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## 11 STUDY-SPECIFIC PRE-IMPLEMENTATION ACTIVITIES

There are a number of 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 finalization of protocol Version 1.0.

The protocol chair and clinical trial specialist (CTS) work closely with other protocol team members to identify and track all requirements that must be met to open each study to accrual; while some requirements apply to all studies, others may be study-specific. These requirements are described in Section 11.1. After all requirements have been met, the CTS 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).

The CTS also coordinates the site-specific study activation process for each study, which, as described in Section 11.2 below, should proceed in parallel with work toward opening each study to accrual.

Sites may not initiate implementation of an IMPAACT study until after the study is opened to accrual and they have received a site-specific study activation notice.

## 11.1 Study Opening Requirements

This section describes requirements that must be met to open a study to accrual.

### 11.1.1 Clinical Trials Agreement

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. In general, terms in the CTA covering access to data conform to DAIDS and Network policies.

When CTAs are required, the DAIDS CTA Team negotiates with the company. The DAIDS medical officer (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 Scientific Review Committee [SRC] review). The CTA Team seeks input and review of CTAs by the protocol chair, MOs, and Statistical and Data Management Center (SDMC) Principal Investigator (PI), who consults with the SDMC representatives on the protocol team, as needed, during the negotiation process. In some cases, study protocols cannot be distributed to participating sites as final 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 and the IMPAACT Operations Center and SDMC. They are not typically distributed to study sites, and sites are not expected to maintain copies of CTAs.

### 11.1.2 ClinicalTrials.gov Registration and Entry of Results for IMPAACT Studies

[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 Health and Human Services issued a [Final Rule for Clinical Trials Registration and Results Information Submission](#) (42 CFR Part 11) that 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 in a timely manner (within one year after the Primary Completion Date, which is the date on which the last participant was examined or received an intervention to collect final data for the primary outcome measure(s)), whether subject to [FDAAA 801](#) or not. 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. All IMPAACT studies are registered.

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 Network.
- Submission of IMPAACT study results to ClinicalTrials.gov (when required) is generally done by SDAC.

Per FDAAA, protocols must be registered no later than 21 days after the first participant is enrolled.

### 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 issues 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 must coordinate 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, the protocol may be 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 must coordinate 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 source and stored at and distributed to participating sites from the DAIDS Clinical Research Product Management Center (CRPMC). General instructions for ordering study products from the CRPMC are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*. For some studies, these general instructions may be supplemented with additional or alternative study-specific instructions provided by the DAIDS Pharmaceutical Affairs Branch (PAB).

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 Investigator of Record (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 long time to obtain; therefore, the process to obtain approval should be initiated as early as possible in the pre-implementation phase of the study.

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 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)-specific visit codes, specimen type code, and applicable data collection material details. The LPC also lists relevant contact information for collaborating laboratories and repositories.

The laboratory technologist (LT) assigned to each protocol is primarily responsible for developing the LPC in close collaboration with the IMPAACT Laboratory Center (ILC) representative. Prior to submitting the draft LPC for final review by the protocol team, the LT coordinates with the ILC representative to arrange for a secondary review by another LT from the Laboratory Technologists Committee (LTC). The protocol team is responsible for reviewing the LPC and ensuring that it matches the protocol Schedule of Evaluations and other relevant sections of the protocol. The full protocol team is responsible for reviewing drafts of the LPC when distributed. Sign-off is required from the protocol chair, LC representative, LDM, and CTS. The final LPC must be available before a study can be opened to accrual.

The LT is responsible for finalizing and maintaining the LPC, requesting its posting and distribution, and ensuring appropriate version control. If the LPC requires updates during study implementation, the LT will coordinate that process. Further details regarding the LPC may be found in Section 17.

### **11.1.6 Participant Enrollment Materials**

The DMC Subject Enrollment System (SES) is used to enroll participants in IMPAACT studies. For most studies, the system is also used to track screening of potential participants. The system requires use of 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, draft versions of the checklists are distributed for protocol team review; sign-off is required from the protocol chair and protocol statistician prior to finalization.

For studies that involve use of a study drug or product that will be provided to participants upon enrollment, a prescription file must also be developed for the study and programmed into the SES. For studies that involve random assignment, the prescription files are linked to the randomization programming. Draft versions of prescription files are reviewed by the protocol pharmacist and protocol statistician, with sign-off required prior to finalization.

Once the eligibility checklists and prescription and randomization files are finalized, DMC staff program them into the SES 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 randomization coordinator sends an announcement to 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 the last bullet in Section 11.1.7.

### **11.1.7 Data Collection Materials**

Data collection instruments (e.g., electronic case report forms [eCRFs]) 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., data collection forms schedules or 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 a data collection forms schedule and listing, or eCRF completion guide, of required data collection instruments based on protocol objectives, schedules of evaluations, and reporting needs. Scientific expertise is sought externally, as appropriate.
- Data collection instruments are distributed to the protocol team for review and comment; sign-off by the protocol chair and statistician is required to complete study builds.
- If select data collection instruments require translation into local languages after they are finalized in English, the DMC team will work with site staff to prepare the local language translations and back-translations. 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 data collection instruments go through a series of reviews:
  - Team review
  - DMC review, including Clinical Data Interchange Standards Consortium (CDISC) standards review, as needed
  - SDAC review
  - IMPAACT eCRF committee
  - Final team review and sign-off
- Once the data collection instruments have been reviewed by the team and final sign-off is received from the protocol chair and statistician, 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 data manager will notify the protocol team and participating sites once the data collection instruments are available.

