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## **1 OVERVIEW OF THE IMPAACT NETWORK**

### **1.1 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 organized for the purpose of evaluating interventions to treat and prevent HIV infection, its consequences, and associated infections in infants, children, adolescents, and pregnant and postpartum women through the conduct of high quality clinical trials.

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 re-competition of leadership grants in 2013-2014, a new seven-year funding cycle began in December 2014.

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, below, for additional details related to NIH support of IMPAACT.

In this Manual of Procedures (MOP), mention of ‘HIV’ refers to HIV-1 unless otherwise stated, as HIV-1 is the most widespread type worldwide and is the most common circulating type among sites participating in IMPAACT studies.

See the IMPAACT Network website for additional details: <http://impaactnetwork.org>.

## 1.2 IMPAACT Mission and Scientific Agenda

IMPAACT's mission is to significantly decrease incident HIV and HIV-associated infections and to decrease mortality and morbidity due to HIV and HIV-associated infections and co-morbidities among infants, children, adolescents, and pregnant and postpartum women. IMPAACT's research agenda includes evaluation of the following:

- New and existing anti-HIV drugs and formulations
- Novel approaches for managing tuberculosis in HIV-infected or at-risk populations
- Biomedical and behavioral interventions to prevent maternal HIV acquisition, perinatal and postnatal HIV transmission, and secondary transmission from perinatally HIV-infected adolescents
- Immunogenicity, safety, and efficacy of high priority vaccines
- Potential for HIV cure through therapeutic interventions aimed at reduction and clearance of HIV reservoirs
- Interventions to prevent and manage complications of HIV infection and treatment

IMPAACT's mission and research agenda are organized into five research areas: HIV treatment, tuberculosis, HIV prevention, HIV cure, and complications and co-morbidities. These research areas are described in detail below.

### 1.2.1 HIV Treatment

Despite licensure of more than 30 ARVs in adults, most new antiretrovirals have not been evaluated for use in pregnant and postpartum women, children, and especially newborns and infants. IMPAACT aims to evaluate the pharmacokinetics (PK), safety, and drug interactions of new and existing ARV agents and formulations leading to optimal dosing and licensing for HIV-infected infants, children, adolescents, and pregnant and postpartum women. Priorities include evaluation of:

- Safety, PK, and drug-drug interactions in HIV-infected infants, children, and adolescents, including new ARVs, new formulations, and novel drug combinations
- Safety and PK of ARVs and drug-drug interactions (e.g., ARVs, TB drugs, and contraceptives) in HIV-infected pregnant and postpartum women

### 1.2.2 Tuberculosis

Tuberculosis (TB) is a major cause of morbidity and mortality among HIV-infected pregnant women and children, and the diagnosis of TB in children is very difficult. Evaluation of new TB drugs and TB vaccines for PK, safety, dosing, and efficacy is lacking in these vulnerable populations as are accurate diagnostic tests for TB in children. IMPAACT aims to evaluate novel approaches for TB prevention, treatment and diagnosis in HIV-infected children, adolescents, and pregnant and postpartum women. Priorities include evaluation of:

- PK, safety, and efficacy of new drugs and drug combinations to prevent and treat TB in HIV-infected and uninfected children, adolescents, and pregnant women
- Novel strategies for diagnosing TB in HIV-infected and uninfected children
- Novel vaccines for prevention and treatment of TB in HIV-infected and uninfected children

### 1.2.3 HIV Prevention

Evaluating interventions that prevent perinatal HIV transmission and allow HIV-infected women to safely breastfeed while optimizing their own and their child's health is a major priority in the developing world. Likewise, secondary transmission from perinatally infected adolescents to sexual partners is a growing area of concern. IMPAACT aims to develop and test biomedical/behavioral interventions to prevent HIV maternal acquisition and perinatal and postnatal transmission, and to prevent secondary transmission from perinatally HIV-infected adolescents to sexual partners. Priorities include evaluation of:

- Interventions to prevent HIV transmission in the perinatal period and during breastfeeding while optimizing infant and maternal health outcomes
- Safe, effective, and feasible interventions to reduce incident HIV infection in pregnant and breastfeeding women and their partners
- Biomedical and behavioral interventions to reduce HIV transmission in youth, including primary prevention (e.g., pre-exposure prophylaxis [PrEP]) and secondary prevention (e.g., adherence to biomedical interventions, retention, and care)

### 1.2.4 HIV Cure

Due to the known timing of acute infection in newborns and potentially stronger immune systems in youth, interventions to achieve a cure or functional cure are promising in these populations. IMPAACT aims to evaluate the potential for HIV cure through therapeutic interventions directed at prevention and clearance of HIV reservoirs in HIV-infected infants, children, and adolescents. Priorities include evaluation of:

