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

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

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

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

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

11.1 Study Open to Accrual Requirements

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

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

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

11.1.1 Clinical Trial Agreements

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

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

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

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

11.1.2 ClinicalTrials.gov Registration for IMPAACT Studies

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

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

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

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

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

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

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

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

11.1.3 United States Food and Drug Administration Review

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

If the FDA finds sufficient safety concerns, a Clinical Hold on the protocol may be issued. In this case, the study may not open to accrual until the concerns are resolved. The FDA may require that the protocol be amended or that additional data be submitted to justify why an amendment is not required. The protocol team coordinates with the DAIDS MO and DAIDS Regulatory Affairs Branch (RAB) to respond to the FDA as soon as possible and within the timeframe specified by the FDA.

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

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

11.1.4 Study Product Acquisition and Shipment to Sites

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

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

11.1.5 Laboratory 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) preloads, which are study-specific visit codes, specimen type codes, and applicable data collection material details. The preloads for specimen collection are finalized and available for site use in LDMS approximately two weeks after the LPC is final. The LPC also lists relevant contact information for collaborating laboratories and repositories.

LPC development typically begins when the protocol is in the final stages of development. The laboratory technologist (LT) is primarily responsible for developing the LPC in close collaboration with the protocol IMPAACT Laboratory Center (LC) representative; the protocol laboratory data manager (LDM) and CRM also contribute to the LPC development. The full protocol team is responsible for reviewing the draft LPC when distributed by the LT or LC representative. If a secondary review by another LT from the Laboratory Technologists Committee (LTC) is warranted, as determined by the LT and LC representative, the LT coordinates with the LC representative to arrange for this review.

The LC representative is responsible for ensuring quality control, appropriate versioning, and internal consistency of the LPC. The LT or LC representative will distribute the LPC to the protocol team for final review and sign-off. Sign-off of the final LPC is required from one protocol chair (chair or vice chair), one LC representative, one LT, one LDM, and one CRM. Sign-off is confirmed by the LC representative and must be completed before the LPC can be finalized and made available to participating sites. The LC representative is responsible for ensuring all required sign-offs are received, ensuring compliance with good documentation practices, including appropriate version control, requesting that the LPC is posted to the study webpage, and distributing the LPC to sites. Additionally, the LC will send the LPC to laboratories processing samples. The final LPC must be available before the study is opened to accrual.

The LPC may be updated over time as experience with study implementation identifies aspects of the study protocol that may require further explanation, in response to frequently asked questions, or when protocol modifications impact LPC directions. When updates are required, the LT and LC representative will coordinate that process. The LC will circulate updated LPC drafts to the protocol team, with the same sign-off requirements as the initial draft if changes are made to laboratory processes or instructions. Note

that LTC review is not required for updates. Sign-off is not required for LPC version changes to update to a new protocol version or to update staff or addresses without laboratory processing changes. Updates will be documented using a version control log that will be made available with the updated LPC upon finalization of the updates. As with the initial version, the LC representative is responsible for ensuring all required sign-offs are received and ensuring appropriate version control.

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

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

11.1.6 Participant Enrollment Materials

The DMC Study 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 uses eligibility checklists that correspond to study-specific inclusion and exclusion criteria which must be programmed into the system for each study. In a process coordinated by the protocol data manager (PDM), draft versions of the checklists are distributed for protocol team review; sign-off is required from the protocol chair(s), DAIDS MO, and protocol statistician(s) prior to finalization.

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

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

11.1.7 Data Collection Materials

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

IMPAACT data collection instruments are developed as follows:

- Development of the data collection instruments for a study typically begins when the protocol is in the final stages of development (i.e., following approval of the protocol by DAIDS SRC).
- The internal DMC study team puts together an eCRF completion guide, consisting of data collection forms schedule(s) and a listing of required data collection instruments based on protocol objectives, schedules of evaluations, and reporting needs. Scientific expertise is sought externally, as appropriate.

