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:

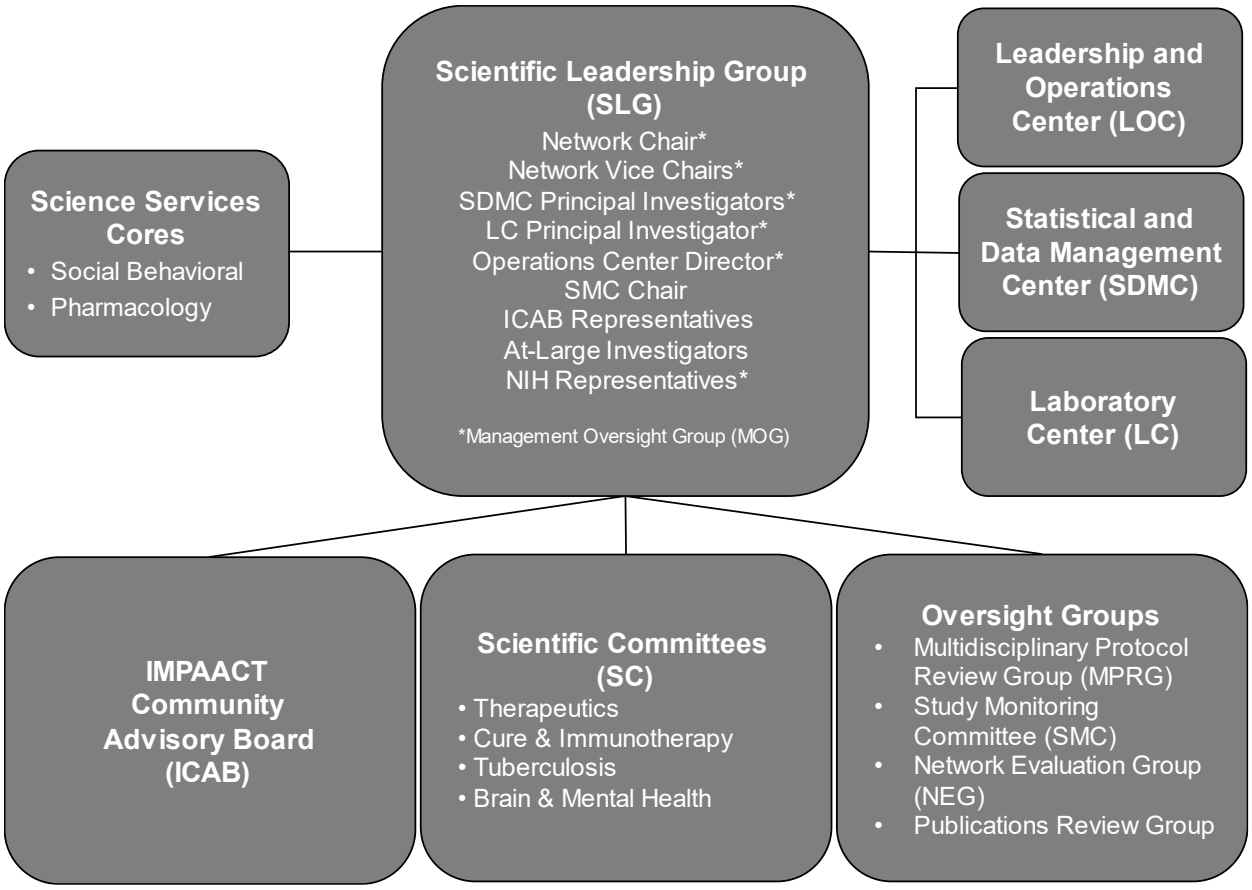
- Investigating potential neuroprotective and neurotoxic effects of ART to preserve neurocognitive development and mental health in infants, children, and adolescents
- Refining and optimizing the evaluation and treatment of neurocognitive and mental health disorders, particularly executive dysfunction, 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).

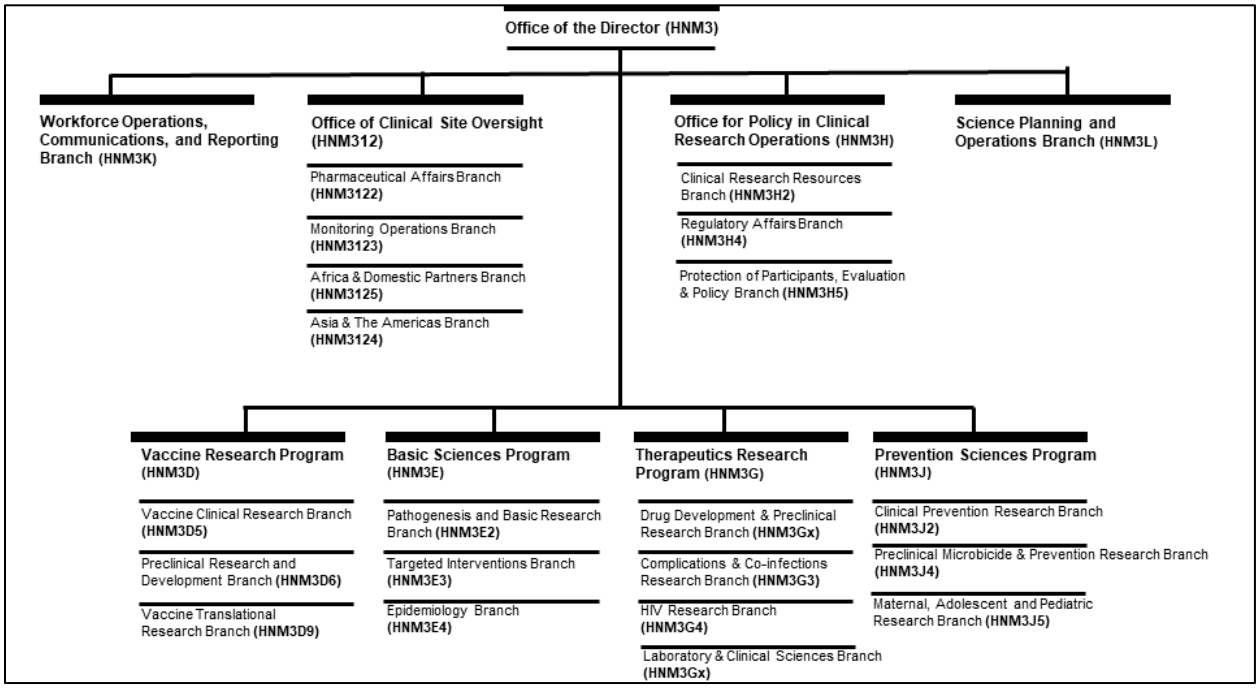
When an IMPAACT study is to be conducted under an Investigational New Drug (IND) application, DAIDS typically holds the IND and negotiates a clinical trial agreement (CTA) with the collaborating pharmaceutical company to document the responsibilities and rights of each party for the clinical trial. The 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.