11 STUDY SPECIFIC PRE-IMPLEMENTATION ACTIVITIES

For each IMPAACT study, there are a number of preparatory steps that must be completed before the study can be designated as **open to accrual**, as defined by the Division of AIDS (DAIDS) Study Statuses and Milestones. 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 the clinical trial specialist (CTS) assigned to the protocol will work with the Protocol Team 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. Once all requirements have been met, the CTS will announce that the study is open to accrual by notifying the protocol team, the IMPAACT DMC coordination group, 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 further described in Section 11.2 below, should proceed in parallel with work toward opening each study to accrual.

Sites may not initiate study implementation (i.e., participant activities such as screening and enrollment) 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 the types of requirements that must be met before a study can be opened to accrual.

11.1.1 Clinical Trials Agreement

A clinical trials agreement (CTA) is typically negotiated between a collaborating pharmaceutical company and DAIDS as the study sponsor to document the responsibilities and rights of each party in the agreement. 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 for IMPAACT studies. The DAIDS Medical Officer (MO) assigned to each study will initiate the CTA development process internally at DAIDS, typically during the protocol development process, when it is determined that one or more pharmaceutical companies will provide study product and/or other support for the study. 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 will consult with the SDMC representatives on the protocol team as needed, during the development and negotiation process. Where applicable, study protocols cannot be distributed to participating sites until the CTA is finalized. The status of a CTA may 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 United States Food and Drug Administration Review

If an IMPAACT protocol is submitted under a new IND application with the United States Food and Drug Administration (US FDA), 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 conduct a safety review and notify the IND sponsor of any issues identified during this review. If no communication is received from the FDA within 30 days, or if questions or comments are received in the absence of a "Clinical Hold" notice, the protocol may be considered "Safe to Proceed." At the time of confirmation that the protocol has been submitted to the FDA, the protocol may be distributed to participating sites to begin the regulatory review process.

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 they may require that additional data be submitted to justify why an amendment is not indicated. The protocol team must coordinate with the DAIDS MO and DAIDS Regulatory Affairs Branch (RAB) to respond to the FDA within the timeframe specified by the FDA or 10 working days of receipt of the FDA comments.

If the FDA is not able to complete its safety 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.

FDA review may continue after the initial 30-day period, and review questions and comments may be received at any time during the lifecycle of the study. As above, the protocol team must coordinate with the DAIDS MO and DAIDS RAB to address any such questions and comments.

11.1.3 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), although study products may be available through other sources and handled on a case-by-case basis. 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. At non-US sites, the site's Pharmacist of Record (PoR) must also communicate with the CRPMC and provide any documentation that may be 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 for 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 regulated under an IND, export approval from the 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.

11.1.4 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, as well as use of the Laboratory Data Management System (LDMS) and laboratory-related data collection instruments. The LPC also lists relevant contact information for collaborating laboratories and repositories.

The laboratory technologist assigned to each protocol is primarily responsible for developing the LPC. The protocol team is responsible for reviewing the LPC and ensuring that it matches the Schedule of Evaluations and other relevant sections of the protocol. The protocol team must approve the LPC prior to finalization, as must the Laboratory Technologist Committee (LTC). The finalized LPC must be available before a study may be opened to accrual.

If during study implementation the LPC requires updates, the laboratory technologist will coordinate that process. If there are any discrepancies between the LPC and the protocol, the protocol must be followed. Further details regarding the LPC may be found in Section 17.

11.1.5 Participant Enrollment Materials

The Data Management Center (DMC) Subject Enrollment System (SES) is used to enroll participants in IMPAACT studies. For many studies, the system will also be used to track initiation of screening for a study. 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 one or more study-supplied agents that will be provided by prescription upon enrollment, a prescription file must also be developed for the study and programmed into the DMC's enrollment system. 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/registration files are finalized, DMC staff program them into the enrollment system and perform all necessary programming and system checks. Final programmed versions of the checklists and the prescription files must be available before a study may be opened for accrual.

The DMC randomization coordinator will send an announcement to the sites and team 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 11.1.6. If the screening checklist is a part of the study, this will also be included in the message.

11.1.6 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., 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. The IMPAACT data collection instruments development process is outlined 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 the 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, schedule(s) 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(s) and statistician(s) 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. The DMC staff will review back-translations to ensure that the translated data collection instruments retain the intended meaning of the original English language data collection 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 signoff
- 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. 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 DMC Forms Administrator informs the Operations Center when the DMC materials are ready for study opening. These include both the data collection instruments, the eligibility checklist, and when applicable, the screening checklist.

The development process for data collection instruments is generally expected to be completed within six weeks of final sign-off on case report forms; final data collection instruments must be available before a study may be opened to accrual.

If during study implementation the data collection instruments require updates (due to a new protocol version, letter of amendment, or clarification memorandum), the protocol data manager will coordinate that process. Final sign-off by the protocol chair(s) and statistician(s) is required to on new and updated data collection instruments. If there are any discrepancies between the data collection instruments and the protocol, the protocol must be followed. Further details regarding this process are outlined in Section 12.