- The data collection instruments go through a series of reviews:
  - Protocol team review
  - DMC review, including Clinical Data Interchange Standards Consortium (CDISC) standards review, as needed
  - SDAC review
  - IMPAACT eCRF Committee (see Section 2)
  - Final team review and sign-off: final draft data collection instruments are distributed to the protocol team for review and comment; sign-off by the protocol chair(s), DAIDS MO, and statistician(s) are required to complete study builds.
- Once the data collection instruments have been reviewed by the team and final sign-off is received as outlined above, internal DMC processes are initiated for Clinical Trials Data Management System (CTDMS) finalization. This process requires six to eight weeks. The final data collection instruments are then posted to the DMC portal. The DMC notifies the protocol team and participating sites once the data collection instruments are available.

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

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

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

11.1.7.1 Collection of Gender Identity

As of 30 May 2019, IMPAACT Network studies began collecting data on gender identity for all studies enrolling participants who are 12 years of age or older. The goals of this data collection are two-fold:

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

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

If gender identity information is being collected, site SOPs should include options for staff training as needed, to better understand transgender communities and the importance of collecting these data. The

Division of AIDS Cross-Network Transgender Working Group has developed a training curriculum for providing care to transgender persons in HIV research settings. The five-module eLearning series is available on the DAIDS Learning Portal (https://daidslearningportal.niaid.nih.gov/). In addition, there are materials on the DAIDS Learning Portal to conduct the trainings in person – including a presentation, facilitator's guide, and accompanying handouts.

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

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

11.1.8 Study-Specific Manual of Procedures

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

Study-specific MOP development typically begins when the protocol is in the final stages of development. The CRM is responsible for coordinating the development and review of all MOP sections in close collaboration with the protocol chair and other protocol team members, some of whom are typically assigned primary authorship responsibilities, as outlined in Table 11-1. Regardless of primary authorship assignments, the CRM will coordinate the development and finalization of all sections, requesting and incorporating input from other protocol team members and site staff as needed prior to finalization.

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

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

- Study overview
- Site preparations for the study
- Study communications and resources
- Participant accrual and retention considerations
- Recruitment, screening, and enrollment considerations
- Study implementation, visits, and procedures considerations
- Informed consent and assent considerations
- Pharmacokinetic (PK) considerations, if applicable
- Pharmacy and/or study drug or study product considerations, if applicable

- Specimen collection and laboratory considerations, if applicable (the majority of laboratory considerations should be included in the LPC; see Section 11.1.5)
- Expedited adverse event (EAE) reporting considerations
- Clinical management considerations
- Data management considerations

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

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

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

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

11.1.9 Study Monitoring Plans

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

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

For studies that include PK evaluations, the LDMs are responsible for developing a Pharmacology Data Management Plan (PK DMP), in collaboration with the protocol pharmacologist(s), statisticians, PK testing laboratory representatives, PDMs, and the Study Data Tabulation Model (SDTM) specialist. In general, this plan should specify the process for monitoring PK sample collection, data quality, and sample shipping for the study, as well as content, format, schedule, and mechanism for transfer of PK assay results and parameter datasets (note that some elements describing data transfer may be included in data transfer agreements). The plan must be consistent with relevant sections of the study protocol and SPDSMP. Drafts of the PK DMP are distributed for protocol team review and input, in an iterative process as needed, to prepare a near final draft to be discussed, with the SPDSMP, during the initial SMC or DSMB review. Input from all team members, and the SMC or DSMB, is incorporated into the final PK DMP, with sign-off obtained from the pharmacologist(s), statisticians, PDMs, LDMs, Laboratory Data Division Chief, Chief DM, and the SDTM specialist. The plan is finalized prior to opening the study to accrual.