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 protocol data manager will coordinate that process. Final sign-off by the protocol chair and statistician is required for new and updated data collection instruments.

### **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 CTS is responsible for coordinating the development and review of all MOP sections in close cooperation with the protocol chair and other protocol team members, some of whom are typically assigned primary authorship responsibilities, as outlined in Table 11-1. For example, the protocol pharmacist may prepare sections of the MOP related to study product management. Regardless of primary authorship assignments, the CTS will coordinate the development and finalization of all sections, requesting and incorporating input other protocol team members and site staff as needed prior to finalization.

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 and DAIDS MO; sign-off requirements for other protocol team members are listed in Table 11-1. Sign-off requirements must be completed before the MOP can be finalized and made available to participating sites.

Topics typically included in study-specific MOPs 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
- Pharmacy and study drug considerations
- Specimen collection and laboratory considerations
- Expedited adverse event (EAE) reporting considerations
- Clinical and toxicity 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 or in response to frequently asked questions. When updates are required, the CTS will coordinate that process. The CTS 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 is required for all updates. The CTS will document updates using a version control log that will be made available with the updated MOP upon finalization of the updates. Depending on the complexity of the study-specific MOP, it may be versioned in its entirety or by section (this will be reflected in the version control log; versioning of the MOP will correspond with the same whole number as the current version of the protocol).

The CTS 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**

<b>Protocol Team Member</b>	<b>Responsibilities and Requirements</b>
<b>Protocol Chair and DAIDS MO</b>	Responsible for review and sign-off of all sections
<b>Protocol Data Manager</b>	Responsible for review and sign-off on sections related to data collection and management
<b>Protocol Lab Specialist and Laboratory Technologist</b>	Responsible for input, review, and sign-off on sections related to specimen collection, processing, testing, shipping, and other related sections
<b>Protocol Investigators</b>	Responsible for input and review of sections related to clinical or other specialized procedures and safety reporting
<b>Protocol Pharmacist</b>	Responsible for input, review, and sign-off of sections related to study product and study product management
<b>Protocol Pharmacologist</b>	Responsible for sections related to PK procedures and considerations for study implementation, if applicable
<b>CTS</b>	Responsible for sections related 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
<b>Protocol Statistician</b>	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 data managers are responsible for developing a study progress, data, and safety monitoring plan (SPDSMP) that details the study data to be monitored; the type, frequency, and content of monitoring reports that will be generated; and responsibilities for generating, receiving, and reviewing 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). Drafts of the SPDSMP 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 Study Monitoring Committee (SMC) or Data and Safety Monitoring Board (DSMB) that oversees the study during the initial SMC or DSMB review. Input from all team members, and the SMC or DSMB, is incorporated into the final SPDSMP, with sign-off obtained from the protocol chairs and DAIDS MO. The SPDSMP should be finalized approximately concurrent with the study protocol and must be finalized before the study is opened to accrual, unless otherwise specified in the protocol.

For studies that include PK evaluations, the laboratory data managers are responsible for developing a Pharmacology Data Management Plan, in collaboration with the protocol pharmacologist and the protocol

data managers. 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, DTAs, in some studies moving forward). The plan must be consistent with relevant sections of the study protocol and SPDSMP. A near final draft of the plan should generally be discussed with the SPDSMP during the initial SMC review or if applicable and requested for an initial DSMB review. Input from all team members is incorporated into the final Pharmacology Data Management Plan, with sign-off obtained from the protocol chairs, pharmacologists, protocol data managers, and laboratory data managers. Finalization of the plan is required prior to opening the study to accrual.

Other study-specific 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 study publication; when applicable, additional SAPs may be prepared for analyses to be performed for secondary publications. For PK studies, protocol pharmacologists are responsible for developing a pharmacology SAP. Drafts of SAPs are distributed for protocol team review and input, in an iterative process as needed. Input from all team members is incorporated into final versions.

The primary SAP must be finalized before the study is opened to accrual, unless otherwise specified in the protocol.

#### **11.1.11 Study Budget**

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 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 budget implications are made after MOG review, e.g., resulting from subsequent protocol review steps such as DAIDS Scientific Review Committee review, the updated budget will be re-submitted to the MOG.

The Operations Center maintains study budgets and coordinates with the Johns Hopkins University (JHU) Finance Office, which executes sub-agreements, sub-contracts, and other funding mechanisms in a timely fashion to ensure all necessary components of the study are implemented per protocol. For example, some screening procedures may require sub-contracts or sub-agreements to be developed, negotiated, 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 CTS will communicate with the LC representative and LT to ensure that all IMPAACT protocol-specific specialty labs and/or contract labs have been notified that they will receive and process study-specific samples. Any budget modifications needed during study implementation will be communicated to the MOG for approval and to the JHU Finance Office prior to finalization.