- Whether very early therapy with intensified combination antiretroviral therapy (ART), that includes agents that block virus entry and/or integration, prevents HIV reservoir establishment in infants and achieves “functional cure”
- Unique cohorts of HIV-infected children and youth likely to achieve cure through interventions that stimulate latent proviruses and enhance HIV-specific immunity
- Immune modulatory agents, including therapeutic HIV vaccines, virus activation or target cell modification strategies to affect cure in perinatally and behaviorally infected youth on long-term suppressive combination ART
- The relationship between viral reservoirs and infant immunity

### 1.2.5 Complications and Comorbidities

Neurocognitive impairment, chronic immune activation/inflammation, serious HIV co-infections and toxicities of long-term ARV exposure are significant causes of disease in these vulnerable populations and need to be addressed to reduce and prevent serious morbidities. IMPAACT aims to determine optimal and feasible methods for the prevention and management of co-infections and co-morbidities of HIV infection and its treatment. Priorities include evaluation of:

- Interventions to prevent or treat cognitive impairment and mood disorders in HIV-infected children
- Vaccines for infectious agents other than HIV that cause significant morbidity and/or mortality in HIV-exposed infants and HIV-infected pregnant women, children, and adolescents
- Adverse events/toxicities from long term treatment in HIV-infected children
- The importance of chronic immune activation/inflammation in children during growth and development and evaluation of interventions to alter it and related complications

### 1.3 IMPAACT Network Organization

The IMPAACT Network is led by the Network chair and vice chair. 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 five scientific committees (SCs), aligned with the five research areas, as above. With input from the IMPAACT Community Advisory Board (ICAB), the SLG with the SCs drive the scientific research agenda aligned with the Network's mission and scientific agenda. To enable the SLG to focus on scientific priorities and leadership, most network management functions are the responsibility of a 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, and the IMPAACT Network mission is furthered. Additional details on the roles and responsibilities of each component included in Figure 1-1 are provided in Section 2.

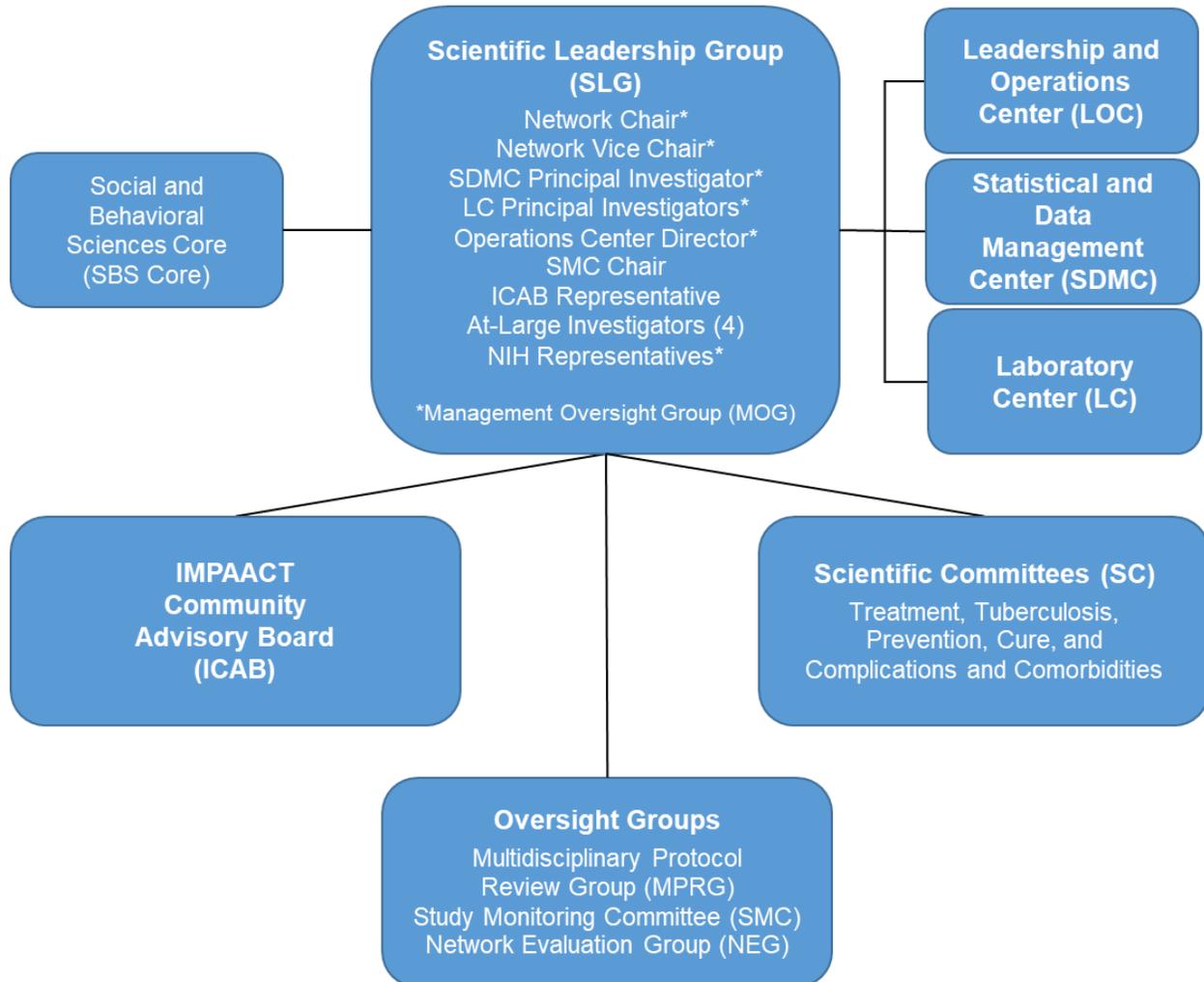
Several advisory groups support the IMPAACT SLG. The IMPAACT Community Advisory Board (ICAB) is responsible for advising the network leadership, SCs, protocol teams, and other network groups on issues related to the planning and implementation of the IMPAACT research agenda and for supporting local (site) community programs through training and information exchange. The Social Behavioral Sciences Core (SBS Core) is a group of experts who help support the IMPAACT Network's research agenda by providing guidance on behavioral sciences aspects of proposals during concept sheet development and, as needed, protocol development. An external scientific advisory group may be convened as needed to provide constructive feedback on the Network's current and planned scientific agenda, including identifying any gaps and providing recommendations for prioritization and future directions.

