12 STUDY IMPLEMENTATION

This section provides guidance on key components of study implementation, including participant accrual and follow-up, data collection and documentation, and study communications.

Upon receipt of the Site-Specific Study Activation Notice, sites may begin study implementation and screening procedures. All study procedures are directed by the version of the protocol currently approved at the site, with operational guidance from the supplementary materials provided by the protocol team (e.g., Laboratory Processing Chart [LPC], study-specific manual of procedures [MOP]); in case of any discrepancies between the protocol and the supplementary materials, the protocol takes precedence.

12.1 Participant Accrual and Follow-Up in IMPAACT Studies

12.1.1 Accrual Projections

As part of protocol development and the site selection process, overall study and site-specific participant accrual targets are established. Overall targets are specified in the study protocol based on the scientific objectives and statistical considerations. Site-specific targets are specified in the site selection and accrual plan developed by the protocol team and approved by the IMPAACT Management Oversight Group (MOG, see Section 10). Unless otherwise specified, the study-specific enrollment period begins on the first day of participant enrollment at any participating study site; site-specific enrollment periods are considered to begin on the first day of participant enrollment at that site. For many studies, the time from the first day of participant screening through the end of participant accrual is also tracked and reported.

Site-specified accrual targets should reflect protocol specifications for distribution of participants (e.g., within specific geographical areas, age groups, etc.); enrollment caps for sites may be specified in the protocol or in the MOG-approved accrual plan, depending on the needs of the study. Otherwise, enrollment targets may be shifted across sites in response to actual accrual/site performance. Protocol teams should consider whether to specify a maximum number of participants to be enrolled for any site to

ensure that one or more sites or populations from a given area are not inappropriately over-represented. Some IMPAACT protocols specify an estimated total number of participants to be enrolled to reach a target number who are fully evaluable as defined in the protocol; in such cases, guidelines for adding participants are typically specified in the protocol. The protocol chair and statistician lead the protocol team in making these determinations, and work with the data manager, clinical trials specialist (CTS), and other team members to ensure that procedures are in place to operationalize accrual targets and restrictions as needed.

For studies in which enrollment targets are shifted across sites, sites inform their Institutional Review Boards/Ethics Committees (IRBs/ECs) of increases or decreases in their enrollment targets in accordance with IRB/EC requirements and revise their informed consent forms to reflect changes as needed.

The Statistical and Data Management Center (SDMC) generates routine study screening, enrollment, and retention reports – for each IMPAACT study overall and by site – for review by the MOG; the reports for each study are shared with the protocol team. When applicable, reports are also generated by cohort or other relevant study-specific groupings. Protocol teams are responsible for closely monitoring accrual and retention on an ongoing basis and taking appropriate action as necessary to ensure that targets are met, in consultation with the MOG as needed.

12.1.2 Screening and Enrollment

For each IMPAACT study, screening and enrollment visit procedures are described in detail in the study protocol and, if applicable, the study-specific MOP. Information pertinent to participant screening and enrollment that is applicable to all IMPAACT studies is provided in the remainder of this section.

Written informed consent must be obtained from all IMPAACT study participants or their legal guardians prior to the performance of any protocol-specified screening or enrollment procedures. See Section 8 for additional information on the informed consent process.

Unless determined otherwise by the protocol team, screening for each study is tracked using the Data Management Center (DMC) Subject Enrollment System (SES) and reasons for screening failures are recorded or entered on a Screening Failure case report form (CRF). When relevant, protocol teams should also implement mechanisms to track recruitment and pre-screening activity. Screening data are monitored closely by the protocol team to identify specific barriers to enrollment (based on reasons for exclusion) and to monitor the pipeline of potential participants at participating sites, both of which inform study feasibility.

For each study, the SDMC provides participating sites with a list of participant identification numbers (PIDs) to be assigned to study participants for purposes of study data management. A PID is assigned to a potential study participant at time of screening for his/her first IMPAACT study. This same PID is used if the participant enrolls to any future network study as well. Detailed information on the structure and format of PIDs, and instructions for assigning them to individual study participants, are available on the DMC portal under Site Support in the Computing Manual: Participant Enrollment Methods.

From both a statistical and operational perspective, it is important to define when participants are considered enrolled in a study. For IMPAACT studies, participants are considered enrolled upon successful entry of required eligibility data into the SES. Successful entry into the SES generates a study identification number (SID) and, when applicable, prescribing information for the study intervention the participant should receive following enrollment.

