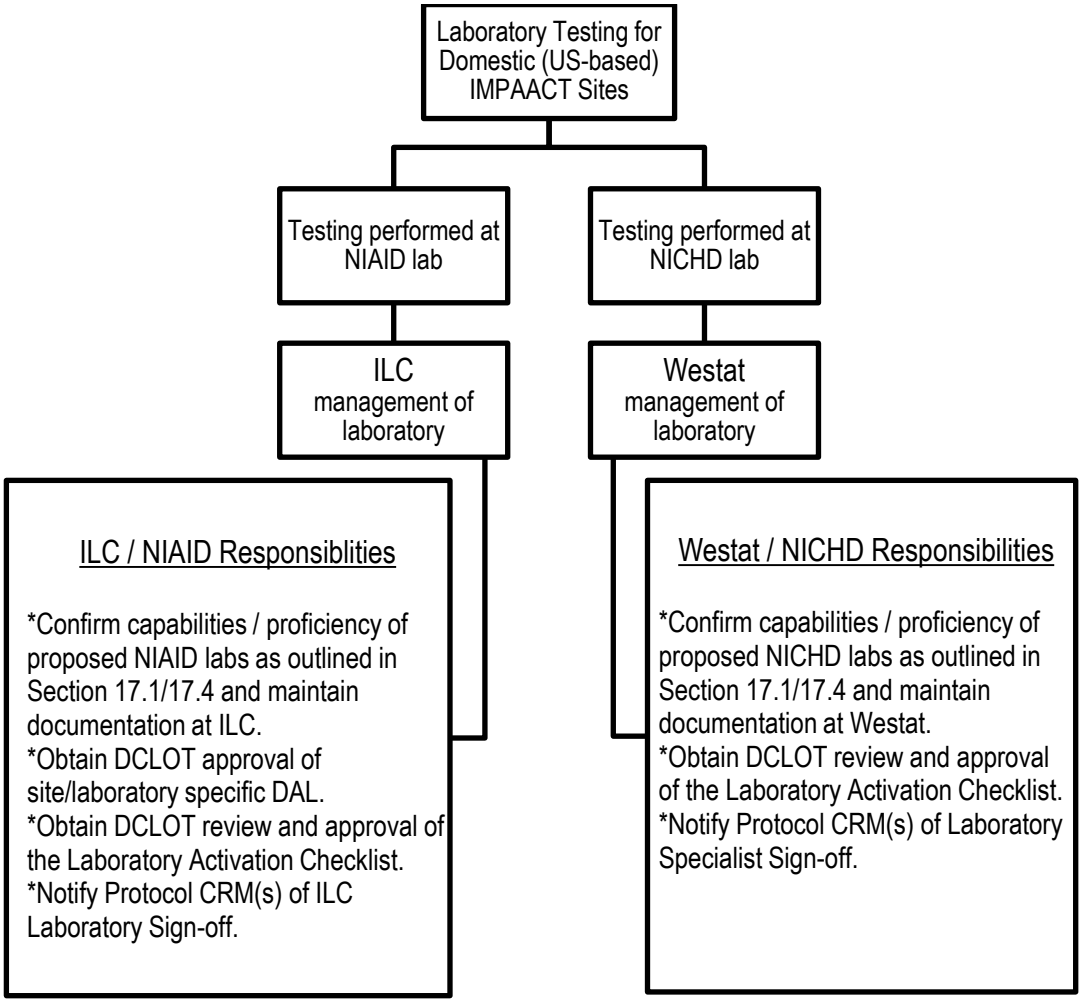
17.4 IMPAACT Laboratory Network Requirements: US Laboratories Affiliated with Sites

All laboratories located within the US (i.e., domestic laboratories) are required to provide the ILC (NIAID-sponsored laboratories) or Westat (NICHD-sponsored laboratories) 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. This documentation should include current copies of:

- Appropriate accreditations and certifications (e.g., CLIA and CAP) for all laboratories performing protocol assays
- Approval by the IQA and satisfactory performance in the EQA program prior to laboratory activation should viable peripheral blood mononuclear cells (PBMCs) be required for the protocol
- All import/export permits required to complete this protocol have been obtained
- 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
- Site/Lab personnel are responsible for updating the respective parties and distribution lists with the appropriate and current site and laboratory contacts
- Attestation from the Laboratory Director and/or Investigator of Record (IoR) or designee that:
  - Appropriate numbers of staff have current International Air Transport Association (IATA) or Department of Transportation (DOT) training
  - Site staff have participated in the requisite protocol-specific training
  - Appropriate numbers of staff have received CPQA certification, if required by the protocol
  - Any other DAIDS requirements

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 protocol duration).

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



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 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 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

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.

GCLP training of study nurses and any other non-lab personnel performing specimen processing and/or testing in the clinic or clinical laboratory is under the purview of laboratory management.

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 NLC – for IMPAACT, this is the ILC for NIAID-supported sites and Westat for NICHD-supported sites. Each network for which the laboratory does protocol 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' will be 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 will be notified via email they have 10 additional days to respond. The laboratory will work 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.

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 protocol-specific Specimen Flow Chart
- Confirmation of successful proficiency testing performance for all study analytes, as monitored by pSMILE, IQA (CD4), and VQA (note: proficiency testing requirements may be adapted, as per guidance from DCLOT)
- Confirmation of appropriate validation and/or verification for protocol-specified assays and instruments
- Normal References ranges/Acceptable results are available for the study population, including age and sex matched norms as applicable
- Confirmation of compliant local laboratory backup arrangements
- Laboratory Director's curriculum vitae (CV) (one time only, unless the Director has changed)
- Approval by the IQA and satisfactory performance in the EQA program prior to laboratory activation should viable PBMCs be required for the protocol
- 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 by the protocol (i.e., Material Transfer Agreements [MTAs], Specimen Transfer Agreements [STAs], regulatory permit, etc.)
- 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

- 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:
  - Appropriate numbers of staff have IATA specimen shipping certifications
  - Staff have participated in all required protocol-specific trainings including CPQA certification, if required
  - All required staff have completed GCLP training

All laboratory testing must 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, 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 international 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 IMPAACT Operations Center contact.

17.5.3 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, EQA procedures used for each analyte, and any backup 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 protocol-specific testing requirements. The PAL also captures information provided by the site laboratory about the protocol-specific specimen management and testing workflow in the associated Specimen Flow Chart document.

The ILC and Westat are 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 will be 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 MiLab system. The MiLab User Manual and instructions to request access are available in the MiPAL Site User Guide in the Training Materials and Resources on the IMPAACT website: https://www.impaactnetwork.org/resources/manual-procedures. Additional 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/.

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) will be responsible for distributing the protocol-specific MiPALs/PALs for completion to sites/laboratories that have been approved to participate in a given study. The site will submit 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 Flow Chart
- HIV Algorithm(s)
- Current pSMILE EQA Summary and Schedule for safety analytes tested in the PAL-designated primary laboratory(ies)
- Closed audit Action Plans for the primary laboratory(ies)
- Completed and LC representative-signed Laboratory Activation Checklist with Attestation

DAIDS-approved PALs and associated documents (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 Laboratory Approval Process

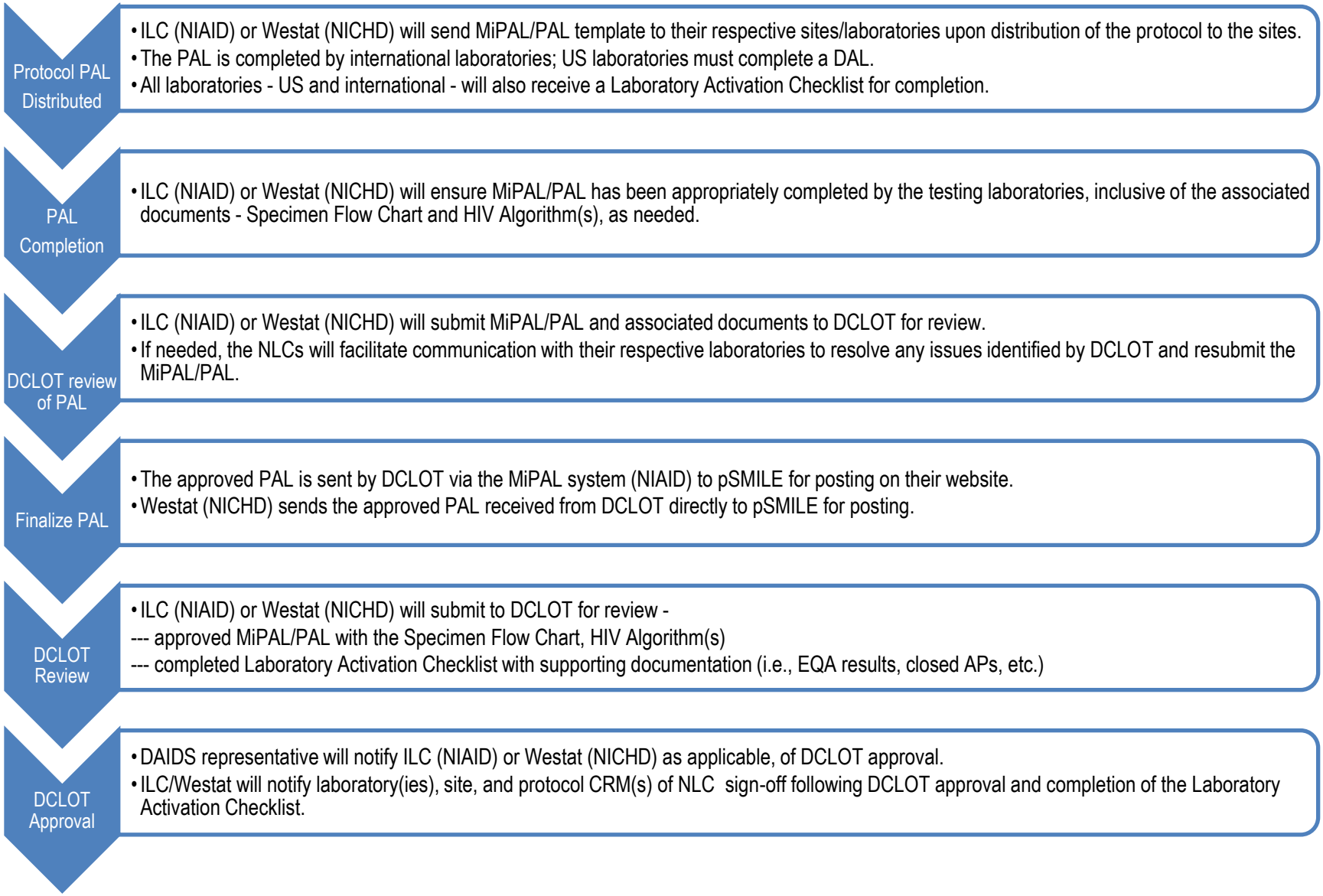
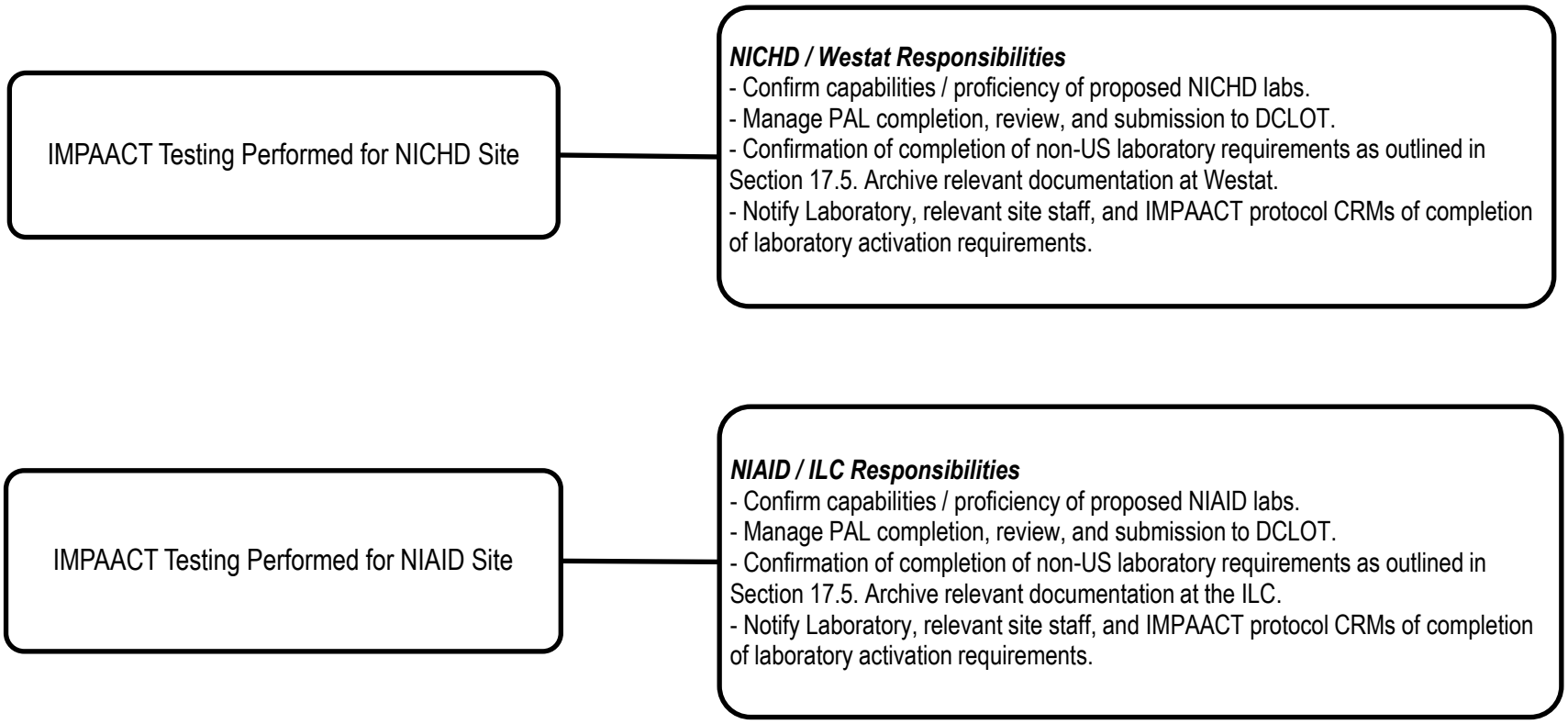


Figure 17-3. Non-US Laboratory Approval



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 will be 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 have access to LDMS quick add templates for most IMPAACT protocols. The use of LDMS quick add templates 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 required to log all expected specimens for a visit into LDMS, and then use the appropriate condition codes and comments to document when expected specimens are not available and update any quick add templates with the observed data.