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

11.1.10 Statistical Analysis Plan

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

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

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

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

11.1.11 Study Budget

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

The Operations Center maintains study budgets and coordinates with the IMPAACT Finance and Contracts Office at Johns Hopkins University (JHU), which executes sub-agreements, sub-contracts, and other funding mechanisms to ensure all necessary components of the study are implemented per protocol. For example, some study procedures may require sub-contracts or sub-agreements to be developed, negotiated, and fully executed prior to opening a study to accrual. Studies with pharmaceutical funding support may require a study-specific funding agreement with the pharmaceutical company to be finalized and fully executed prior to opening a study to accrual. Some study procedures or shipping of specimens during study follow-up may allow sub-agreements and sub-contracts to be developed during study implementation. The LC representative will ensure that all IMPAACT protocol-specific specialty laboratories and/or contract laboratories have been notified that they will receive and process study-specific samples. Budget modifications needed during study implementation will be communicated to the Finance and Grants Office and may require MOG approval prior to finalization.

Protocol modifications, such as LoAs or full protocol amendments, may have implications on the study budget. The proposed modifications, along with any associated changes to the budget, must be reviewed and approved by the MOG 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 must obtain required approvals and successfully complete the DAIDS protocol registration process as described in Sections 11.2.1 and 11.2.2 prior to study activation. Sites are also required to complete a study-specific delegation of duties (DoD) log, as described in Section 11.2.3, prior to study activation.

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

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

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

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

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

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

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

11.2.1 IRB/EC and Other Regulatory Approvals

Consistent with 45 US Code of Federal Regulations (CFR) 46 (and 21 CFR 56 for IND studies), all sites must obtain institutional review board (IRB)/ethics committee (EC) approval of IMPAACT study protocols. Approval must also be obtained from other regulatory and/or approving entities as described in the DAIDS Protocol Registration Manual. Sites located in the US rely upon approval by a single IRB

(sIRB) for cooperative research. The sIRB reviews and approves each participating site's informed consent and assent forms; additional review may occur if required by the local IRB per their agreement with the sIRB; refer to Section 8 for further information on the sIRB. Each site should complete study-specific submissions to IRBs/ECs and other regulatory entities as soon as possible following distribution of the final study protocol and protocol amendments, if applicable. The site IoR is responsible for ensuring that all applicable review and approval requirements are met and adequately documented. It is recommended that sites request that IRB/EC and other regulatory entity approval letters reference the following:

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

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

11.2.2 DAIDS Protocol Registration

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

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

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

11.2.3 Study-Specific Delegation of Duties Log

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

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

11.2.4 Financial Disclosures

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

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

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

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

11.2.5 Clinical Trials Insurance

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.

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

- Grant number and name of grantee organization
- Name of country
- Type of CTI coverage required
- Explanation of why the institution does not carry this insurance

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

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

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

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

11.2.6 Pharmacy Requirements

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

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

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

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

11.2.7 Data Management Requirements

Completion of data management activation requirements is generally confirmed by the PDM, who notifies the CRM when requirements have been met. The protocol team may require translation and back-translation of study-specific data collection instruments as an activation requirement. If so, translated instruments must be independently back-translated into English for review and approval by the DMC. Other data management requirements for activation may include completion of training applicable to the study, such as for Medidata Rave and the SES, and availability of relevant materials and equipment on site for study implementation.

11.2.8 Laboratory Requirements

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

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

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

11.2.9 Study-Specific Standard Operating Procedures

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

11.2.10 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 a site SOP for regulatory inspection readiness that describes the roles, responsibilities, and procedures for preparing for and participating in regulatory inspection visits. This SOP is intended to be applicable across studies conducted at a given site, and therefore is 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. At most sites outside the US, sites translate site-specific informed consent and assent forms (if applicable) into local language(s); to facilitate development of the study-specific forms, the CRM shares Word versions of the sample informed consent and/or assent forms, as provided in the protocol, to sites following distribution of Protocol Version 1.0 and any subsequent full version protocol amendments.

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

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