The Division of AIDS (DAIDS) policy on essential documents (Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials) requires study sites to document IMPAACT study screening and enrollment activities on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Sample logs that may be adapted for local use at participating sites are often provided in study-specific MOPs. The DAIDS policy on essential documents specifies that participant initials be recorded on screening and enrollment logs, in addition to PIDs. For IMPAACT studies, in agreement with DAIDS, participant initials need not be recorded on screening and enrollment logs if doing so presents a potential threat to participant confidentiality. However, in such cases, a separate document must be available to document the link between a participant's name and PID.

12.1.3 Follow-Up Visits

For each IMPAACT study, the expected duration of participant follow-up, as well as the number and type of follow-up study visits or contacts that are scheduled to take place during the course of the study, are specified in the study protocol. In addition to specifying target visit dates, the protocol also specifies allowable visit windows for certain follow-up visits. Visit windows are defined as the period of time around the target date during which the visit procedures must be performed. In addition to allowable visit windows, narrower target visit windows within which the visit is expected to be performed may also be defined and used when reporting participant retention and the number of visits conducted early or late. Sites are encouraged to conduct visits within the visit window. When scheduled follow-up visits cannot take place during the allowable visit window, sites should contact the protocol team; the visit may be considered missed or changes to visit procedures may be required.

Interim visits are those that are not scheduled per protocol and are in addition to regular study visits. Interim visits or contacts may take place for a variety of reasons (e.g., a participant may be sick, need additional study product, additional laboratory tests, etc.). The interim visit must be source documented; unless immediate reporting is specified (e.g., an adverse event that meets the criteria for expedited reporting), data are recorded or entered on CRFs at the next scheduled study visit, or as instructed by the protocol team and protocol data manager.

When necessary and unless otherwise specified in the study protocol, sites may conduct "split" visits in which the evaluations required for a given study visit are conducted over a period of more than one visit to the clinic.

12.1.4 Participant Transfer between IMPAACT Sites

During the course of IMPAACT studies, participants may leave the geographic area where they were enrolled and relocate to another area where the same study is taking place. To maximize retention, participants who relocate from one study area to another may be encouraged to continue their participation in their new location, unless otherwise directed by the study protocol. To accomplish this, study staff at both the originating site and the receiving site complete the process of a participant transfer.

All transfers should be performed using the Participant Transfer Request utility on the DMC portal. To complete a transfer using this utility, both sites must have completed the protocol registration process with the DAIDS Protocol Registration Office and have been issued a site-specific study activation notice from the Operations Center.

Key considerations are as follows:

- Care should be taken by both the originating site and the receiving site to protect participant privacy and confidentiality throughout the transfer process.
- The originating site is responsible for initiating each transfer using the Participant Transfer Request utility.
- The originating site is responsible for all aspects of study-related documentation and data management for study visits occurring before the transfer, including completion of CRFs and resolution of data queries for visits occurring before the transfer. Should additional data queries for pre-transfer visits arise after the transfer has been completed, the originating and receiving sites should work together as needed to resolve the queries.
- After all documentation has been completed and all data queries have been resolved, the originating site is responsible for preparing copies of the participant's study records (source documents and CRFs/eCRFs):
  - Original source documents — including original CRFs/eCRFs that serve as source documents — are retained at the originating site; certified copies are provided to the receiving site.
  - Original CRFs/eCRFs (excluding CRFs/eCRFs that serve as source documents) are provided to the receiving site; certified copies are retained at the originating site.
- The originating site is responsible for providing participant-specific contact details and participant-specific pharmacy details to the receiving site.
- The participant must provide written informed consent to continue study participation at the receiving site; receiving site staff are responsible for conducting and documenting the informed consent process per site standard operating procedures (SOP), using the informed consent form currently approved by the receiving site IRBs/ECs.
  - Note: Exceptions to this requirement may be applicable when the same informed consent form is approved for use at both the originating site and the receiving site.
- The receiving site is responsible for completing the transfer using the Participant Transfer Request utility. The receiving site is then responsible for all aspects of study-related documentation and data management for the transferred participant.
- The protocol data manager is copied on all correspondence generated by the Participant Transfer Request utility. When the receiving site completes the transfer through the utility, the data manager updates the clinical database to recognize that the transfer has been completed and the receiving site has taken full responsibility for the participant and study data going forward.
- If the study participant is on more than one study, this process needs to be completed for each study for which she/he is transferring study follow-up.

Due to concerns regarding confidentiality, documentation and other factors, temporary transfers (when a participant will be away from his/her originating site and potentially followed at another participating site for a short period of time) are typically not allowed.