IMPAACT laboratories that process viable 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. Additional fields and worksheets required for viable PBMCs are described in the cross-network PBMC Processing SOP: https://www.hanc.info/resources/sops-guidelines-resources/laboratory/cross-network-pbmc-processing-sop.html.

Additional information about entering PBMC specimen information into LDMS is available via the following online tutorial as part of FSTRF Films: https://www.ldms.org/training/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 laboratories 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 QC 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 by DAIDS-approved proficiency testing providers. All laboratories – both US and non-US – are required to participate in the IQA PBMC Cryopreservation program. Panels are sent to the sites based on the assays performed for the specific IMPAACT study in which the site is participating.

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 to ensure that the appropriate testing panels have been ordered and are being tested by the laboratory. The ILC (NIAID) or Westat (NICHD) will work with the various EQA providers 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 protocol testing. Proficiency testing is on 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 DAIDS-approved EQA providers, please refer to the DAIDS Requirements for Non-US Laboratories websites:

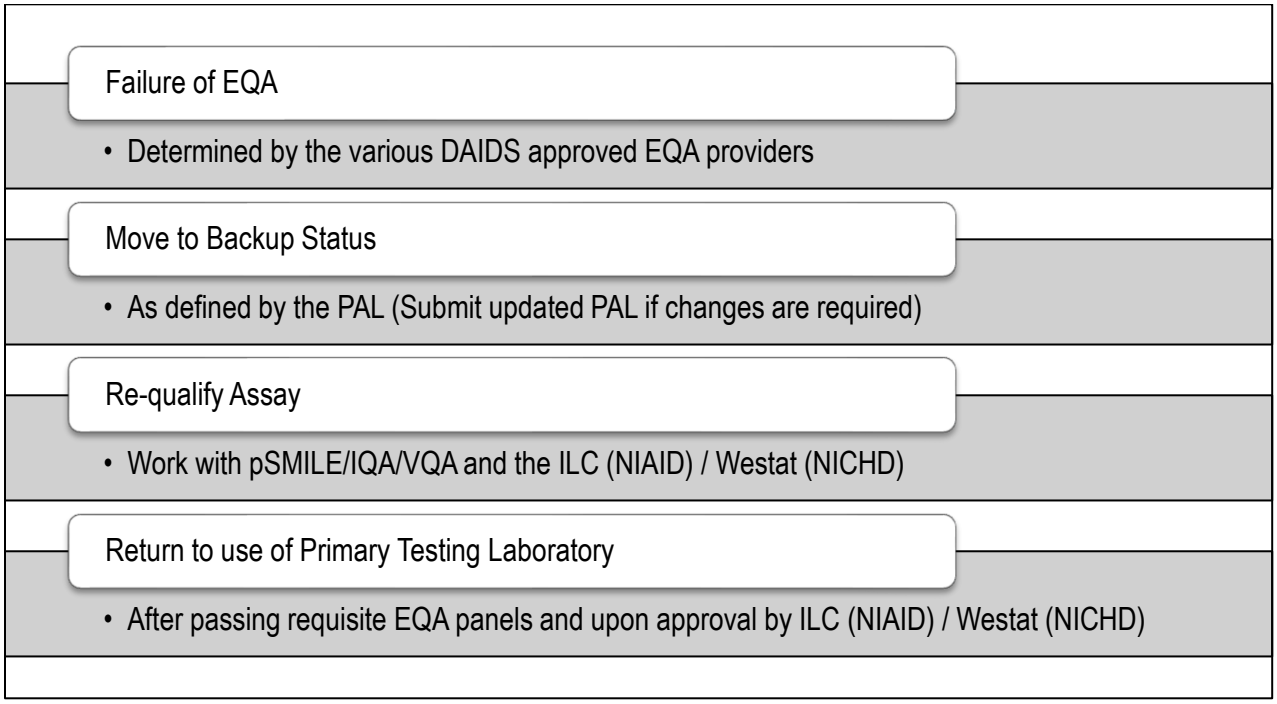
https://www.niaid.nih.gov/research/daids-clinical-research-policies-non-us-labs
https://psmile.org/index.cfm

17.9 Testing Backup Plans

IMPAACT requires all international laboratories to establish/identify a backup testing plan (i.e., a second instrument or alternative laboratory) for all analytes used for protocol testing 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 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.

Figure 17-4. 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 DAIDS EQA providers . 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.

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

Each laboratory should prepare a validation plan for the new method/instrument that will be established. Validation should be submitted to the appropriate DAIDS EQA provider(s) (i.e., IQA, VQA, etc.) for review. Validations requiring pSMILE review should be 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. In some cases, the ILC or EQA provider may work with the laboratory in advance to establish a validation plan. Once the DAIDS EQA providers have deemed a validation complete, the ILC (NIAID) or Westat (NICHD) will approve use of that instrument/method 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 on the pSMILE website at http://resources.psmile.org/resources/equipment.

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

Any change of test method, kit, or instrument after a trial has begun enrolling (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 (NIAID) or Westat (NICHD) representatives of a planned change in testing method/kit/instrument mid-protocol **before** implementing the change. This notification should include 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.
- Demonstration of successful EQA performance using the new method/kit/instrument. Please refer to Section 17.8 on EQA for additional information.

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 or Westat 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.

17.10.2 Registrational and IND Studies

For registrational studies for which DAIDS is the Sponsor and for selected other studies, documents are collected as determined by the DAIDS electronic trial master file (eTMF) study-specific index.

17.11 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 QMP.

- 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 as well as 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 QMP should describe the overall QA/QC systems in place for clinical trial 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/documents-and-records/quality-management-plans/guideline-for-development-of-a-quality-management-plan/view

17.12 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 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 also have the capacity to use LDMS to create the required shipping documents and files.

17.13 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, 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

17.13.1 Shipping Frequency and Monitoring

Shipments to the NIAID (BRI) and NICHD (Fisher BioServices) 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: Shipments to BRI will be 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 will be 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 will 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 will not be able to ship according to the time frame defined in the LPC or in the specimen request letter.

17.13.2 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 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 protocol testing laboratories. Each label is to be scanned into LDMS prior to packing the shipment, with the exception of PBMCs where the labels should be scanned prior to labeling the specimen tube.

17.13.3 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. 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.

Before shipping, laboratories need to 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 protocols (designated for storage in -70°C freezers) together to the designated repository in the same freezer storage box, provided the specimens for a given protocol are separated by an empty slot from specimens for a second protocol.

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.

17.14 Specimen Archive and Destruction

IMPAACT will periodically evaluate 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 will review the protocol template informed consent form and confirm with the DMC if specimens are available in centralized repositories. If specimens are available and the protocol informed consent form allows for future use of samples, the Operations Center will submit a repository spreadsheet listing to the DMC, for the DMC to add the applicable studies to the Specimen Repository Website.

Separately, the ILC and Repository Advisory Group (RAG) coordinator or designee will 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 will generate a protocol status report of eligible studies that meet the timeline for evaluation and coordinate with the DMC Laboratory Data Division Chief, or designee, to confirm if specimens are currently available, and the Operations Center to identify any specimen storage and shipment restrictions within the applicable protocol.

Following this initial review, the DMC will query the protocol team to confirm if all protocol testing has been completed for *POS-PAC* studies. At a minimum, consensus should be obtained from protocol chairs, LDMs, and statisticians. 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 will notify the site laboratories and repositories, as applicable, that specimens must be destroyed. For protocols whereby long-term storage and future testing are permissible, the RAG coordinator will generate a memorandum for IMPAACT Management Oversight Group (MOG) review. The MOG will determine if specimens, or a subset of specimens, should be transitioned to a centralized repository, destroyed, or remain locally at site laboratories. The RAG coordinator will distribute the MOG decision to the applicable protocol team members, including the DAIDS and NICHD medical officers, protocol chairs, statisticians, LDMs, and clinical research managers (CRMs). The DMC will notify applicable laboratories and repositories as needed to facilitate destruction, shipment, or ongoing storage as per the MOG response. At this time, the DMC will also notify laboratories to destroy specimens collected from participants who do not consent, or withdrew consent, for future use of specimens (i.e., for non-protocol-specific testing). The DMC will monitor that the 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: The DMC will provide 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 when specimen destructions are required. Upon team or ILC approval, the CRS may contact the laboratories and repositories to request specimen destructions.
- A freezer failure or a thawed or otherwise compromised shipment: The CRS or laboratory shall communicate with the ILC 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 when specimen destructions are required due to a protocol deviation.

Upon team or ILC approval, the CRS may contact the laboratories and repositories to request specimen destructions.

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, IRB/Ethics Committees (EC), 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 code for destroyed), 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. The DMC will report status of specimen destruction to the RAG.

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 protocols, including MTAs, STAs, and permits (when applicable to the site and protocol).

- MTAs/STAs between the sites of specimen origin and testing/end user **laboratories are the responsibility of the respective site**. These agreements will be facilitated by the ILC (NIAID) and Westat (NICHD). For NIAID sites, these MTAs should be submitted through the MiMTA portal in MiLab for easier tracking. The ILC (NIAID) and Westat (NICHD) 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 (NIAID-supported sites) for archiving in MiLab and filed by the sites as well.
- MTAs/STAs between site laboratories and the Network repositories, BRI (NIAID)/Fisher BioServices (NICHD), will be facilitated by the ILC (NIAID) and Westat (NICHD) for their respective laboratories. For NIAID sites, these MTAs should also be submitted through the MiMTA portal in MiLab for easier tracking purposes. 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 the repository and shipping laboratories are the responsibility of the site whose specimens are being shipped. Final copies of the executed MTAs/STAs are to be provided to the ILC (NIAID) or Westat (NICHD) as noted above for archiving in MiLab.
- 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.

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 (i.e., domestic) laboratories performing clinical testing must be CLIA certified or equivalent and are inspected every two years. Current certifications must be provided to the ILC (NIAID sites) or Westat (NICHD sites).

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

17.16.1 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.

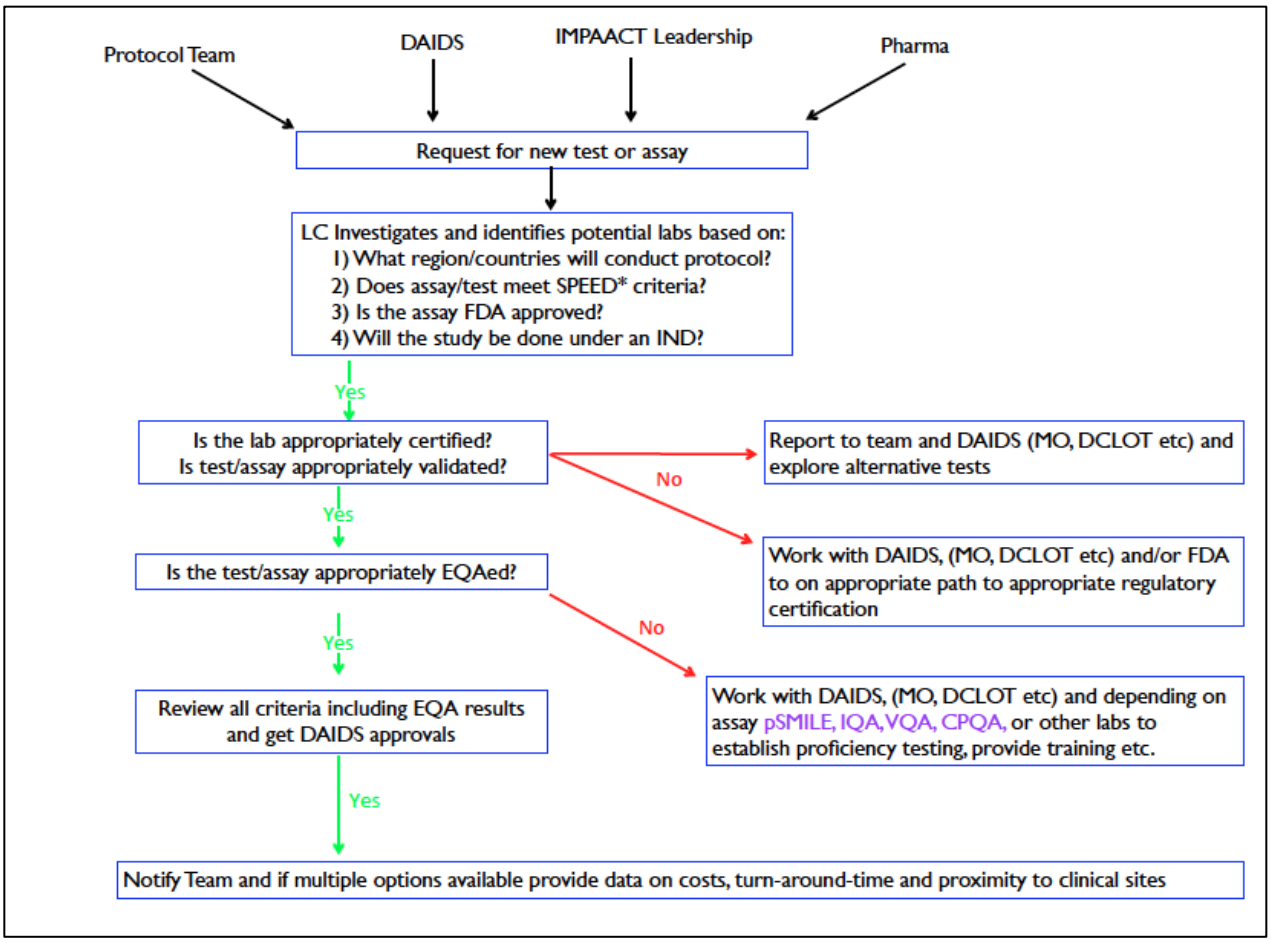
17.16.2 Laboratory Monitoring by IMPAACT

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 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 QA/QC problems identified through proficiency testing or site visits or by the site during study preparation or implementation.

17.17 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 17-5.

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 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 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.

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 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. 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.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 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 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

A copy of the relocation checklist must be submitted to impaact.qaqc@fstrf.org and the NICHD/Westat representative, if applicable.