The central resources of the IMPAACT Network include the Leadership and Operations Center (LOC), the Statistical and Data Management Center (SDMC), and Laboratory Center (LC), who coordinate closely in the development, implementation, and oversight of network studies and other network management and operations activities. The resources and services provided include supporting the network leadership, structure, and functioning; providing comprehensive biostatistical and data management leadership and services; and facilitating laboratory preparedness and performance, coordination, and oversight of the Network's laboratories.

Three additional network committees provide oversight, under the direction of the SLG and MOG. The Multidisciplinary Protocol Review Group (MPRG) reviews protocols on behalf of the SLG prior to submission to the NIAID Sciences Review Committees. For designated studies, a Study Monitoring Committee (SMC) monitors participant safety and the progress and quality of IMPAACT study conduct. The Network Evaluation Group (NEG), on behalf of the MOG, develops performance metrics for the various network entities.

In addition to the groups included in Figure 1-1, research sites and protocol teams support the overall development and implementation of IMPAACT studies. IMPAACT research is conducted through the NIAID- and NICHD-supported sites throughout the world. Investigators and other representatives of these sites, including community representatives, participate in all levels of the IMPAACT Network structure. Further detail on clinical research sites (CRSs) is described 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 dissemination of their results. Further detail on the composition and functions of protocol teams is 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 and National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS (DAIDS) policies as a condition of receipt of Federal funding. Each clinical research site also adheres to relevant local regulations and policies. In addition, 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. The IMPAACT Network also follows good documentation practices, as described further in Section 3. These policies and procedures are contained in the following:

- IMPAACT Network Manual of Procedures (MOP):** This manual provides general guidelines for network members and describes IMPAACT policies and procedures for all sites, study teams, and staff. The IMPAACT Operations Center coordinates development and maintenance of the Network MOP in collaboration with representatives the SDMC, LC, and Network leadership; representatives of the MOG are responsible for reviewing sections prior to their release.

- **Study-specific Implementation Materials (e.g., MOP, Laboratory Processing Chart [LPC], Participant Enrollment and Data Collection Materials):** In addition to study protocols, conduct of each IMPAACT study may be guided by study-specific implementation materials, including a study-specific MOP, LPC, 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. In the event 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 Standard Operating Procedures (SOP):** Standard Operating Procedures (SOPs) for site operations and for study operations ensure standard, uniform performance of site and study-related tasks and compliance with IMPAACT procedures, [International Conference on 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 [Food and Drug Administration](#) (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 is to assist and facilitate, not to direct the research activities.