12.1.5 Investigator-Initiated Termination of Participants

IMPAACT study participants (or their parent or legal guardian) may withdraw their consent to participate in IMPAACT studies at any time, for any reason. Investigator-initiated termination of IMPAACT study participants should occur only under extraordinary circumstances. For instance, termination may be considered if there is potential for harm to study staff or significant disruption of study operations.

In studies involving investigational products or interventions, Investigators of Record (IoRs) will not routinely terminate study participants solely because the participants are non-adherent to the protocol-specified regimen for use of the investigational product or intervention.

Prior to terminating a participant from an IMPAACT study, the IoR should seek approval of members of the protocol team designated in the study protocol; at a minimum, the protocol chair, medical officer(s), and statistician must be consulted. Designated members of the protocol team assess the scientific, operational, and statistical implications of the requested termination and determine whether the termination may take place.

The CTS or other designated protocol team member document and provide the determination in writing (email or meeting minutes are acceptable) to the site. Site staff must always record reasons for termination in participant study records.

12.1.6 Participant Unblinding During Study Implementation

Protocol teams should indicate unblinding procedures in the protocol, including guidelines to determine if and when individual participant management unblinding is appropriate. Any deviation from the guidelines below must be explicitly stated in the protocol; such "non-standard" unblinding are reviewed and approved by the Statistical and Data Analysis Center and the IMPAACT Multidisciplinary Protocol Review Group prior to protocol finalization. Additional details concerning background on blinding as well as procedures for unblinding during study conduct for safety or per-protocol and procedures for unblinding following study closure can be found in Appendix I.

12.2 Data Collection

The DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* specifies the essential documents that study sites must maintain for DAIDS-sponsored studies.

In its policy on Requirements for Manual of Operational Procedures, DAIDS requires study sites to establish an SOP for maintaining essential documents. All study sites must comply with this requirement and follow their SOP for maintaining essential documents for the studies.

Site staff should also ensure that essential documents are subject to quality control (QC)/quality assurance (QA) procedures per the DAIDS policy on Requirements for Clinical Quality Management Plans.

The above-referenced DAIDS policies are available at:
https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf

12.2.1 Participant Research Records

The United States Code of Federal Regulations and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidance requires study site staff to maintain adequate and accurate participant "case history records" containing all information pertinent to the study for each IMPAACT study participant.

12.2.1.1 Participant Research Record Contents

Participant research records should contain all of the following elements:

- Basic participant identifiers such as PIDs or initials (Note that initials or other participant identifiers other than PID number should never be entered on a CRF or submitted to the DMC or study clinical database.)
- Documentation that the participant (or parent or legal guardian) provided written informed consent to participate in the study prior to the conduct of any study procedures
- Documentation that the participant met the study's eligibility criteria
- A record of the participant's random assignment (if applicable)
- A record of the participant's exposure to investigational products (if applicable)
- A record of all contacts, and attempted contacts, with the participant including all clinic visits, off-site visits (e.g., at home or work), and all verbal and written contacts
- A record of all procedures performed by study staff during the study
- Complete source documents
- All CRFs and other study data collected from the onset of screening through end of participation
- Study-related information on the participant's condition before, during, and at the conclusion of study participation, including:
  - Data obtained directly from the participant (e.g., interview responses)
  - Objective data ascertained by study staff (e.g., exam and laboratory findings)
  - Objective data obtained from non-study sources (e.g., medical records)

In addition to the above, the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Trials requires that all protocol deviations involving participants be documented in participant's study records, along with reasons for the deviation and attempts to prevent or correct the deviations, if applicable. See Section 12 regarding IMPAACT requirements for reporting protocol deviations.

12.2.1.2 Concept of Source Data and Source Documentation

The ICH/GCP guidance defines source data and source documentation as follows:

- The term "source data" refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- The term "source documents" refers to original documents, data and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification as being accurate and complete; microfiche; photographic negatives; microfilm or magnetic media; x-rays; participant files; and records kept at the pharmacy, the laboratories, and medico-technical departments involved in the trial).

Source documents are commonly referred to as the documents — paper-based or electronic — upon which source data are first recorded.

IMPAACT study sites must adhere to the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Trials. This policy contains both requirements and recommendations. Study sites must comply with all requirements

and are advised, but not required, to comply with all recommendations. Source documentation includes original documents and certified copies that include documentation pertaining to a participant while on study.

For each IMPAACT study, participant case history records typically consist of some or all of the following:

- Narrative chart notes
- Visit checklists or flow sheets
- Laboratory reports
- Medical records or clinic charts
- CRFs
- Randomization log or other documentation (when applicable)
- Investigational product dispensing and accountability records (when applicable)
- Other source documents and non-CRF data collection tools or questionnaires

As a condition for study activation, each site must have an established SOP for source documentation that specifies the use of these documents as source documents (see Section 11).