IMPAACT laboratories will 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 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/
- 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: https://www.fedex.com/en-us/service-guide/dangerous-goods/resources.html
- 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/

18 NETWORK EVALUATION

The IMPAACT Network is committed to excellence in all aspects of its research. The Management Oversight Group (MOG) is responsible for overseeing a comprehensive process for evaluation of the Network with both ongoing and periodic components. The purpose of the evaluation process is to ensure that IMPAACT-affiliated National Institute of Allergy and Infectious Diseases (NIAID)-funded and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-funded clinical research sites (CRSs) and other Network entities are functioning appropriately, and contributing to the successful development, execution, oversight, completion, and publication of studies and other activities that advance the IMPAACT research agenda. A robust system of ongoing and periodic performance evaluation through the procedures outlined in this section serves to document the success of Network entities in meeting evaluation standards and identify areas for improvement. It informs leadership decisions about changes that may be necessary to improve functioning and performance while ensuring participant safety and data integrity. It also provides information needed to facilitate appropriate allocation of Network resources.

Evaluations are performed on an ongoing basis by the MOG; comprehensive periodic reviews are conducted by the Network Evaluation Group (NEG), on behalf of the MOG. The Laboratory Center (LC) closely monitors the ongoing performance of specialty and site laboratories on behalf of the MOG. In addition to the ongoing and periodic evaluation activities of the MOG, LC, and NEG, the overall scientific direction and leadership of the Network, including the work of the scientific committees (SCs), will be evaluated approximately mid-funding cycle, or as needed, by an external scientific advisory group, on behalf of the Scientific Leadership Group (SLG). The group is directly advisory to the SLG and consists of experts in the Network's research areas who are free from conflicts of interest. Details related to the external scientific advisory group are provided in Section 2; the remainder of this section focuses on the ongoing and periodic evaluations by the MOG and NEG.

Ongoing Evaluation

The MOG routinely monitors the status of IMPAACT studies, which reflect the collective efforts of Network entities, and performance of clinical research sites through review of reports generated by the Operations Center and Statistical and Data Management Center (SDMC).

The Operations Center generates a monthly Study Operations Report that provides updates on the status of studies in development and ongoing, participating CRSs, participant accrual, and study implementation issues. The SDMC generates monthly participant accrual and retention reports, by study and by CRS, as well as monthly site data management reports that provide information on data timeliness, data completeness, error responsiveness, and query responsiveness.

The LC closely monitors the ongoing performance of specialty and site laboratories. The DMC can provide laboratory data management reports to the LC as requested, covering various data management, shipping, and specimen handling areas.

Additionally, the IMPAACT Study Monitoring Committee (SMC) provides the MOG with updates on study reviews. As described in detail in Section 13, the SMC routinely monitors participant safety, study

progress, and the quality of study conduct for designated IMPAACT studies. Key SMC review findings and recommendations are summarized for the MOG monthly; the MOG is also notified immediately of any SMC findings or recommendations that may have a significant impact on study implementation. Problems and performance deficiencies may also be reported to the MOG by the SCs and Network central resources (Operations Center, SDMC, LC). Similarly, for studies overseen by a Data and Safety Monitoring Board (DSMB), any urgent findings or recommendations are shared with Network leadership as outlined in Section 13.

Ongoing evaluation of CRS performance is also performed by protocol teams through review of the same participant accrual and retention reports provided to the MOG, as well as review of study-specific monitoring reports provided by the SDMC, consistent with specifications of each study protocol and study progress data and safety monitoring plan (SPDSMP). Protocol team members from the Operations Center, SDMC, and LC also continually monitor all available information on CRS performance and notify teams and the MOG of any issues or concerns.

Through all of these mechanisms, the MOG continuously evaluates Network activities, sites, and studies so that performance problems are identified as soon as possible and can be addressed in a timely manner. Findings and recommendations identified during ongoing MOG evaluations are communicated to sites, study teams, and other Network entities as needed to ensure resolution and corrective action.

Periodic Evaluation

On behalf of the MOG, the NEG develops and carries out the Network evaluation program. The NEG is chaired by a member of the SLG; membership includes:

- IMPAACT Operations Center representative
- IMPAACT SDMC representative
- IMPAACT LC representative
- IMPAACT Community Advisory Board (ICAB) representative
- CRS representative
- Division of AIDS (DAIDS) representative
- NICHD Coordinating Contractor representative

The NEG oversees periodic evaluations of all IMPAACT-affiliated sites, as described in the remainder of this section. As each evaluation is completed, an evaluation report is generated and submitted to the MOG for review and action. This report focuses on critical aspects of study implementation at the site level, such as participant accrual and retention, data quality, laboratory performance, and regulatory issues. Evaluation reports are shared with the entities whose work was evaluated and with Network sponsors, as appropriate. Site community engagement programs are evaluated separately as determined by the ICAB in consultation with the MOG. At the request of the MOG, the NEG may evaluate and report on other Network entities in a similar manner.

18.1 Network Evaluation Plan and Performance Measures

The NEG develops performance metrics and an evaluation plan, utilizing the approach described below:

- Objectives, and the activities necessary to achieve them, are identified, reviewed, and adjusted as needed prior to each periodic evaluation by the NEG to determine their appropriateness and relevance to the performance of the Network at the time of the review.
- For each activity, the NEG identifies indicator(s) of whether objectives are being satisfactorily met; see Table 18-1. These are reviewed and adjusted as needed prior to each periodic evaluation to determine their appropriateness and relevance to the performance of the Network at the time of the review.
- Indicator data are compiled to determine the extent to which objectives are being met; see Table 18-1.
- Based on the compiled data, the NEG submits an evaluation report to the MOG, highlighting successes and making recommendations for improvement.
- Evaluation reports are also sent to NIAID clinical trials unit (CTU) principal investigators (PIs) and CRS leaders (for their site), NICHD site PIs (for their site), Laboratory PIs and Directors, the Network sponsors, Operations Center, SDMC, and LC.
- Sites are provided the opportunity to confirm the accuracy of their evaluation results and are requested to respond to the NEG's findings and recommendations, as needed. Responses are reviewed by the NEG and recommendations for any follow-up actions are provided to the MOG. See Section 18.4 for a description of follow-up actions and possible outcomes.

18.2 Performance Criteria for IMPAACT-affiliated NIAID-funded Clinical Research Sites

Site performance within each study and across studies is reviewed for the period of evaluation (a 12-month time period, generally), with consideration of the number and stage of studies in which each is participating, recency of site engagement, and external factors that may impact site readiness and accumulation of sufficient data for meaningful evaluation.

Site performance measures and standards, as determined by the NEG, are specified in Table 18-1.

Table 18-1. Performance Measures and Standards for NIAID Clinical Research Sites

Criterion	Measure(s)	Standard/Satisfactory	Source
Protocol Implementation Timeline	Time to enrollment once site receives the final protocol for submission to the institutional review board/ethics committee (IRB/EC) and other regulatory entities: • Date protocol distributed to site • Date of protocol registration approval • Date of study-specific activation • Date of first enrollment at site Note: includes protocols finalized for implementation during the evaluation period	Informational only	Operations Center, NIAID Clinical Research Management System (CRMS), SDMC
Participant Accrual	• Number of participants enrolled across the life of the study and within past 12 months compared to site-specific accrual target for study • Projected number enrolled versus actual number (projected number is based on site-provided goals as indicated in the MOG-approved site selection and accrual plan) Note: includes studies currently enrolling and studies closed to accrual during the evaluation period	>90% over the study accrual period for studies that have closed to accrual in the evaluation period Note: for NIAID-funded sites: DAIDS may consider discontinuing core funding for sites with <5 new enrollments or <3 in complex or high-priority studies	SDMC (with projections provided by the sites through the Operations Center)
Participant Retention	• Number of participants on study for the past 12 months • Number of participants reported to the data management center (DMC) as lost to follow-up for any reason (e.g., participant withdrawal, participant did not return/could not be located by the site) in past 12 months and over life of the study Note: includes studies currently enrolling and studies closed to accrual during the evaluation period	>90% overall retention or as per protocol	SDMC

Table 18-1. Performance Measures and Standards for NIAID Clinical Research Sites

Criterion	Measure(s)	Standard/Satisfactory	Source
Clinical Data Management	• Data timeliness: percent of visit tracking and study event tracking electronic case report forms (eCRFs) keyed within 14 days. Assesses the amount of time to key visit tracking and study event tracking eCRFs based on the participant's visit date.	≥ 90%	SDMC
	• Data completeness: percent of eCRFs entered. Assesses the current form status of Rave eCRFs that are not marked as overdue.	≥ 95%	SDMC
	• Error responsiveness: percent of errors answered within three days. Assesses site responsiveness to Site from System queries (errors). These are queries automatically triggered on the eCRF, immediately after saving the record.	≥ 95%	SDMC
	• Query responsiveness: percent of queries answered within 14 days. Assesses site responsiveness to Site from DM and Site from Coder queries.	≥ 90%	SDMC
	• Regulatory: percent of serious adverse events (SAEs) reported within three days to DAIDS Adverse Experience Reporting System (DAERS), including SAEs for studies in eData	100%	SDMC
Laboratory Data and Specimen Management	• Lab Query Responsiveness: Respond to queries within two weeks	≥ 90%	SDMC
	• PBMC Storage Shipping Compliance: store viable PBMCs in LN2 or <196C, or ship within five weeks of collection (e.g., to a repository)	≥ 95%	SDMC
	• BRI Repository Shipment Evaluations: overall resolution and responsiveness to shipment problems based on the total number of shipments. See Shipment Evaluation SOP.	≥ 90 composite score	SDMC

Table 18-1. Performance Measures and Standards for NIAID Clinical Research Sites

Criterion	Measure(s)	Standard/Satisfactory	Source
Laboratory Quality Assurance	• Safety Testing (50% of score) • DAIDS Virology Quality Assurance (VQA) Test Performance (25% of score) • Immunology Quality Assessment (IQA) Test Performance (12.5% of score) • Peripheral blood mononuclear cell (PBMC) Cryopreservation (12.5% of score)	≥ 90% composite score	LC
Outstanding Laboratory Critical Action Items	• Resolution of critical action items within 90 days of notification	≤ 90-day resolution	LC, Westat
Protocol Deviations	• Listing of reportable protocol deviations per site (see Section 12)	Informational only	SDMC

18.3 Overall Network Productivity

Overall Network function and productivity are evidenced in a number of ways, including but not limited to, development, review, and approval of new study proposals (concept sheets, data analysis concept sheets [DACS], new works concept sheets [NWCS]) and protocols; initiation of new studies and completion of ongoing studies; results reporting, presentation, and publication; and evidence of impact on public health policy and/or product licensure or labeling changes.

18.4 Outcomes and Actions

As noted above, each Network entity evaluated will be provided an opportunity to review evaluation findings and confirm their accuracy.

Sites with below-standard performance measures will generally have 30 days to provide the NEG with a written plan for corrective action in the relevant performance areas, if requested by the NEG and if corrective actions are not otherwise facilitated through the protocol team or other Network entities. The NEG may offer technical assistance and guidance and may recommend actions to facilitate improvement. Improvement must be demonstrated within six months or reasons provided for why this cannot be achieved. In such cases, an alternate time period must be agreed to by the NEG.

If a site fails to meet the standard for a specific measure(s) in two or more consecutive periodic evaluation cycles, the NEG may recommend to the MOG specific actions such as temporary closure of enrollment screens, pending review of site or laboratory procedures in that area(s).

A site's failure to meet the Network's performance requirements in two consecutive evaluation cycles – or by an earlier timepoint as determined by the MOG – may result in the withdrawal of protocol funds and/or a recommendation that Network affiliation with the site be terminated, with appropriate close-out activities to be completed. A site that is not meeting performance standards and is at risk of losing Network affiliation is provided the opportunity to summarize any extenuating circumstances that they would like considered before a final decision is made. The final decision on the site status with the Network will be determined by the MOG in consultation with the sponsors after considering the recommendations made by the NEG.

Network sponsors' requirements and/or cross-network evaluation of site performance and contributions – including the determination of whether the site is needed to support the scientific agenda of one or more networks – may result in a change in funding status, irrespective of the Network's evaluation.

19 DATA ANALYSIS AND PUBLICATIONS PROCEDURES

19.1 Overview, Key Principles, and Definitions

Publications in peer-reviewed journals and presentations at scientific conferences represent the most significant products of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network's research. The results of IMPAACT studies are to be published and shared in a timely manner in accordance with the National Institutes of Health (NIH) Public Access Policy. This section describes the process and requirements for preparation and review of abstracts, manuscripts, and other documents through which study-related results are disseminated. These procedures are intended to ensure timely development and dissemination of high-quality products reporting the results of IMPAACT studies or otherwise using IMPAACT-related data.

All abstracts and manuscripts using IMPAACT data must undergo an IMPAACT Network review before being submitted to a conference or journal (through submission to impaact.pubscoord@fstrf.org, as

described in detail below). The results of the main study (primary manuscript) must be submitted – and ideally published – prior to those of sub-studies and secondary manuscripts, unless otherwise approved by the IMPAACT Management Oversight Group (MOG).

These procedures should be reflected in the terms of Clinical Trial Agreements (CTAs), Memoranda of Understanding (MOUs), or alternative agreements approved by the IMPAACT MOG for studies with co-sponsoring agencies, companies, or other clinical trials networks, and studies in which data are collected and analyzed by a network or group other than the IMPAACT Statistical and Data Management Center (SDMC).

All IMPAACT publications must meet the criteria for authorship, disclosure, scientific integrity, and other requirements of peer-reviewed scientific journals.

Table 19-1. Definitions

Abstract	Brief report of IMPAACT study data prepared for submission to a conference; may be a regular abstract or a late-breaker abstract, as determined by conference submission requirements.
Closed to Follow-up ***[DAIDS study status]***	The study has permanently closed to accrual, all participants have completed study agents/products, and all follow-up visits have been completed. Last participant has completed the last study visit and all participants are "off study." Equivalent to "Study Completion" in ClinicalTrials.gov.
Data Analysis Concept Sheet (DACS)	A proposed investigation involving analysis of existing data from an IMPAACT (or Pediatric AIDS Clinical Trials Group [PACTG]) study to be undertaken by the Statistical and Data Analysis Center (SDAC) with IMPAACT funding. If the IMPAACT Network has not designated the study as concluded or openly available for use by investigators outside of the protocol team, the objectives of the proposed investigation should not overlap with the objectives stated in the study protocol or with secondary analyses defined by the protocol team after receipt of the final analysis report. The objectives should also not overlap with those specified in an approved IMPAACT DACS or New Works Concept Sheet (NWCS) that is not yet completed.
Data Request (DR)	A proposed investigation for which existing data from an IMPAACT (or PACTG) study are being requested for analyses to be performed without IMPAACT funding. (Note that an SDAC statistician may be among the proposing investigators but would not be seeking IMPAACT support for the work). If the IMPAACT Network has not designated the IMPAACT study as concluded or openly available for use by investigators outside of the protocol team, the objectives of the proposed investigation should not overlap with the objectives stated in the study protocol or with secondary analyses defined by the protocol team after receipt of the final analysis report. The objectives should also not overlap with those specified in an approved IMPAACT DACS or NWCS that is not yet completed. The statistical design of the research project and associated data analyses must be undertaken by the proposing investigators without IMPAACT funding.