DAIDS staff participate on IMPAACT study teams, as described in Section 4, and governing committees, as described throughout the Network MOP. They also facilitate the communication between other partners, such as other funding agencies, pharmaceutical companies, the US FDA, and IMPAACT leadership. See Figure 1-2 for the overall DAIDS organizational structure.

Organizationally, 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).

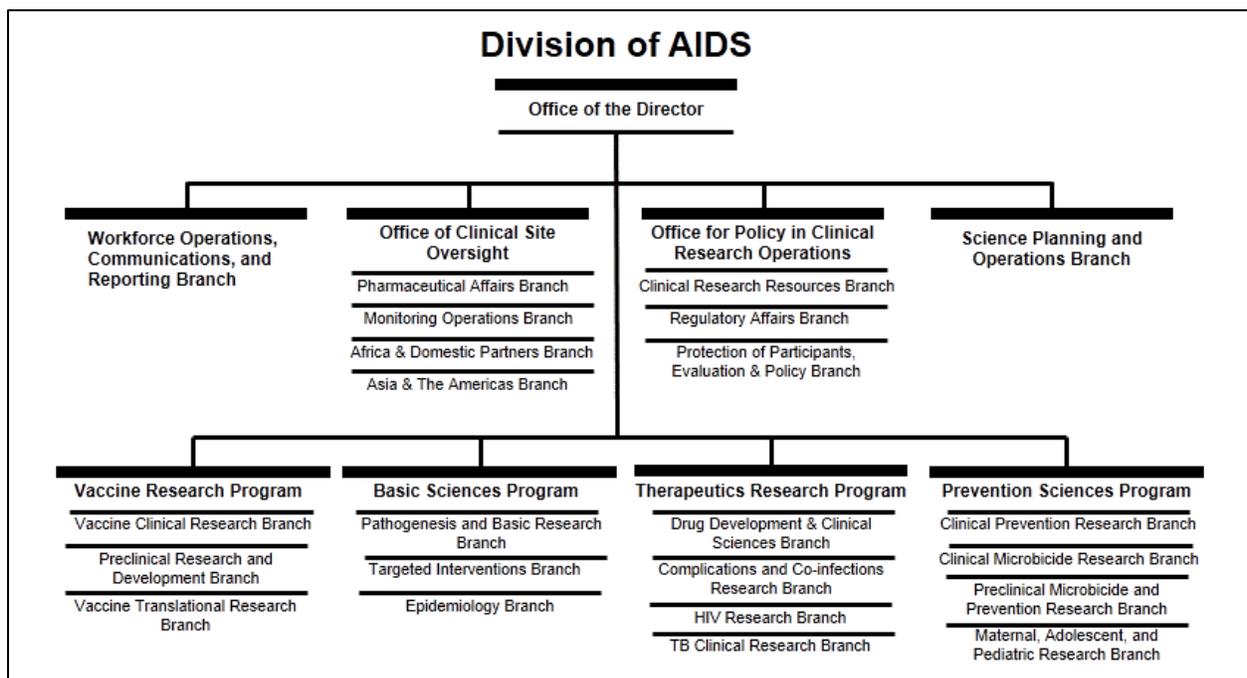
When an IMPAACT study is to be conducted under an Investigational New Drug (IND) application, DAIDS typically holds the IND and negotiates a clinical trial agreement (CTA) with the collaborating pharmaceutical company to document the responsibilities and rights of each party for the clinical trial. The 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 11.1.1 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 detail 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: Accessed on 2 October 2018 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, representatives participate across all areas of the Network.

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).

### **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 U.S. 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 protections matters (i.e., 45 CFR 46, 21 CFR 50, and 21 CFR 56), 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 clinical research sites 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 Clinical Research Sites associated with the HIV/AIDS Clinical Trials Networks
- Coordinates a range of clinical site management activities for network
- Serves as a resource on operational and regulatory issues and ensures that appropriate clinical research standards, policies, and procedures are used by clinical research sites
- 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 site progress of 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
- Advise 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. PAB assesses the pharmaceutical aspects of each protocol and communicates its assessment during 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 to 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 site 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 of study product returns
- Executing final disposition 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 protocol

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 study teams, as described in Section 4, and governing committees, as described through 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 clinical research sites 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 study teams, as described in Section 4, and governing committees, as described through 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 over 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 negotiation of 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 informed consent language. The approved language is subsequently distributed with the protocol for relevant Institutional Review Board/Ethics Committee (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, each covered entity is responsible for ensuring compliance with this requirement, as set forth in [Title 45 CFR 160](#) and [164](#).