11.1.7 Study-Specific Manual of Procedures

During the process of protocol development, each protocol team will determine if a study-specific manual of procedures (MOP) is needed. A study-specific 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 instructions to optimize adherence to study protocols and standardization of study procedures across sites.

When a team agrees to develop a study-specific MOP, development will typically begin when the protocol is in the final stages of development. The CTS is responsible for assembling the MOP in close cooperation with the Protocol Chair and other protocol team members, some of whom may be assigned primary authorship and review responsibilities for certain sections. For example, the Protocol Pharmacist may prepare sections of the MOP related to study product management, and the Laboratory Center (LC) representative and/or laboratory technologist may prepare sections related to laboratory considerations that are not otherwise covered by the LPC. Likewise, protocol team clinicians often develop or carefully review sections of the MOP related to clinical procedures, safety monitoring, and participant management (including clinical management and management of study product use).

Regardless of primary authorship assignments, the CTS will coordinate the development and review of all sections and incorporate final versions of all sections into the MOP. Technical input and review may be sought from other protocol team members and site staff prior to finalization.

For studies for which a MOP is developed, a final implementation version should be available before the study is opened to accrual. Further updates of the MOP may then follow 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. If there are any discrepancies between the study-specific MOP and the protocol, the protocol must be followed. Further details regarding this process may be found in Section 12 of this manual.

If a need for additions or modifications to the study-specific MOP is identified after distribution of the first final implementation version, the CTS will draft or obtain the new text and obtain review and comment from appropriate protocol team members; sign-off will be determined as needed. The CTS will also update a version control tool as needed. After review comments are incorporated, the new text and the version control log will be considered final and ready for distribution.

The study-specific MOP will be versioned with the same whole number as the current version of the protocol, such as 1.0, 2.0, etc. Depending on the size and complexity of the MOP, it may be versioned as a whole or by sections. This will be reflected in the version control tool.

As updates are finalized, the CTS will notify the protocol team and participating sites that they are available. It is the responsibility of the site IoR to ensure that all manuals on site are kept up-to-date and that updated procedural information is communicated to all applicable study staff in a timely manner.

11.1.8 Study Monitoring Plan

The protocol statistician(s), along with the data manager(s), drafts a study monitoring plan which provides details on what data will be monitored, the types and frequency of reports that will be generated, who will generate them, who receives and reviews them, as well as their content. The protocol team's SDMC members work with the protocol team leadership and Medical Officers to specify the core team members who will provide critical oversight of a study including receipt of limited-distribution reports. For protocols with planned review by a Study Monitoring Committee (SMC) or a Data and Safety Monitoring Board (DSMB), a near final draft of the study monitoring plan (i.e., almost to version 1.0) is distributed to the SMC or DSMB for discussion during the study's Protocol Initiation Review (PIR). The study monitoring plan is reviewed and finalized as version 1.0 before programming for monitoring reports is initiated or before screening is initiated, whichever occurs first. The MOs must review the study monitoring plan prior to the PIR and prior to finalization. The protocol team's SDMC members work with the core team to specify other required reviewers of near complete drafts of the study monitoring plan prior to the PIR and prior to the finalization of the plan (commonly the core team reviews drafts, but individual members of the full team, such as industry representatives or scientific specialists, may be designated by the core team as required).

11.1.9 Protocol Budget

Protocol-specific budgets are developed during protocol development and require review and approval from the MOG prior to opening the study to accrual. The Operations Center works with the Protocol Chair and other team members as needed to develop the protocol-specific budget, to include not only site and protocol-specific specialty laboratory costs but also those for the central resources (Operations Center, SDMC, and LC) and any other inputs. Typically, the protocol 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 Protocol Development), 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 the following review steps such as Clinical/Prevention Scientific Review Committee (C/PSRC), the updated budget will be submitted to the MOG.

The Operations Center will maintain the protocol budgets and will coordinate with the Johns Hopkins University (JHU) Finance Office, which will execute 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 laboratory technologist to ensure that all IMPAACT protocol-specific specialty labs 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 or full amendments, may have implications on the protocol budget. These modifications, along with any subsequent changes to the budget, will be reviewed and approved by the MOG prior to finalization (see Section 9: Protocol Development).

11.2 Site-Specific Study Activation

For all studies, sites are required to obtain IRB/EC and other applicable regulatory entity approvals and successfully complete the DAIDS protocol registration process as described in Sections 11.2.1 and 11.2.2. Study products are generally required on site before the site is activated to begin screening and enrollment; however, depending on the length of the screening process and other details such as study product shelf-life, the protocol team may determine that having study product on site should not be considered an element of activation.

During the process of protocol development, the Protocol Team will begin considering additional elements required for site-specific study activation and compile a study-specific listing of regulatory, operational, and other applicable requirements that must be met in order for participating sites to be approved to implement the study. This is typically referred to as the "Site-Specific Activation Checklist."