Table 19-1. Definitions

IMPAACT Publications Review Group	Group responsible for reviewing IMPAACT manuscripts and abstracts on behalf of the Network prior to journal/conference submission. The group includes the IMPAACT Network chair and vice chair(s); the SDMC PI or designee; the Laboratory Center (LC) PI; representatives of NIAID, NICHD, and NIMH; and the relevant IMPAACT Scientific Committee (SC) chair. The protocol clinical research managers (CRMs) are also included in the distribution to the Publications Review Group. The Network chair serves as the chair of the IMPAACT Publications Review Group.
Masthead authors	Individuals listed as authors on a manuscript or abstract.
National Institutes of Health Manuscript Submission System (NIHMS)	An online system for submitting and managing final, peer-reviewed manuscripts in accordance with the NIH Public Access Policy.
New Works Concept Sheet (NWCS)	A proposed investigation involving use of existing biological specimens from an IMPAACT (or PACTG) study that may or may not require IMPAACT funding and may or may not involve analysis work by the SDAC. If the IMPAACT Network has not designated the study as concluded or openly available for use by investigators outside of the protocol team, the objectives of the proposed investigation should not overlap with the objectives stated in the study protocol or with secondary analyses defined by the protocol team after receipt of the final analysis report. The objectives should also not overlap with those specified in an approved IMPAACT NWCS that is not yet completed.
Participant Letter	A letter for study participants (or parents/legal guardians) summarizing or describing the study results and their implications or changes to an ongoing study necessitated by emergent findings from that study, another investigation, and/or other external factors such as a relevant change in treatment guidelines.
Primary Completion Date (PCD)	Date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome measure. May or may not be the same as the closed to follow-up date, depending on the study design.
Primary manuscript	Manuscript that reports findings related to the primary study objective(s) and outcome measures as described in the study protocol. Findings associated with secondary objectives may also be included. A protocol may have more than one primary publication. For example, a protocol may have more than one primary publication when a study is conducted in multiple stages and has a primary objective for each stage.
Protocol team	The team members whose names appear in the protocol roster, which usually includes pharmaceutical/industry representatives and other study sponsors/collaborators.
Publications Coordinator	Operations Center staff member who facilitates and tracks development, submission, review, and outcome of manuscripts and abstracts that use IMPAACT data, through the following address: impaact.pubscoord@fstrf.org.
Publication costs	Author fees associated with publishing peer-reviewed manuscripts.

Table 19-1. Definitions

PubMed Central (PMC)	The NIH digital archive of full-text, peer-reviewed journal articles; its content is publicly accessible and integrated with other databases (http://www.ncbi.nlm.nih.gov/pmc/).
Secondary manuscript	Manuscript that reports findings related to secondary study objectives and outcome measures as described in the study protocol, or scientific questions outside the primary objectives, e.g., baseline data reports, cross-protocol data, or analysis of specimens collected as part of a study but used for analyses not previously specified in the study protocol.
Site Investigator Letter	Limited scientific summary of the main trial results; disseminated to participating sites prior to public presentation or publication of the results or when changes to an ongoing study are necessitated by emergent findings from that study, another investigation, or other external factors such as a relevant change in treatment guidelines.
Writing team	A subgroup of the protocol team that collaborates to write an abstract or manuscript. Under certain circumstances, specialists who are not protocol team members may be included.

19.2 Key Responsibilities

Protocol Chair Responsibilities

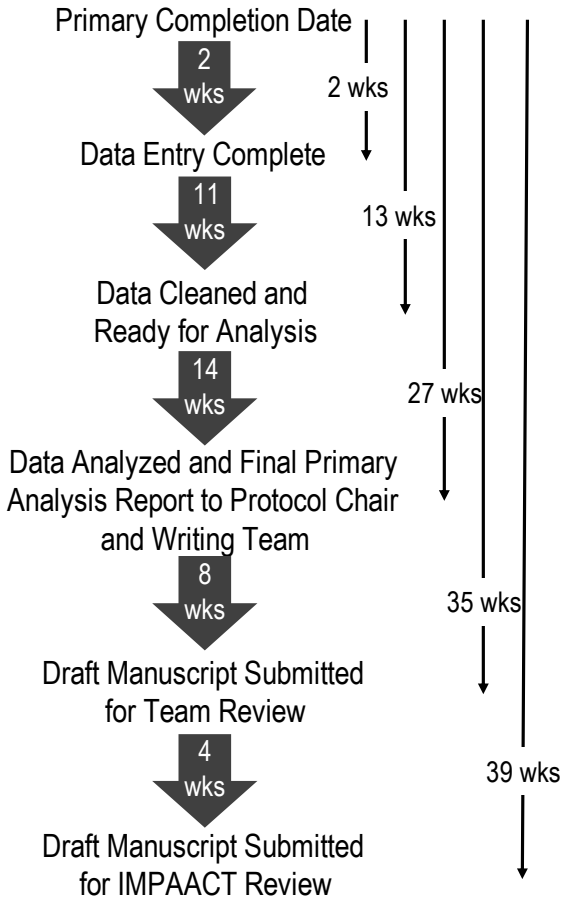
The protocol chair assumes overall responsibility for ensuring publication of the study findings in a timely manner. The results of each study should be reported in at least one peer-reviewed publication addressing the primary objective(s) within the timeline outlined in Figure 19-1. The protocol chair may designate a writing team to draft manuscripts or abstracts; the lead author is then responsible for completion and submission for IMPAACT review within the timeline specified in Figure 19-1, with continued oversight by the protocol chair. The protocol chair ensures that analysis and publication of secondary or sub-study results do not interfere with the analysis or publication of the primary study results and works closely with the publications coordinator at the IMPAACT Operations Center to track the manuscript development progress and to address any concerns that may arise.

For studies likely to generate multiple manuscripts, the protocol chair may elect to designate a subset of the protocol team to function as a study-specific publications committee to assist in performing the responsibilities described for the protocol chair. This committee may review and prioritize manuscript/abstract proposals from team members and others and should, at minimum, include the protocol chair and statistician(s), with other protocol team members included as needed. The SDMC contributes to the planning and prioritization of various manuscripts for a study, ensuring that analyses for each can be completed as scheduled. Prioritization is critical as all planned primary and secondary analyses cannot be expected to proceed at once. The list of secondary analyses will need to be carefully reviewed and prioritized, and in some cases, the analyses may have to be completed by someone outside of the SDMC.

Publications Review Group

On behalf of the Network, the IMPAACT Publications Review Group is responsible for reviewing all manuscripts and abstracts reporting on Network studies and related investigations prior to submission to a conference or journal. The group's review ensures high quality products and publications, scientific rigor, and compliance with IMPAACT publications procedures, as outlined in this section. The Network chair serves as the chair of the IMPAACT Publications Review Group. Membership includes the IMPAACT Network chair and vice chairs; the SDAC principal investigator (PI) or designee; the Laboratory Center (LC) PI; Operations Center representatives; and representatives of the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH); and the relevant scientific committee (SC) chair. The protocol clinical research managers (CRMs) are also included in the distribution to the Publications Review Group.

Figure 19-1. Timeline to Primary



19.3 Preparation, Review, and Completion of Analyses

19.3.1 Timeline Considerations

The timeline and process for preparation, review, and completion of primary analyses for publications, are outlined in Table 19-2 and described in the remainder of this section. The timelines for secondary analyses, and for ancillary studies, may vary based on prioritization and data availability.

The primary analyses timeline is in relation to the primary completion date (PCD) and/or the closed to follow-up date. These dates may be the same or different depending on the study design, as outlined below:

- For studies in which the PCD and the closed to follow-up date <u>are the same</u>, data analyses for publications and results entry into ClinicalTrials.gov will typically be completed after the closed to follow-up date to describe and report the final primary and secondary outcome measures.

- For studies in which the PCD <u>precedes</u> the closed to follow-up date, data analyses for results entry into ClinicalTrials.gov will typically be completed at two or more different times (first, related to data collected through the PCD, and subsequently, related to data collected through the final data collection date for each secondary outcome measure that requires a longer follow-up). Publications may also, but are not required to, be completed at the time of results entry into ClinicalTrials.gov; protocol teams should discuss plans for publications and results dissemination, ensuring consistency with protocol specifications as well as with any Study Monitoring Committee (SMC) and/or Data and Safety Monitoring Board (DSMB) recommendations.

The protocol data manager (PDM) is responsible for notifying the protocol team of the anticipated and actual PCD and closed to follow-up date. Procedures for data entry and clean-up, resolution of data queries, and database lock, if applicable, for all data should be initiated upon confirmation of the PCD and/or closed to follow-up date.

Timelines for studies with regulatory submissions may be adjusted, in consultation with the protocol team.

19.3.2 Update Statistical Analysis Plan(s)

For primary and secondary manuscripts, with input from the writing team, the statistical analysis plans (SAPs) and pharmacokinetic (PK) SAP are reviewed and, as needed, updated prior to the initiation of data analysis. Additional analyses may become important once the results become known; these may be completed and sent to the writing team for inclusion in the manuscript during the writing period. For manuscripts related to other and/or exploratory objectives, separate SAPs may be developed by the statistician in collaboration with the writing team(s).

The protocol statistician is responsible for updating the SAP, in close collaboration with the writing team. For pharmacokinetic (PK) studies, the protocol pharmacologist is responsible for updating the PK SAP.

The preparation of analysis plans for DACSs, NWCSs, and DRs will vary but the process is generally as described in Table 19-4.

19.3.3 Final Data Entry

Protocol teams should determine appropriate timelines for completion of data entry, data cleaning, and data analysis, following the guidance provided in Figure 19-1 and adjusted for study-specific considerations (e.g., timelines may be extended for larger studies or may be modified to align with agreed-upon regulatory deadlines). Additional exceptions may be considered for laboratory data that may require additional time for shipping, testing, and/or analysis after the PCD or close to follow-up date. The PDM and laboratory data manager (LDM), in consultation with the protocol team, are responsible for communicating these study-specific timelines with sites.

Refer to Section 14 for detailed instructions on site close-out communications and responsibilities.

19.3.4 Final Data Clean-Up

After all remaining data have been entered by sites, the PDM will continue to send out any additional queries to the sites to address delinquent or discrepant data.

In general, this data query period and subsequent completion of the database clean-up is expected to take approximately 14 weeks, although this time may be extended in some circumstances, such as for studies with many new sites or if data clean-up needs to be paused for preparation of a conference abstract or poster/presentation. Four weeks prior to the Study Database Closure/Database Complete Date, the PDM will send a notification to the sites that final Rave database lock will occur.

It is of the utmost importance that the protocol team agree that the study database is complete, that no more changes can be made to it, and that the final analysis will be based on the existing data in the database. The PDM will inform the protocol team of the extent of any missing data throughout the

conduct of the study. To confirm that Rave database freeze and lock can proceed as planned, the SDMC will review data for completeness approximately two to four weeks prior to database freeze. If this review indicates that data necessary for any planned analysis are not being cleaned in a timely fashion, the SDMC will send a message to the clinical research site (CRS) indicating that the site must rectify this situation.

Sub-studies involving eCRFs

The data clean-up timeline for a sub-study involving electronic case report forms (eCRFs) should be the same as that for the main study so final Rave database lock for the main study will not be delayed by the sub-study. By default, sub-study analysis will follow these guidelines. If, however, it is clear that there will be resource constraints involving analysis, they should be considered during the development of the sub-study and indicated in the analysis plan. It is acceptable that sub-study analysis might not begin until after the main study analysis has been completed. Clear communication between the main and sub-study teams is essential to ensure that the sub-study team can adhere to this timeline.

Sub-studies not involving eCRFs

Data clean-up for sub-studies not involving eCRFs should be done in accordance with good documentation practices and relevant institutional policies and procedures. Once the data clean-up has been completed, however, the analysis and manuscript preparation should proceed as described below. The assay and data clean-up timeline, except for any specimen eCRFs that are cleaned according to the main study timeline, should be determined by each sub-study team.

19.3.5 Study Database Lock

Once review of data completeness and accuracy is conducted, study monitoring is complete, and the protocol team agrees, the protocol statistician will indicate to the PDM that database freeze and lock should proceed as planned. After database lock has occurred, all routine completeness reports, queries, and discrepancy checks will cease. The date of database lock is the Study Database Closure/Database Complete Date, upon which the database will be considered complete to begin finalizing analysis.

For protocols in which the PCD precedes the closed to follow-up date, the database will not be closed until all follow-up data are entered; however, the study database snapshot date for the primary analysis will be confirmed by the PDM.

Laboratory data not entered via eCRFs

Any non-eCRF laboratory data required for the final analysis report must be finalized by the Study Database Closure/Database Complete Date (e.g., virology outcome measures included as primary or secondary outcome measures). In some circumstances, due to the length of time required to conduct specialized assays, it might not be possible to complete last visit specimen testing, data entry, and cleaning within the specified period after the study closes to follow-up; the planned Study Database Closure/Database Complete Date is updated to accommodate such special circumstances.

Limited non-eCRF laboratory data to be included as secondary components of the primary manuscript could be analyzed by the statistician for inclusion during the manuscript writing period; these data would not need to be finalized by the Study Database Closure/Database Complete Date but would need to be finalized before the start of the manuscript writing period, which begins when the applicable final analysis report is received by the writing team.

19.3.6 Completion of Final Analysis

After the Study Database Closure/Database Complete Date, the protocol statistician conducts the data analysis and prepares a final analysis report in accordance with the SAP. For PK studies, generally, the protocol pharmacologist conducts the PK data analysis and prepares a final PK analysis report in accordance with the PK SAP. As described further in Section 19.3, text describing the background, study design, and other trial aspects should ideally be drafted for primary and secondary manuscripts while data analyses are underway.