Protocol modifications, such as Letters of Amendment (LoA) 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 prior to development of the LoA or full protocol amendment (see 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 are required to 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 log, as described in Section 11.2.3 prior to study activation.

Additional study activation requirements are further described in the sections below, as follows:

- Section 11.2.4: Financial disclosures
- Section 11.2.5: Clinical trials insurance
- Section 11.2.6: Pharmacy requirements (for studies that include study products)
- Section 11.2.7: Data management requirements
- Section 11.2.8: Laboratory requirements
- Section 11.2.9: Study-specific standard operating procedures (SOPs)
- Section 11.2.10: Study-specific training (see also Section 16)
- Section 11.2.11: Site-specific SOP for regulatory inspection readiness
- Section 11.2.12: Local language translation of study documents

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 CTS is responsible for coordinating the development and review of the checklist in close cooperation with the protocol chair 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 is required from the protocol chair and DAIDS MO; sign-off requirements for other protocol team members will be determined per the applicable requirements. The CTS 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. Other

team members typically involved in the process include the protocol data manager, LC representative, and protocol pharmacist. The CTS 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.

Once all site activation requirements have been met, the CTS will grant site readiness approval through the DMC portal to the study-specific screening and enrollment screens in the SES. The CTS 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 CFR 46 (and 21 CFR 56 for IND studies), all sites must obtain IRB/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](#). Each site should complete study-specific submissions to their 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
- 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 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 DAIDS 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 CTS as constituting completion of this study activation requirement.

## 11.2.3 Study-Specific Delegation of Duties Log

As of 1 November 2017, DAIDS requires clinical research sites to maintain study-specific Delegation of Duties Logs, as follows:

- *For all studies in which the site was enrolling participants as of 1 November 2017:* A study-specific Delegation of Duties Log, meeting DAIDS requirements and signed by the IoR, was to be in place no later than 1 November 2017.
- *For all new studies in which the site would enroll participants after 1 November 2017:* A study-specific Delegation of Duties Log, signed by the IoR, was to be in place prior to initiating the study. The IMPAACT Operations Center worked with study teams to implement this requirement during the site-specific study activation process, generally, by distributing a template study-specific Delegation of Duties Log for site use. For studies in which site-specific study activation had already been granted but a study-specific Delegation of Duties Log was not yet in place, a study-specific Delegation of Duties Log, meeting DAIDS requirements and signed by the IoR, was to be in place prior to initiating the study or as of 1 November 2017 (whichever was soonest).
- *For ongoing studies in which the site was no longer enrolling participants on or after 1 November 2017:* A study-specific Delegation of Duties Log was strongly encouraged by IMPAACT, but not required.

Additional DAIDS guidance may be found at <https://rsc.niaid.nih.gov/clinical-research-sites/delegation-duties-logs>.

During the activation process, the protocol CTS may provide sites with suggested study-specific duties or roles in addition to the standard listing of roles and responsibilities.

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 delegation of duties 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 and kept up-to-date on-site throughout the course of the study; additional details about this requirement are provided in Section 7 of this manual 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 CTS 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 (HANC). 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 each site.

## 11.2.5 Clinical Trials Insurance

As of 10 August 2018, 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>.

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, Version 1.0, dated August 9, 2018. 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.

Note: Sites participating in ongoing DAIDS sponsored studies must ensure that CTI is procured by 1 November 2018. Insurance certificates for ongoing studies must be provided to the site's OCSO Program Officer.

## 11.2.6 Pharmacy Requirements

Completion of pharmacy-related activation requirements is generally confirmed by the DAIDS protocol pharmacist, who notifies the CTS when requirements have been met. Generally, study products are required 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, 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 protocol data manager, who notifies the CTS when requirements have been met. 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 Subject Enrollment System, and availability of relevant materials and equipment on site for study implementation.

### **11.2.8 Laboratory Requirements**

Confirmation of relevant local laboratory certifications and/or approvals is typically required prior to activation. Initiation or completion of specimen or material transfer agreements may also be required prior to activation to ensure that samples may be shipped in a timely manner as applicable for the study.

Completion of laboratory-related activation requirements is generally confirmed by the protocol Laboratory Center representative (for NIAID-sites) or by Westat (for National Institute of Child Health and Human Development [NICHD] sites), who notifies the CTS when requirements have been met (see Section 17).

### **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 CTS.

### **11.2.10 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.

### **11.2.11 Site-Specific Standard Operating Procedure for 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 site SOPs describing roles, responsibilities, and procedures for preparing for and participating in regulatory inspection visits. These SOPs are intended to be applicable across studies conducted at a given site, and therefore are not study-specific. A template SOP that may be adapted for use at each site and an SOP review checklist are available from DAIDS. For activation of each IND study, the site IoR or designee is required to confirm that this SOP is available at the site.

### **11.2.12 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. 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 assist with the translations.

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.