For studies conducted under an IND, all sites must also complete required study-specific FDA financial disclosures as a condition for study activation; additional details about this requirement are included in Section 7.0 and on the DAIDS Regulatory Support Center website (http://rsc.tech-res.com/protocolregistration/). For most studies, additional study-specific requirements will be specified and tailored to the needs of the study as determined by the protocol team, to ensure site readiness for study implementation. Additional requirements may include:

- Availability of specialized personnel and/or specialized equipment or supplies on site
- Availability of study products and/or required concomitant medications on site
- Availability of translated study implementation materials
- Development of study-specific SOPs and/or source documents
- Confirmation of access to CTDMS
- Confirmation of relevant local laboratory certifications and/or approvals
- Completion of specimen or material transfer agreements
- Completion of required study start-up training

The CTS assigned to the protocol will compile the requirements specified by the team into a listing or checklist for distribution to study sites and will coordinate the process of documenting when requirements have been met for each site. Other team members may also be involved in this process; for example, the Protocol Data Manager, LC representative, and Protocol Pharmacist are often involved in determining

when data-related, laboratory-related, and pharmacy-related requirements have been met. As needed, the CTS will actively follow up with each site on the status of each requirement, with the aim of confirming all requirements as rapidly as possible and, ideally, by the time that the DAIDS protocol registration process has been completed.

Once all activation requirements have been met, the CTS will notify the DMC to grant the site access to the study-specific screening and enrollment screens in the DMC randomization system. The CTS will also issue a site-specific study activation notice announcing that the site may initiate study implementation. No study-specific screening or enrollment ("on study") procedures may be conducted by a site 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 Institutional Review Board/Ethics Committee (IRB/EC) approval of IMPAACT study protocols. Approvals 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. The site IoR is responsible for ensuring that all applicable review and approval requirements are met and adequately documented. It is suggested that sites request that IRB/EC and other 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 recommended, but not required, that the expiration date of the approval also 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 the approval documentation is provided in a language other than English, the document must also be translated into English.

11.2.2 DAIDS Protocol Registration

After obtaining approval from all responsible 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 received the necessary IRB/EC and other applicable regulatory entity approvals and have provided to DAIDS all documentation pertaining to investigator qualifications and responsibilities that are required by US regulations and the National Institutes of Health (NIH). The process also verifies that site-specific informed consent forms contain the necessary information to comply with US regulations. Upon successful completion of the process, the site will receive a Registration Notification or a Registration with Required Corrections Notification, which will also be copied to the Operations Center, and subsequently noted by the CTS as constituting completion of a study activation requirement.

11.2.3 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 study sites. Input on the plan is also obtained from site staff to ensure that all perceived training needs are considered. Once the plan is finalized, the operational approach is communicated to the study sites, and training timelines and materials are developed. The Operations Center coordinates this training with the protocol chair, SDMC, and LC to lead these efforts, with input from other key protocol team members as needed.

The objectives of study-specific training are to:

- Establish a common understanding of key aspects of the study, including the background and rationale, objectives and outcomes, design, study intervention, and schedule of evaluations
- Ensure that site study staff are informed and familiar with:
    - Day-to-day study implementation requirements, in accordance with the protocol, LPC, participant enrollment procedures (including screening and screen failures), data collection schedule, data collection instructions, study-specific MOP, and all relevant regulations, guidelines, policies and procedures
    - Study-specific communication procedures and the operational resources and utilities available to them in support of day-to-day study implementation
- Ensure standardization of study implementation across sites so that data can be combined for analysis

If a study design is straightforward and the participating sites have experience with similar studies, the training plan may specify telephone or web-based training ("start-up calls"). In contrast, if the study design is unique or complex, or if the sites are less experienced, an in-person training may be required. In-person training may also be required when training on specialized study procedures is needed. In addition, a combination approach can be taken. For example, telephone and web-based training could be planned for experienced sites while in-person training would be offered to less experienced sites or for a targeted study-related purpose, such as specialized laboratory procedures/assays. Cost-efficiency and effectiveness are also key considerations in determining the best approach. 'Live meeting' or web-based trainings are used as much as possible to conserve time and travel and to maximize participation.

When in-person training is necessary, options include regional training events for study staff from multiple sites as well as individual on-site training events. Study-specific trainings may include sessions for community educators and Community Advisory Board (CAB) members, focused on community education and outreach, participant recruitment and retention, human subjects and participant safety protections, community perceptions and potential misconceptions of the study.

Advance preparation is essential to the success of any study-specific training. To maximize training effectiveness, each training is scheduled as close as possible to the time of study initiation.

Following each training, all materials are provided to the training participants for both review and reference. Materials are also posted on the IMPAACT website, typically on the study-specific page.

In some cases, additional training needs for specific sites may be identified. The IoR is responsible for ensuring that site study staff members are adequately trained to serve their designated site- and study-specific functions. The Protocol Chair, CTS, and other protocol team members will work with the IoR to support and facilitate response to the identified training needs.

11.2.4 Local Language Translation of Study Documents

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. See Section 7 for more information on translation of protocol documents. 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 National Institute of Child Health and Human Development (NICHD) coordinating center may be able assist with the translations.

When translated materials are required for study implementation, this will be reflected in the listing of study activation requirements. 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.