The draft final analysis report generated at SDAC is reviewed internally by SDAC before it is sent to the writing team. The protocol statistician(s) (or the non-SDAC statistician where applicable) and pharmacologist distribute their final analysis reports to the writing team(s) and notify the IMPAACT publications coordinator that the final analysis reports have been distributed, as outlined in Table 19-2. Additional analyses may become important once the results become known; these may be completed and sent to the writing team for inclusion in the manuscript during the writing period.

For protocols in which the PCD precedes the closed to follow-up date, a final primary analysis report(s), separate from secondary and other analysis reports, should be prepared and distributed to the writing team within approximately seven months, as per Figure 19-1, following the PCD.

Once all participants are off study and the primary analysis report(s) (includes all applicable primary analyses for a given study, such as primary safety and primary PK analyses) is completed and distributed to the writing team, the study status should be updated to "participants off study & primary analysis complete" (POS/PAC) by the CRM. This status also applies if it has been determined that no primary analysis can be done, and all participants are off study.

19.3.7 ClinicalTrials.gov Results Entry

The protocol statistician is responsible for preparing results for all non-PK primary and secondary outcome measures. For studies with PK data as part of the primary and secondary outcome measures, the protocol pharmacologist is responsible for preparing results for the PK outcomes and providing this information to the statisticians for entry into ClinicalTrials.gov.

SDAC is responsible for collating and entering all results for study outcome measures in ClinicalTrials.gov. Results for all primary outcome measures must be entered into ClinicalTrials.gov within one year of the PCD. Results for secondary outcome measures with completion dates prior to or concurrent with the PCD must also be entered within one year of the PCD. These entries are required regardless of whether the results have been published.

To coordinate this, the protocol statistician will distribute the Plan for ClinicalTrials.gov Results Entry, with updated deadlines for results submission, to the writing team, protocol chair, CRM, and protocol pharmacologist (refer to Section 11 for details on initial development of the plan prior to opening to accrual). The statistician will also provide a template to the protocol pharmacologist for submission of the PK results to SDAC for entry in ClinicalTrials.gov, as outlined in the Plan for ClinicalTrials.gov Results Entry.

Refer to Section 7 for detailed instructions on ClinicalTrials.gov management and timelines.

Table 19-2. Timeline for Primary Analysis Planning

Event	Timeline	Procedures	Responsibilities
Primary analysis planning	Six months prior to PCD for primary and secondary outcome measures with batched laboratory data	• Create timeline with planned dates • Create specimen shipping and testing plan for laboratory data • Check status of Material Transfer Agreements & laboratory contracts • Initiate data transfer agreements	Statistician (with PDM/LDM) LDM LC LDM
Update statistical analysis plans	Three months before anticipated PCD or closed to follow-up date (whichever comes first)	• Update the statistical analysis plans prior to initiation of final analyses (SAPs are finalized prior to opening studies to accrual; for protocols opened before this policy was implemented, the SAPs should be finalized at this point)	Protocol statistician, lead author and other writing team members
Primary completion date or closed to follow-up date (whichever comes first); final data entry period begins	Day 0	• Notify protocol team	Protocol data manager
Receipt of final analysis report by writing team	Seven months after Day 0	• Submit final primary analysis report to writing team • Notify publications coordinator that the analysis report has been transmitted	Protocol statistician

19.4 Development and Review of Publications

19.4.1 Formation of Writing Team

For primary and secondary publications, including manuscripts and abstracts, the protocol chair is responsible for designating lead authors and members, which typically include the protocol chair(s), vice-chair(s), statisticians, CRMs, and other protocol team members, e.g., immunologist, virologist, pharmacologist, or other content expert(s), as appropriate. Site investigators should be considered when developing the writing team. It is understood that others (e.g., protocol team members, etc.) may contribute to the publication as needed; however, the writing team is responsible for developing a complete publication. Further detail on authorship guidelines is included in Section 19.7.

The writing team for the primary publication is typically designated when the study is approaching the PCD or closed to follow-up date (i.e., approximately four to six months before whichever date comes first); if a study is prematurely terminated such that advanced planning is not possible, the writing team will be formed as soon as possible after study closure.

The writing teams for secondary publications are typically designated within six months of receipt of the primary analysis report by the protocol chair. Specifically, the process of developing the list of proposed secondary analyses (new or specified in the protocol), potential publications, and writing teams is expected to begin when the primary analysis report is received by the protocol chair and to be completed within six months. As noted above (Section 19.1), the secondary analyses must be prioritized by the protocol team (or designated sub-group), with guidance from the IMPAACT Publications Review Group as needed, with identification of any analyses to be performed without SDMC support.

The formation of writing teams for DACSs and NWCSs will vary but the process is generally as described in Table 19-5.

19.4.2 Primary Publications

The timeline and process for development and review of primary manuscripts is outlined in Table 19-3 and described in the remainder of this section. Manuscripts reporting the primary results of IMPAACT studies, including primary and applicable secondary outcome measures, are generally expected to be developed and submitted for internal IMPAACT review within nine months of the PCD or closed to follow-up date (whichever comes first). While timeline requirements are specified for primary manuscripts in Table 19-3, the procedures and responsibilities are applicable for all primary publications, including manuscripts and abstracts.

For each IMPAACT study, it is generally expected that the primary publication be submitted prior to secondary and sub-study publications, unless otherwise specified in the study protocol or otherwise approved by the IMPAACT MOG (e.g., based on the recommendation of a DSMB). However, for studies with multiple cohorts, groups, or other subsets, group-specific publications may be prepared prior to publication of any primary manuscripts. Also, publication reporting baseline findings or those reporting on the study design may also be prepared prior to the primary publications. The planned approach to publications may be described in the SAP. The protocol chair will ensure that analysis and publication of secondary or sub-study results do not interfere with the analysis or publication of the primary study results and will work closely with the CRMs to track the publication development progress and to address any concerns that may arise.

19.4.3 Secondary Publications

The timeline for analysis of secondary publications may vary based on prioritization and data availability (e.g., completion of laboratory assays). The timeline and process for development and review of secondary manuscripts are outlined in Table 19-4 and further described in this section. While timeline requirements are specified for secondary manuscripts in Table 19-4, the procedures and responsibilities are applicable for all secondary publications, including manuscripts and abstracts. Following receipt of the primary final analysis report by the protocol chair, the protocol team (or designated subset) begins developing a list of proposed secondary analyses, potential publications, and writing teams, if applicable, which is maintained by the protocol CRM with the protocol chair.

The list should include the following for each secondary publication:

- Proposed lead author and brief title and description of each publication,
- List and status of laboratory samples and assay results required for the publication, and
- Expected timeline for analysis completion, considering the steps outlined above for primary publications. As all secondary data analyses cannot proceed at the same time, preparation of secondary publications typically requires prioritization.

The lead author for each secondary publication will review the applicable SAP and work with the protocol team or writing group on any updates; if some relevant analyses were completed as part of the primary analysis, the remaining analyses are to be completed within a specified time frame. Once the secondary analysis report is submitted to the writing team, the draft publication is expected to be submitted to the publications coordinator for IMPAACT review within 12 weeks of receipt of the analysis report, inclusive of eight weeks for publication development and four weeks for review by masthead authors, protocol team members, and sponsors/collaborators (unless otherwise specified in the CTA or other third-party agreement, as described for primary manuscripts). As described in Section 19.3.2, it is generally expected that secondary and sub-study publications be submitted after the results of the main study/project primary publication have been submitted. The IMPAACT review process for secondary publications is the same as for primary publications.

19.4.4 Publications from DACS and NWCS

Procedures for submission and review of DACSs and NWCSs are described in Section 15. Any publications associated with a DACS or NWCS should include standard IMPAACT acknowledgements and should include the study number(s) (e.g., IMPAACT 2010) associated with the project. The timeline and process for development and review of publications from DACSs and NWCSs are outlined in Table 19-5. The timeline for preparation of the relevant analysis report may vary depending on a number of factors, including availability of data and assay completion. However, once the analysis report is available, the expectations and procedures for publication development and review are the same as for primary and secondary publications.

19.4.5 Publication from DR

Procedures for submission and review of DRs are described in Section 15. Any publications associated with a DR should include an acknowledgement of provision of data by IMPAACT; however, the timeline and process for development and review of publications from a DR need not follow the procedures outlined in Table 19-5. Any abstracts or manuscripts resulting from a DR should be sent to the IMPAACT publications coordinator prior to journal submission for review by the IMPAACT Publications Review Group and to confirm the appropriate acknowledgements.

Table 19-3. Timeline for Development and Review of Primary Manuscripts, including Timetable for Writing Team Formation and Manuscript Development and Review

Event	Timeline	Procedures	Responsibilities
Formation of writing team (see Section 19.4.1)	Approximately four-six months before anticipated PCD or closed to follow-up date (whichever comes first)	• Notify team that the study is nearing PCD or closed to follow-up status • Remind protocol chair/lead author of timeline and need to designate a writing team • Discuss writing team formation and agree on communications plan (e.g., materials to develop for participants, sites, and/or communities; how sites/participants are to be notified)	Protocol statistician CRM Protocol chair/lead author, CRM
Manuscript preparation begins; three-month (12-week) clock starts	Writing period should take no more than eight weeks after the writing team's receipt of the final analysis report, leaving at least four weeks for review by masthead authors, writing team, protocol team (including NIH, pharmaceutical company representatives, etc.) and incorporation of comments/revisions	• Remind protocol chair/lead author of manuscript submission deadline • Oversee timely completion of manuscript and adherence to timelines • Determine number and order of masthead authors • Develop full manuscript within eight weeks • Distribute for review by team/authors/sponsor/site Investigators of Record/pharmaceutical representatives and incorporate comments within four weeks • Begin compilation of the appendix of contributors	CRM and publications coordinator Protocol chair Protocol chair/lead author and other members Protocol chair/lead author and CRM
Manuscript submission for IMPAACT review	12 weeks after analysis report provided to writing team	• Submit manuscript to publications coordinator (impaact.pubscoord@fstrf.org) indicating protocol number, primary/secondary manuscript, and to which journal the team will be submitting, if known: – If submitting to an Open Access journal, notify the publications coordinator for determination of Open Access fee coverage (see Section 19.13 for more information) • Forward manuscript to IMPAACT Publications Review Group and relevant SC chair (if applicable) for review, with notification to the protocol chair/lead author • Confirm appropriate appendix of contributors and inclusion of Network and NIH acknowledgements	Protocol chair/lead author Publications coordinator Publications coordinator

Table 19-3. Timeline for Development and Review of Primary Manuscripts, including Timetable for Writing Team Formation and Manuscript Development and Review

Event	Timeline	Procedures	Responsibilities
IMPAACT review complete (unless revision/resubmission required)	Ten business days after submission for IMPAACT review	• Forward review comments and approval (or resubmission request) to protocol chair/lead author • If manuscript is approved, address reviewer comments and proceed with next step • If approved with revision and resubmission requested, submit response and revised manuscript within four weeks to publications coordinator • If disapproved, submit a revised manuscript within eight weeks (substantial changes to be agreed upon by authors, protocol team (including pharmaceutical company representatives, if applicable), primary reviewer, and IMPAACT Publications Review Group chair)	Publications coordinator Protocol chair/ lead author
IMPAACT-approved primary manuscript submitted to journal	Within four weeks of IMPAACT approval	• Submit manuscript to journal and send copy to publications coordinator • Ensure authors' disclosure of potential conflicts of interest as required by journal policy • See Section 19.7 for additional guidance related to journal submission and procedures for various outcomes	Protocol chair/ lead author
Acceptance for publication	Following journal submission	• Communicate outcome of submission to publications coordinator • Ensure publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH policy, prior to signing the journal publication agreement (or similar copyright transfer agreement) • Ensure authors' disclosure of potential conflicts of interest as required by journal policy • If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central: – Submit a request with the final peer-reviewed version (e.g., Microsoft Word document), all tables, figures, and supplementary information, and a copy of the signed publication agreement (or similar copyright transfer agreement) to the publications coordinator – Submit manuscript to PubMed Central via the NIHMS on behalf of the corresponding author and supply the author with an NIHMS ID – Approve the release and PubMed Central formatting of manuscript upon receipt of the email notification from NIHMS	Protocol chair/ lead author Protocol chair/ lead author Publications coordinator Protocol chair/lead author

Table 19-4. Timeline for Development and Review of Secondary Manuscripts, including Timetable for Writing Team Formation and Manuscript Development and Review

Event	Timeline	Procedures	Responsibilities
Determination of secondary analyses, secondary writing teams, prioritization, and timelines	Within six months after final primary analysis report is received by the protocol chair	• Submit list of secondary analyses specified in the protocol, newly planned analyses, and potential secondary manuscripts to the publications coordinator List should include: • Proposed lead author and brief title and description of each manuscript • List and status of laboratory samples and assay results required • Expected timeline for analysis completion, considering the steps outlined above for primary manuscripts • Where necessary, IMPAACT Publications Review Group guidance will be sought on prioritization of secondary analyses/manuscripts and/or which analyses may need to be completed without SDMC support • Monitor adherence to timelines; update as necessary	Protocol chair Protocol chair and statistician Protocol chair and CRM
Writing team formation (see Section 19.4.1)	May vary	• Form writing team	Protocol chair/lead author
Manuscript preparation begins; three-month (12-week) clock starts	Writing period should take no more than eight weeks after the writing team's receipt of the final analysis report, leaving at least four weeks for review by masthead authors, writing team (including NIH, pharmaceutical company representatives, etc.), and incorporation of comments/revisions	• Remind protocol chair/lead author of manuscript submission deadline • Oversee timely completion of manuscript and adherence to timelines • Determine number and order of masthead authors • Develop full manuscript within eight weeks • Distribute for review by team/authors/sponsor and incorporate comments within four weeks • Begin compilation of the appendix of contributors	CRM or publications coordinator Protocol chair Protocol chair/lead author and other members Protocol chair/lead author and CRM

Table 19-4. Timeline for Development and Review of Secondary Manuscripts, including Timetable for Writing Team Formation and Manuscript Development and Review

Event	Timeline	Procedures	Responsibilities
Manuscript submission for IMPAACT review	12 weeks after analysis report provided to writing team	• Submit manuscript to publications coordinator (impaact.pubscoord@fstrf.org) indicating protocol number, primary/secondary manuscript, and to which journal the team will be submitting, if known: – If submitting to an Open Access journal, notify the publications coordinator for determination of Open Access fee coverage (see Section 19.13 for more information)	Lead author
		• Forward manuscript to IMPAACT Publications Review Group and relevant SC chair (if applicable) for review, with notification to the lead author	Publications coordinator
		• Confirm appropriate appendix of contributors and inclusion of Network and NIH acknowledgements	Publications coordinator
See Table 19-3 for all remaining procedures (including timelines, and responsibilities): IMPAACT review complete (unless revision/resubmission required), IMPAACT-approved secondary manuscript submitted to journal, and Acceptance for publication)			

Table 19-5. Timeline for Development and Review of Manuscripts from DACSs and NWCSs, including Timetable for Writing Team Formation and Manuscript Development and Review

Event	Timeline	Procedures	Responsibilities
DACS or NWCS submitted and approved (See Section 15)	Unless otherwise determined by the protocol team and MOG, one year after protocol team confirmation of secondary analyses to be completed and published by the team	• Once the study data are openly available for use by investigators outside of the protocol team, proposals for use of data and specimens are submitted via a DACS or NWCS and reviewed as described in Section 15	Proposing investigators (may be protocol team members or investigators outside of the team)
Writing team formation	May vary	• Form writing team • Notify publications coordinator of lead author	Lead author
Manuscript preparation begins; three-month (12-week) clock starts	Upon receipt of analysis report; timeline same as specified above for primary and secondary manuscripts	• See Table 19-3	See Table 19-3
See Table 19-3 for all remaining procedures (including timelines, and responsibilities): Manuscript submission for IMPAACT review, IMPAACT review complete (unless revision/resubmission required), IMPAACT-approved secondary manuscript submitted to journal, and Acceptance for publication)			

19.5 Tracking of Manuscript Preparation

The guidelines and procedures outlined in this section apply to primary and secondary manuscripts as well as manuscripts developed from DACSs or NWCSs. Timelines may vary for manuscripts from DRs.

If the publications coordinator does not receive a final draft manuscript within 12 weeks following distribution of the final analysis report for the primary analyses by the SDMC, they will query the protocol chair and writing team for an explanation and proposed new timeline in writing. Requests for extensions must be approved by the IMPAACT Publications Review Group chair.

Further delays without sufficient justification may result in replacement of the lead author (and/or writing team), as determined by the protocol chair (if different from the lead author) and the IMPAACT Publications Review Group chair in consultation with other members and endorsed by the Scientific Leadership Group (SLG). The new lead author will be given a reasonable amount of time to complete the manuscript.

19.6 IMPAACT Publication Review Process

Publications based on IMPAACT data must be reviewed and endorsed internally prior to journal or conference submission. Prior to submission to the publications coordinator for IMPAACT Publications Review Group review, draft publications reporting study or study-related results must receive approval by the co-authors, be shared for review by the protocol team (at minimum, the protocol chair(s), protocol statistician(s), Medical Officers MO(s), CRM(s) and, if applicable, pharmaceutical representatives), and undergo any necessary review by industry or other sponsors/collaborators as specified in the CTA, other third-party agreement, or internal processes. Internal organizational reviews may also be conducted (e.g., SDAC, NIH, and/or pharmaceutical company reviews) but must be coordinated in keeping within the overall timeline. The lead author is responsible for ensuring that all applicable reviews are completed, and approvals are obtained prior to conference submission.

Once the review and approval steps above are completed, the lead author must submit a final draft, appendix of contributors (if applicable), Network and NIH acknowledgements, and the name of the journal or conference planned for submission to the publications coordinator to initiate the review process.

The publications coordinator will review the submission to ensure that all applicable materials are included. The publications coordinator will submit the draft to the IMPAACT Publications Review Group, with a copy to the relevant SC chair. A primary reviewer is assigned by the IMPAACT Publications Review Group chair to review the manuscript or abstract in detail and determine whether to endorse it for journal or conference submission. The primary reviewer may be a member of the IMPAACT Publications Review Group, an SC chair or vice chair, a member of the IMPAACT SLG, or another reviewer with specific expertise in the topic area.

When United States (US) government (e.g., NIH) staff are co-authors, publications must be approved by their institute/agency. The US government staff person is responsible for obtaining the necessary approvals. Different government agencies have different review time requirements, so authors and the US government staff person should take those requirements into consideration during the publication review process.

IMPAACT Publications Review Group Timelines and Outcomes

The primary reviewer and IMPAACT Publications Review Group have ten working days from receipt of the manuscript in which to comment. For conferences with a large number of abstracts expected (e.g., AIDS, CROI), the draft abstract must be submitted to the publications coordinator at least ten working days prior to the deadline for the abstract to be submitted to the conference organizer. For other conferences, the draft abstract must be submitted at least five working days prior to the conference submission deadline. If the data necessary to complete the abstract are not available within the designated time frame, an alternative review process may be determined by mutual agreement of the writing team and IMPAACT Publications Review Group chair.

Review outcomes and other comments are compiled by the publications coordinator and shared with the corresponding author (copying any others included in the submission) at the end of the comment period. All IMPAACT Publications Review Group members are not required to comment but forfeit their right to do so after ten working days. The review will result in one of the following outcomes:

- Endorsed for journal or conference submission with or without comments for author consideration; no further review required
- Revision and re-review required with comments to be addressed as appropriate
- Disapproval

IMPAACT endorsement for submission must be obtained before the publication may be submitted to a journal or conference. If the publication is endorsed for submission with reviewer comments, the writing team will address those comments as appropriate and then proceed with preparation for submission.

If revision and resubmission is requested, a response and revised publication must be submitted by the lead author to the publications coordinator within four weeks of receipt of the review comments.

If disapproved, the publications coordinator may arrange for a discussion of potential next steps by the primary reviewer, Publication Review Group chair, lead author, other writing team members, and other Publications Review Group reviewers, as needed. If agreement cannot be reached, the matter may be referred to the MOG. It is generally expected that a revised manuscript will be resubmitted within eight weeks.

Substantial changes to the publication, in response to either a revise and resubmit or disapproval, must be agreed upon by the writing team, masthead authors, and protocol chair and may require re-review by the pharmaceutical company or other sponsors/collaborators prior to resubmission to the publications coordinator for IMPAACT Publications Review Group review.

Review of Publications from Laboratory Projects

Manuscripts and abstracts from IMPAACT laboratory projects must undergo IMPAACT Network review as described above; however, for these manuscripts, it is not expected that study teams will review, unless data from the study were used. For these types of publications, the LC PI or designee will serve as the primary reviewer.

19.7 Journal Submission

The final manuscript is submitted to the journal selected by the lead author in consultation with the protocol chair, and a copy is sent to the publications coordinator.

If a journal requests a statement about access to data, use the following:

> *"The data cannot be made publicly available due to the ethical restrictions in the study's informed consent documents and in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network's approved human subjects protection plan; public availability may compromise participant confidentiality. However, data are available to all interested researchers upon request to the IMPAACT Statistical and Data Management Center's data access committee (email address: sdac.data@fstrf.org) with the agreement of the IMPAACT Network."*

Revisions Comments from the journal reviewers should be handled at the writing team level. If significant changes are required, the lead author is responsible for notifying the publications coordinator, who will work with the IMPAACT Publications Review Group chair to determine if additional IMPAACT review is required.

Rejections If the manuscript is rejected, the writing team chair must inform the publications coordinator of future plans for the manuscript. Generally, manuscripts should be resubmitted within eight weeks, unless additional major analyses are required. The lead author must circulate the revised manuscript to the protocol chair and masthead authors prior to resubmission. In addition, if there are substantive changes (e.g., differences in the conclusions or findings described), re-review by the protocol team, pharmaceutical companies, and other sponsors/collaborators is required, and a copy of the reviewers' critique and the revision should be sent to the publications coordinator for transmittal to the IMPAACT Publications Review Group, with re-review and approval by the primary reviewer required prior to resubmission.

Accepted manuscripts Upon acceptance of the manuscript for publication by the journal, the lead author is responsible for providing an electronic copy of the manuscript to the publications coordinator, masthead authors, and the protocol team.

If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, the writing team chair should follow the Public Access Policy described in Section 19.11.

19.8 Conference Submission

The corresponding author will inform the publications coordinator of the conference's decision and, if known and accepted, the abstract's number and presentation type (e.g., poster or oral presentation) within ten days of notification by the conference organizer and provide the final accepted version of the abstract.

If the abstract is accepted and the protocol team determines that a site investigator letter and/or a participant letter are needed, these will be prepared and typically distributed to participating study sites at least two days in advance of the conference presentation; however, the terms of any NIH or conference embargo will take precedence. If NIH or Network leadership determines that a press release should be issued, its development and release will follow the procedures outlined in Section 6.

If an abstract is rejected by the conference organizer and the authors decide to revise and resubmit it, it must undergo re-review by co-authors, the protocol team, and the IMPAACT Publications Review Group prior to resubmission, if substantive changes are made.

Preparation of Conference Presentation Materials

If an abstract is accepted, the lead author must circulate the draft slides and/or poster to co-authors and the protocol team (at minimum the protocol chair(s), protocol statistician(s), MO(s), and CRM(s)), including NIH representatives and pharmaceutical industry and other collaborators, for review. Posters and slides do not need to be reviewed by the IMPAACT Publications Review Group. Use of the IMPAACT logo (available on the Network website, https://www.impaactnetwork.org/resources/network-logos-templates, or from the Operations Center) and appropriate contributors (Section 19.9.3) and acknowledgements (Section 19.10) are required on all abstract posters and presentations.

The accepted abstract will typically be sent by the CRM to the Investigators of Record of all participating sites at least two days before conference presentation; however, the terms of any NIH or conference embargo will take precedence.

Within two weeks of the conference presentation, the lead author should send a copy of the final materials presented to the publications coordinator for posting on the IMPAACT website.

19.9 Authorship

The guidelines and procedures outlined in this section apply to primary and secondary publications, as well as publications developed from DACSs or NWCSs.

19.9.1 Guidelines for Authorship

The masthead should include those individuals who have made substantial intellectual contributions to the specific publication, as defined in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/icmje-recommendations.pdf, updated January 2024):

"Authorship credit should be based only on:

- *Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND*
- *Drafting the work or reviewing it critically for important intellectual content; AND*
- *Final approval of the version to be published; AND*
- *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

In addition to being accountable for the parts of the work done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged—see Section II. A.3 below. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3.

Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript."

19.9.2 Decision for Authorship and the Author Order

The lead author is responsible for identifying and confirming co-authors during the publication development process. The list and order of names on the masthead should be finalized by the time it is ready for submission; the decision should be a reflection of individuals' intellectual contributions. The number of masthead authors of a publication may be limited by the journal or conference guidelines. When authorship must be limited, it is preferable for each organization/entity involved (e.g., protocol chair, Data Management Center (DMC), LC, Operations Center, SDAC, DAIDS, NICHD, NIMH, each participating site) to be represented by a single author. The first author of the manuscript is usually the lead author.

It is recommended that site investigators at sites that enrolled large numbers of participants or other IMPAACT investigators with specific expertise in the topic of the publication be invited to participate on the writing team early in the analysis plan development process so that they have the opportunity to meet these authorship criteria. Generally, for studies that enrolled participants from fewer than six institutions, one investigator from each institution contributing study participants may be considered for masthead authorship. For studies involving more than six institutions, institutions with high participant enrollment may have one investigator considered for masthead authorship. Site representation may also be determined based on the number of participants included in a specific sub-analysis. The address of each co-author should reflect their own site. If the protocol chair or vice chair is from a high enrolling institution and is already an author, they can place another investigator from that institution on the masthead. In cases where the large numbers of enrollees render the inclusion of a single representative from each site with high accrual infeasible, the team may consider developing an alternative plan for allowing masthead authorship by investigators from participating sites.

In instances where study work is completed or substantially conducted at one institution and a masthead author relocates to another institution prior to the publication being submitted to a journal or conference, both the author's current and former institutions should be cited. It is the responsibility of the relocated author and the site leader of the former CRS to ensure that both institutions are cited in the publication.

The relative roles of each member of the writing team will be determined as soon as the writing team is formed. Any disputes regarding study authorship or position on masthead should be addressed first with the lead author and protocol chair. Decisions concerning authorship may be appealed, if necessary, to the IMPAACT Publications Review Group chair.

19.9.3 Appendix of Contributors

In addition to the authors listed on the masthead, study-related primary and secondary manuscripts must include an appendix acknowledging contributors who were not listed on the masthead. Other contributors (e.g., protocol team members who are not masthead authors, site investigators/staff) will be listed in the appendix. All participating site institutions enrolling participants will be acknowledged in the article and generally listed in order according to the number of participants enrolled. The listing will include up to four persons per participating institution, including SDAC, DMC, LC, Operations Center, sponsoring NIH institutes, and industry or other collaborators, as well as the participating sites. The listing will be compiled by the lead author, protocol team chair, and CRM. The publications coordinator will confirm that there is an appropriate appendix of contributors upon submission for IMPAACT review.

For NWCSs and DACSs, a statement acknowledging the participating CRSs of the parent studies is sufficient.

If no appendix of contributors is allowed by the journal, the acknowledgements should include those specified in this section, with the number of individuals cited per institution to conform to the journal's specifications.

In general, this policy to acknowledge contributors applies to any conference presentation materials.

19.10 Acknowledgements

19.10.1 Network and NIH Acknowledgements

The IMPAACT Network and the specific protocol number should be included in the title and body of the manuscript or abstract (i.e., IMPAACT XXXX).

The grant acknowledgment and disclaimer on behalf of NIH should be as follows:

> *"Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH."*

Any publications associated with a DACS, NWCS, or DR should include the IMPAACT grant acknowledgement and NIH disclaimer, as described above.

19.10.2 Other Acknowledgements

If the work represented by the publication was directly supported by other sponsors, they should be acknowledged accordingly and in keeping with the terms of any applicable CTAs, MOUs, or other collaboration and sponsor agreements. For example, if study products were supplied by the manufacturer free of charge for use in the study, this should be acknowledged. It is the responsibility of the lead author and protocol team chair to ensure appropriate acknowledgement of contributors, sponsors, and collaborators.

19.11 Public Access Policy

The IMPAACT Network will comply with the NIH Public Access Policy. The complete information on this policy is available at the following website: https://publicaccess.nih.gov/policy.htm. The Public Access Policy requires that all manuscripts accepted for publication that are based on studies with NIH funding be submitted to the PubMed Central digital archive, where they will be available to the public. The final, peer-reviewed manuscript accepted for journal publication is the version to be submitted.

Some journals have made arrangements with the NIH to submit manuscripts accepted for publication without any further required action by the authors. The list of these journals can be reviewed at the following website: http://publicaccess.nih.gov/submit_process_journals.htm. For manuscripts submitted

to journals not on this list (not already complying with the Public Access Policy), authors must inform the journal that the manuscript is subject to the Public Access Policy when submitting it for publication, and make sure that any copyright transfer or other publication agreement allows the final peer-reviewed manuscript to be submitted to NIH in accordance with the policy. When the final peer-reviewed manuscript has been accepted for publication, the author must send a copy of this version of the manuscript and a copy of the signed publication agreement (or similar copyright transfer agreement) to the publications coordinator, who will submit the manuscript to PubMed Central via the NIHMS on behalf of the corresponding author and supply the author with an NIHMS ID, copying the SDMC's publications tracking group (cbar.pubs@sdac.harvard.edu). The lead author approves the release and PubMed Central formatting of the manuscript when receiving the email notification from NIHMS.

The publications coordinator will follow up with authors on the status of manuscripts that have been approved for journal submission by the IMPAACT Publications Committee and will track the progress on journal submission, submission to PubMed Central, and assignment of ID numbers.

19.12 Communications Plans and Dissemination of Study Results

The release of study results provides an opportunity to share findings that could influence the standard of care in the communities where IMPAACT studies are conducted or the design and/or conduct of ongoing or future trials. With input from the NIH sponsors and other collaborators, the protocol team (at minimum the protocol chair(s), protocol statistician(s), MO(s), and CRM(s)) is responsible for determining the appropriate plans and timing for communication of study results depending on the nature and status of the study, whether the findings may impact study participants, or the standards of care. Communicating interim results, prior to their publication, requires additional approval from IMPAACT leadership. Pharmaceutical representatives should be informed of this planning when there is a CTA between DAIDS and the company for the study. This determination should generally be made around the time that the final analysis report is provided to the writing team and protocol chair by SDAC or before. The timing of development and implementation of the communications plan and materials may be dictated by a recommendation for early release of findings by the DSMB or SMC overseeing the study. At the discretion of IMPAACT leadership and/or as dictated by recommendations from the DSMB or SMC overseeing the study, select individuals or groups may be briefed about study results prior to public release. Signed confidentiality disclosure agreements may be required.

19.12.1 Communications Plan for Results Dissemination

A study-specific communications plan is typically developed by the CRM in close collaboration with the protocol team (and lead author, if not part of the protocol team) to provide a framework around dissemination of key study results. Plans are generally developed ahead of results reporting in the following cases:

- Dissemination of primary analyses, particularly when results may impact guidelines/standards of care or when results are from Phase IIb/III/IV studies
- Dissemination of multiple analyses at one event, for example, when multiple abstracts presenting results from the same study are being presented at one conference

This plan includes the following information:

- Key members of the communications team (e.g., protocol chair, protocol statistician, designated spokespeople, etc.) and their roles
- Specified timelines and activities planned for release of the study results within the team and externally
- Key stakeholders (e.g., protocol team members, site staff, sponsors, community advisory boards, host country officials, collaborating institutions, other US government and non-US public health agencies, and investigators/sponsors of other studies that may be impacted by the study results) to be informed of the results
- Disclosure of study results (particularly of Phase IIb/III trials) by the protocol statisticians to study investigators, other protocol team members, IMPAACT leadership, and sponsors, as applicable

Results are released in an accurate, well-controlled, and timely manner to host country officials, study participants, community representatives, sponsoring industry collaborators, relevant non-governmental organizations, and other governments. Ideally this will happen before, or at the same time as, the results are released to the general public. Particular care is to be taken to coordinate the release of results with officials in host countries and in the communities where the study was conducted.

Study results may be shared with participating sites, sponsors, and collaborators through a number of means, including Site Investigator Summaries, Participant Letters, Lay Summaries, talking points, and question and answer documents.

19.12.2 Materials for Participant and Community Audiences

Typically, publications (e.g., manuscripts, abstracts) presenting results of a primary study analysis are accompanied by other documents reflecting the same messages as the publication in an appropriate format for participant and community audiences; these may include a Participant Letter, talking points, lay summary, or question and answer documents intended primarily for use by participating study sites to use when sharing results with key stakeholders. These documents are generally developed by the CRM(s) and reviewed by members of the protocol team; consistency within and between these supplementary documents and the final publication is confirmed prior to distribution. At minimum, the protocol chair(s), protocol statistician(s), MO(s), study community program manager, and CRM(s) should review the materials prior to distribution. These materials may also be developed for IMPAACT-related secondary abstracts or manuscripts that may have clinical relevance (i.e., may impact clinical care) to study participants and communities.

Dissemination of materials for participant and community audiences is generally expected to align with dissemination of conference abstracts to site investigators, i.e., at least one day before conference presentation. Dissemination of materials related to a manuscript publication is also expected to follow this timeline. The CRM is responsible for dissemination of the approved summary to participating study sites and team members.

Materials may be tailored to the study and sites participating in the study; however, all materials for dissemination to participants and communities should generally meet the following guidelines:

- Written as concise as possible (ideally no more than one to two pages in length)
- Language is clear and understandable:
  - Written in 6th to 8th grade level language and reading ease between 70 and 80
  - Avoids jargon; when not possible to avoid jargon, clearly explains terminology
- Includes the protocol number, title, and any study acronym
- Briefly describes the study purpose and includes the number and location of study participants
- Notes the current status of the study
- Includes the key findings of the publication and any implications for participants and/or communities

When the manuscript is published, or the abstract is presented, community- or external stakeholder-facing materials may also be posted on the study-specific webpage of the IMPAACT website.

19.13 Publication Costs

Through the Operations Center, IMPAACT will cover review fees and pages charges for primary and secondary manuscripts if they have been primarily funded by the Network and properly credited to the Network. Any additional author fees charged for approved manuscripts, including costs for publishing in an Open Access journal and charges for color figures, may be covered on a case-by-case basis as determined by the IMPAACT Publications Review Group chair.

IMPAACT will not cover Open Access costs for publishing in journals that do not require Open Access. Authors submitting a request for IMPAACT to cover Open Access costs in a journal that requires Open Access (e.g., PLOS ONE), must provide justification for submitting to this type of journal. If the publication cost is for a color figure(s), authors must provide justification for publishing in color.

Once confirmation is received that the IMPAACT Operations Center will cover the publication costs, the publications coordinator will provide the author with information for the invoice. Costs associated with ordering reprints will not be covered by IMPAACT and remain the responsibility of the author.

Publication costs for manuscripts resulting from NWCSs and DACSs will not be covered.

19.14 Concluding a Study

Per DAIDS Study Statuses, a study is classified as concluded once it is ended and no further activity or resource expenditure on it is expected. The study must meet all of the following events prior to being classified as concluded:

- All protocol-required data analyses are finished, or it has been determined that no analysis can be done.
- Primary manuscript has been accepted for publication or determined to be "not publishable" in any journal.
- Primary manuscript is published if primary manuscript has been accepted for publication.
- Other manuscripts from study's original plan have been accepted for publication or it has been determined that the analyses are "not publishable."
- Final Report or Executive Summary is submitted to DAIDS.

Note that the requirement for a final report or executive summary is satisfied when SDAC sends the primary analysis report to the writing team, which includes a DAIDS MO.

Prior to indicating that a study is concluded, the team should consider specimen destruction requirements, as described further in Section 17. In addition, the Operations Center and DMC will determine if the study qualifies for inclusion in the Specimen Repository website (https://www.specimenrepository.org). Studies meet requirements to be added to the website if the following conditions are met:

- The study informed consent forms allow for or specifically request consent for long-term storage and future testing, and
- Samples are available to be shipped or are stored at the IMPAACT specimen repositories (e.g., BRI for NIAID sites and Fisher for NICHD sites).

The Operations Center will update the DAIDS study status, as applicable.

APPENDIX I UNBLINDING PROCEDURES

I.1 Purpose

This appendix provides guidelines for unblinding the treatment assignments of participants enrolled in IMPAACT studies.

I.2 Scope

This appendix defines the concepts of "blinding" and "unblinding" the treatment assignment of study participants (and/or their parents/guardians), provides guidelines for when to unblind, and outlines procedures for how to unblind when it is determined that unblinding is appropriate.

I.3 Definitions

I.3.1 Blinding

The term "blinded" refers to a study in which knowledge of individual participant treatment or intervention assignment is withheld from one or more individuals participating or involved in the study. These individuals may include study participants (and/or their parents/guardians), study site staff, and protocol team members.

- **Single-blinded study:** The site investigator, other site staff, protocol team members, and/or sponsor staff involved in treatment evaluation are aware of which treatment the participant is receiving, but the participant is not, or vice versa
- **Double-blinded study:** The participant, site investigator, other site staff, protocol team members, and sponsor staff involved in treatment evaluation are unaware of the treatment assignment
- **Partial-blinded study:** Within a study arm, some of the study products are blinded and others are open-label (e.g., known active drugs [open] plus active drug or placebo [blinded])

I.3.2 Unblinding

For purposes of this appendix, "unblinding" means revealing the treatment to which an individual participant has been assigned. This may include revealing the treatment assignment to the participant, site investigator, other study site staff, primary care physician, protocol team members, Network, and/or sponsor members.

- **Full unblinding at completion of the study:** Under typical circumstances, all assignments of all participants are unblinded after the final clinical database lock has occurred, per instructions in the protocol. Full unblinding may also occur before the final clinical database lock has occurred if warranted based on interim results of the study or results of another study.
- **Partial unblinding:** Partial unblinding occurs when one or more study products or arms are unblinded, but others remain blinded. Thus, some aspect of the assignment of some participants remains blinded.
- **Emergency unblinding of an individual participant's assignment for medical reasons:** Urgent, unplanned unblinding prior to full study unblinding may be performed to protect participant safety when, as determined by the site Investigator of Record (IoR) or designee, knowing the participant's assignment would affect **immediate** medical management of the participant, e.g., for drug identity during an acute reaction.
- **Early unblinding of an individual participant's assignment for non-urgent medical reasons:** Unplanned unblinding of a participant's assignment before full study unblinding may be performed for reasons that are not urgent and would not affect immediate medical management but may affect other aspects of a participant's medical care. Examples include:
  - A participant becomes pregnant or contracts an illness before full study unblinding, and the participant or the participant's medical care provider requests the assignment because this information might affect decisions regarding the participant's medical management.
  - A participant with HIV wants to enroll in another study for which knowledge of the assignment is required for eligibility determination.
  - A participant wants to donate an organ or stem cells to a relative, and documentation of assignment would facilitate evaluation of the participant as a donor.

I.4 Roles and Responsibilities

Table I-1 outlines team member roles and responsibilities for unblinding.

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Protocol Team	• Specifies extent of blinding and incorporates unblinding guidelines in the protocol • Determines the planned unblinding date in advance, along with the timeline for study closure • Prepares information for site staff to communicate to study participants (and/or their parents/guardians) when their assignment is discussed
Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC)	• Reviews safety/efficacy data and may make recommendations to unblind all or part of a study prematurely (i.e., prior to the planned unblinding date)

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Data Management Center (DMC) User Support	• Provides emergency unblinding information to the IoR or designee when the site pharmacist of record (PoR) is otherwise unavailable to provide this information and the IoR or designee cannot access the Emergency Unblinding Utility on the DMC portal • Available 24 hours a day, seven days a week, except for five US holidays (New Year's Day, Memorial Day, Independence Day, Thanksgiving Day, and Christmas Day) • Grants access to the Emergency Unblinding Utility to IoR. Grants access to the Emergency Unblinding Utility to designees, with approval of the IoR
Division of AIDS at the National Institute of Allergy and Infectious Disease (DAIDS/NIAID)	• Reviews DSMB recommendations to unblind all or part of a study prematurely (for studies overseen by a NIAID DSMB)
IMPAACT Management Oversight Group (MOG)	• Reviews SMC recommendations to unblind all or part of a study prematurely (for studies overseen by an SMC) • Aids the protocol team in reaching a decision to unblind, as needed
Protocol Chair	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • If consulted by a site IoR, may provide input on the need for unblinding of an individual participant (neither consultation nor approval are required) *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Discusses early unblinding of an individual participant with the site IoR and relevant protocol team members, e.g., via conference call or email • Communicates the team's decision in writing (email is sufficient) to the site IoR, with a copy to relevant protocol team members • In consultation with the protocol statistician, approves release of assignments *Partial Unblinding Based on Interim Study Monitoring Review Recommendation* • If a DSMB or SMC recommends partial unblinding due to interim analysis results or results of another study, decides whether to unblind the relevant arms in consultation with relevant protocol team members, IMPAACT Network leadership, and study sponsor
Protocol Statistician (if protocol statistician is blinded, the Unblinded Statistician)	*Full or Partial Study Unblinding* • Obtains assignments for a study prior to initiation of planned analyses *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Actively takes part in discussing early unblinding with other relevant protocol team members • Along with the protocol chair, approves the release of assignments

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
DAIDS Medical Officer (DAIDS MO)	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • If consulted by a site IoR, may provide input on the need for unblinding of an individual participant (neither consultation nor approval is required) *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Actively takes part in discussing early unblinding with other relevant protocol team members
Investigational New Drug (IND) Holder	*Full or Partial Study Unblinding* • Provides input in unblinding discussions, as appropriate *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Provides input in unblinding discussions, as appropriate
Protocol Data Manager (PDM)	• In all situations except emergency unblinding of an individual participant's assignment, transmits unblinding request to the Chief Data Manager or designee • Prepares unblinding memorandum(s) for team review and finalizes memorandum(s) incorporating team input
Chief Data Manager or Designee	• In all situations except emergency unblinding of an individual participant's assignment, is responsible for providing unblinded treatment assignments *Full or Partial Study Unblinding* • Prepares unblinded listings of assignments for each site and distributes these to the sites along with the unblinding memorandum on the date specified by the team *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Receives team-approved request for individual unblinding from the PDM and provides assignment to site IoR or designee
Protocol Pharmacologist and/or Testing Laboratory	*Full or Partial Study Unblinding* • Requests approval from the protocol team to receive assignments required for pharmacokinetic analyses (e.g., to identify participants on a specific drug for targeted assay). This may not require full unblinding.
Clinical Research Site (CRS) Coordinator	*Full or Partial Study Unblinding* • Follows study-specific communication guidance (typically provided in the study-specific manual of procedures) with respect to inclusion of assignment information when contacting protocol team members and/or the DMC • Along with the IoR, receives unblinding information from the DMC for full or partial study unblinding and forwards to the site personnel specified in the unblinding memorandum

Table I-1. Roles and Responsibilities for Unblinding

Team Member	Responsibility
Site Investigator of Record (IoR) or designee	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • Determines need for emergency unblinding (input of study sponsor or protocol team not required) • Requests assignment for individual participant from the site PoR or, if the PoR is not available, uses the Emergency Unblinding Utility on the DMC portal. Access to the Utility is granted to IoRs listed in the NIAID Clinical Research Management System (CRMS). If cannot access the Emergency Unblinding Utility, contacts the DMC User Support Department. • Approves DMC User Support requests for designees' access to the Emergency Unblinding Utility on the DMC portal • Documents the unblinding and notifies individuals or groups designated in the protocol (copying the PoR) • Ensures that relevant institutional review boards/ethics committees (IRBs/ECs) and regulatory entities are notified • Ensures that assignments are shared only with persons who need to know the assignments and that no other unblinding occurs *Early (Non-Urgent) Unblinding of Individual Participant's Assignment for Medical Reasons* • Determines need for early unblinding in consultation with the group or individuals designated in the protocol • Requests assignment using the Unblinding Request Program on the DMC website • If request is approved, receives assignment memorandum from the Chief Data Manager or designee at the DMC • Ensures that relevant IRBs/ECs and regulatory entities are notified • Ensures that assignments are shared only with persons who need to know the assignments and that no other unblinding occurs
Site Pharmacist of Record (PoR)	*Emergency Unblinding of Individual Participant's Assignment for Medical Reasons* • Provides assignment for individual participant to site IoR or designee upon request • Files the unblinding request and the assignment provided in the pharmacy records for the study • Notifies the DAIDS Pharmaceutical Affairs Branch (PAB) protocol pharmacist of the unblinding • Ensures that the requested assignment is shared only with the IoR or designee and that no other unblinding occurs

I.5 Reasons and Guidelines for Unblinding

Conventionally, full unblinding takes place after the final clinical database lock has occurred, which happens after all study data have been entered into the database for all participants, data cleaning has been completed, endpoints have been reviewed (if applicable per the protocol), and the protocol team has declared the study dataset to be complete. On a date pre-determined by the protocol team, assignments are provided to all participating sites for each participant enrolled in the study.

It is critical to the objectives of any blinded study that the objectivity of the protocol team, site IoRs, other site staff, and participants (and/or their parents/guardians) be maintained. Any unblinding prior to the

final clinical database lock can result in bias and should therefore be avoided. Unblinding of individual participant assignments as participants reach study endpoints or come off study may severely compromise the integrity or objectivity of the study. Unplanned unblinding prior to the final clinical database lock should be undertaken only to protect participant safety or to fulfill safety reporting and other regulatory obligations. Unblinding plans that deviate from this appendix must be approved by the protocol statistician and the IMPAACT MOG.

Planning to unblind the assignments of all participants individually as they come off study is unconventional, as the potential for bias in the reporting of results for other participants is substantial. If a protocol team plans to perform unblinding in this fashion, this must be stated in the protocol so the plan can be reviewed and approved by the IMPAACT Multidisciplinary Protocol Review Group (MPRG).

Unblinding to obtain stratification information for randomization is not permitted. The purpose of stratification is to maintain balance of prognostic factors between treatments; even if blinded participants must be stratified as "unknown," analyses can still be conducted with very little loss in efficiency, and balancing is not likely to be affected. The Study Enrollment System (SES) can provide blinded assignment information internally to inform assignment to subsequent steps of the same study and to pre-specified rollover studies.

I.5.1 Guidelines for Emergency Unblinding of Individual Participant Assignments for Medical Reasons

The need for emergency unblinding of individual participant assignments is expected to be extremely rare.

If needed immediately to guide management of a serious illness or medical emergency occurring in a study participant, the site IoR or designee may obtain a participant's assignment from the site PoR independent of the study sponsor or protocol team. If the site PoR is not available, the IoR or designee may obtain the assignment, also independent of the study sponsor or protocol team, from the DMC. In this case, the IoR or designee should use the Emergency Unblinding Utility on the DMC portal (www.frontierscience.org). IoRs listed in the NIAID CRMS are given access to this utility. Designees must request Emergency Unblinding Utility access through DMC User Support and will be granted access upon approval by the IoR. If the IoR or designee does not have access to the Emergency Unblinding Utility, they may obtain the assignment from the DMC's User Support Department, which is available 24 hours a day, seven days a week (**+716-834-0900, ext. 7302; user.support@fstrf.org**), except for five US holidays (New Year's Day, Memorial Day, Independence Day, Thanksgiving Day, and Christmas Day).

Note: the guidelines in this section do not apply for participants who have died, because knowledge of assignment will not affect immediate management in such cases.

Requests for unblinding should be made by the IoR or designee to the PoR in writing, and the PoR should provide the participant's assignment directly to the requesting IoR or designee in writing. In cases of extreme emergency in which it is not possible for the unblinding request to be made in writing, the IoR or designee may make the request orally but must provide a written statement of the request to the PoR within 24 hours, including the reason why the request could not initially be made in writing. The PoR is responsible for documenting the unblinding in the pharmacy records for the study.

In cases of extreme emergency when the PoR is unavailable, the IoR or designee may perform the unblinding via the Emergency Unblinding Utility on the DMC portal.

In cases of extreme emergency when the PoR is unavailable and it is not possible for the assignment to be obtained via the Emergency Unblinding Utility, the IoR or designee may request the unblinded assignment from the DMC in writing by emailing DMC User Support (user.support@fstrf.org) and alerting them of the request via phone. In cases of extreme emergency in which it is not possible for the unblinding request to be made in writing to the DMC, the IoR or designee may make the request orally but must provide a written statement of the request within 24 hours to the DMC, including the reason why the request could not initially be made in writing.

In these cases of extreme emergency when the DMC receives an oral or written unblinding request from the IoR or designee, the DMC will provide the unblinded assignment in writing. In cases of extreme emergency when requested by the IoR or designee, when it is not possible for the assignment to be delivered by the DMC in writing, it should be provided orally by the DMC. The DMC will provide a written confirmation of the unblinded assignment within 24 hours and document the unblinding in the study database.

The IoR or designee must notify the relevant group or individuals specified in the protocol (e.g., the Clinical Management Committee, the DAIDS protocol pharmacist) of the emergency unblinding within 24 hours of the unblinding via email. The notification should include the participant identification number (PID), date, and time of the request, and reason for unblinding but should NOT include the unblinded assignment; the site PoR should be copied on the notification. Relevant site IRBs/ECs and regulatory entities must also be notified. The written request for unblinding and the PoR's or DMC's written response (with the assignment) must be filed in the site's pharmacy records for the study or study database, respectively. The PoR must notify the DAIDS PAB protocol pharmacist (via email) of the emergency unblinding within 24 hours of the unblinding.

Unblinded assignments should be shared with as few individuals as possible on a need-to-know basis. Care should be taken to prevent additional unblinding to maintain study integrity. The site IoR and site PoR are responsible for preventing additional unblinding beyond those who need to know and for protecting information that may identify the participant.

I.5.2 Guidelines for Early (Non-Urgent) Unblinding of Individual Participant Assignments for Medical Reasons

Unblinding information should be shared with as few individuals as possible.

Site IoRs or designees may request a participant's assignment before a study is fully unblinded for reasons that are not urgent and do not require immediate (emergency) unblinding but may affect the participant's medical care. Examples are provided in Section I.3.2.

The site IoR or designee will consult with the individuals or group specified in the protocol regarding the need for unblinding (e.g., via email or conference call) and then submit the request for unblinding using the Unblinding Request Program on the DMC portal. Decisions will be made by the group or individuals designated in the protocol on a case-by-case basis (see Section I.6.1). Early unblinding for this reason should generally not occur until all primary outcome data have been entered and cleaned, all queries related to these data have been resolved, and any clinical endpoints have been reviewed by designated reviewers. When earlier knowledge of a participant's assignment may affect the participant's medical care and/or would otherwise be in the participant's best interest, this requirement can be waived by the group or individuals designated in the protocol.

When this type of unblinding is approved, the knowledge of the participant's assignment should be

limited to the fewest number of people possible on a need-to-know basis. The PDM will inform the Chief Data Manager or designee of the team's decision and the Chief Data Manager or designee will prepare a memorandum that provides the assignment to the site IoR or designee and states, as determined by the protocol team, to whom the assignment may be provided by the IoR or designee. These individuals may include:

- Attending study or primary care clinician
- Study coordinator and/or study nurse
- Site PoR
- Participant

In some instances, only the site IoR (or designee) and participant's treating clinician will need to be unblinded. Protocol team members, including the protocol chair(s) and PDM, should not be unblinded.

If eligibility determination for a new study requires unblinding of an assignment from a study that is still ongoing, the decision of whether to unblind must be made by the original study team. In some cases, unblinding to determine eligibility may be inappropriate until after final clinical database lock. If the participant is on-study, the participant will be interacting with the community and site personnel still involved in the study, possibly biasing the site staff for the duration of the participant's involvement in the study.

I.5.3 Partial Unblinding for a Continuing Study

On occasion, a decision may be made to partially unblind one arm or one aspect of several arms due to the publication of interim study results. In cases such as these, the protocol team prepares a memorandum that includes guidance on the aspects of data entry specified in Section I.5.4 that need to be completed prior to unblinding. The Chief Data Manager or designee sends the partial unblinding instructions and the memorandum to the sites.

I.5.4 Unblinding after Final Clinical Database Lock

Unblinding a study may consist of:

- Informing study participants (and/or their parents/guardians) of their assignments
- Informing the sites of the assignments for their study participants
- Informing study chairs or other protocol team members of the study results
- Informing study chairs or other protocol team members of assignments
- Some combination of the above

When a study has been closed to follow-up, either at the scheduled closure or following a decision to close the study early, the conditions outlined below must be met before unblinding participants (and/or their parents/guardians), sites, and protocol team members.

Data must be entered and cleaned for primary outcome measures. Endpoint verification, if applicable, must be complete. Secondary outcome measure data should ideally be cleaned as well, but this requirement can be relaxed when unblinding is deemed a more immediate necessity by the protocol team. Laboratory samples must have been collected, but laboratory test results are not required to be finalized or entered into the study database. The time necessary to finalize and lock the clinical database can be six months or more after the last participant's last visit.

I.6 Procedures

I.6.1 Unblinding Individual Participant Assignments

Requests can be made to unblind individual participant assignments on a case-by-case basis as described in Sections I.5.1 and I.5.2.

When the site IoR or designee determines that an individual participant's assignment is urgently needed for immediate medical management, the assignment should be provided by the PoR or the DMC independent of the sponsor and protocol team and with no additional requirements as described in Section I.5.1.

For non-urgent early unblinding of an individual participant's assignment for medical reasons, two requirements should be met:

- Case report forms that capture self-reported and subjective data (e.g., questionnaire responses, adverse events) must be entered into the study database. This requirement may be waived if the provision of the assignment sooner is determined to be in the best interest of the participant.
- After initially conferring with the group or individuals designated in the protocol (e.g., via email or conference call), the participant's assignment must be requested using the Unblinding Request Program on the DMC website:
  - The purpose of this program is to collect information that the protocol team and DMC need to promptly and efficiently process unblinding requests. All fields on the screen should be completed, including the study number, PID, step number, site number, information about the IoR or designee, date the information is needed, and a detailed reason for the unblinding. Once the request is submitted, an email message will be automatically sent to the group designated in the protocol and will provide site staff with a copy in the appropriate email account. It may take one or more days for the team to respond.
  - The protocol chair will communicate the team's decision via email to the person who made the request, with a copy to the group or individuals designated in the protocol.
  - After the team approves the unblinding request, the PDM informs the Chief Data Manager or designee of the approval. The Chief Data Manager or designee sends the assignment information to the IoR or designee via encrypted email within 24 hours of the team's approval.
  - Documentation of the communication is maintained by both the site and the DMC.

I.6.2 Unblinding the Assignments of All Participants for a Study

Under typical circumstances, the assignments of all study participants will be unblinded after final clinical database lock, as outlined in Section I.5.4.

Procedure to unblind the assignments of all participants
During preparation for study closure, the protocol team should establish plans and timelines for unblinding. The team should also prepare any information needed to support site personnel in communicating assignments to study participants (and/or their parents/guardians). The DMC supplies a standard unblinding memorandum to the team for review and for the addition of any study-specific language the team wishes to include. The Chief Data Manager or designee prepares unblinding listings for each site with the unblinding memorandum on the date specified by the team.

Unplanned or sudden unblinding
The following standard approach will be followed. Any deviations from this standard must be specified in the protocol and reviewed and approved by the IMPAACT MPRG.

- Sudden (or unplanned) unblinding of one or more arms due to *interim analysis results or results of another study*: The decision to unblind one or more arms of an ongoing study is made by the team in conjunction with the MOG (which includes National Institutes of Health representatives and Network leadership). This can occur based on a recommendation from the DSMB or SMC or the results of another study.
- Participant contact: if a decision is made to unblind, participants (and/or their parents/guardians) should be unblinded as soon as possible following the relevant procedure from Section I.5. Every effort should be made by the sites to contact participants (and/or their parents/guardians) who are currently on-study and who have completed follow-up in order to provide and explain the assignments in the context of the relevant study results.
- Implications of unblinding on study data: when assignments are unblinded based on an interim analysis, the results of that interim analysis are expected to be reported in publications. Data from visits that occurred before the interim review but that were not in the database at the data cutoff date for the interim analysis report have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In the context of unblinding due to either interim analysis results or other study results, if analyses are reported on clinical data or samples collected after the unblinding date, the conditions under which these data were collected must be made clear in any publication.

It is important to note that, if all arms are not unblinded, participants on the remaining arm(s) (and/or their parents/guardians) are at a minimum partially unblinded in most cases.

I.6.3 Unblinding of External Entities for a Special Request

On rare occasions, an external body such as the US Food and Drug Administration may request that certain information from a study be unblinded. Such requests must be approved by the study team and the MOG.

I.7 References

- DAIDS Emergency Unblinding Policy, https://www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring
- DSMB or SMC guidelines (Section 13)
- Unblinding Request Program
- Emergency Unblinding Utility

I.8 Questions

Questions and comments regarding this policy may be directed to IMPAACT.OperationsCenter@fstrf.org.