Supplemental information on use of chart notes, visit checklists, and CRFs as source documents is provided below. Also provided below is information related to investigational product dispensing and accountability records, document organization, and record retention requirements.

The DAIDS SOP for source documentation requires that a site must document which CRFs, if any, will be used as source documents. Study staff must follow the specifications of this SOP consistently for all study participants throughout the study. In the event that study staff are not able to record source data directly onto forms designated as source documents, the following procedures should be undertaken:

- Recording the data onto an alternate source document
- Entering the alternate source document into the participant's study chart
- Transcribing the data from the alternate source document onto the appropriate CRF
- Recording a chart note stating the reason why an alternate source document was used

12.2.1.3 Chart Notes

Chart notes must be used to document the following:

- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents

All chart notes or other tools used as source documentation must document the PID of the study participant to whom they pertain, the identity of the study staff member who entered information, and the date of the entry. Study sites are strongly encouraged to adopt a common format — such as the Subjective-Objective-Assessment-Plan (SOAP) format for all chart notes — to help ensure adequacy and consistency of note content and maximize adherence to GCP standards. Alternative standardized formats are acceptable and may be adopted by study sites.

12.2.1.4 Visit Checklists

In some studies, visit checklists may be a convenient tool for study staff to fulfill the requirement of documenting all procedures performed with each study participant. Note that checklists alone often are not sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits to explain why procedures, in addition to those specified on a checklist, may have been performed or why procedures specified on a checklist were not performed. Chart notes also may be required to document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

Study procedures for which visit checklists are used as source documentation must contain the PID, the initials or signature of the authorized study staff member completing the procedures, and the date the procedure was completed. Individual study staff members must initial only those procedures that they complete. In addition, if procedures listed on a single checklist are completed across multiple dates, the date upon which each procedure is completed must be clearly noted. Additional detailed guidance related to proper use of visit checklists may be provided in each study-specific MOP.

12.2.2 Case Report Form Distribution, Completion, and Data Entry

The DMC distributes CRFs to the participating sites in a format dependent on the Clinical Trials Data Management System (CTDMS) in use for the study.

For studies in eData, the formats include:

- Bulk CRFs: Preprinted CRFs bundled by form or visit type
- Electronic CRFs: PDF versions of the CRFs are furnished to the site through the Forms Management Utility on the DMC portal and the site is responsible for printing them

For studies in Medidata Rave, the formats include:

- Electronic CRF (eCRF) completion guide: PDF versions of the CRFs with instructions for preparation of collection of the study data are available on the DMC portal
- Print matrix: PDF versions of forms as they appear in the CTDMS, which may be downloaded by site personnel from the DMC portal
- eCRFs for Participant Interviews of Questionnaires: PDF versions of these CRFs are furnished to the site through the Forms Management Utility on the DMC Portal, and the site is responsible for printing them
- Study staff may use these tools to develop documentation for collection of participant data for entry into Medidata Rave.

Aspects of CRF completion and data entry vary depending on the CTDMS in use for the study (either Medidata Rave or eData). Some studies that are currently being implemented using eData may continue to use eData, while other studies have or will be migrated to Medidata Rave. New studies utilize Medidata Rave. Refer to the protocol and associated documents for the CTDMS to be used. In addition, the Laboratory Processing Chart (LPC) and protocol Manual of Procedures (MOP) should be used in scheduling participant visits and specimen collection.

12.2.2.1 Data Management Procedures for Studies using eData

Data for IMPAACT clinical trials are collected on protocol CRFs by designated study staff at each clinical research site and then key-entered into the Data Management System (eData). Designated study staff should perform quality control checks on the data before submitting the keyed CRF data to the central database. DMC personnel train site staff on the appropriate completion and recording of data on the CRFs, and form-specific instructions are, in most cases, printed on each CRF.

Site data staff should use CRF notebooks developed and distributed by the DMC. These notebooks provide the framework for collecting the necessary study data based on the schedules of evaluation in the study protocol. The Data Collection Forms Schedule in the CRF notebooks should aid in scheduling participant visits and specimen collection.

12.2.2.2 Data Management Procedures for Studies using Medidata Rave

Data entered into Medidata Rave is completed by designated study staff. Site staff should perform quality checks of the data prior to and while entering the data, as well as after saving the data in Medidata Rave. Site staff should utilize reports within Medidata Rave to resolve queries and address delinquencies. Reports for quality review of participant data, productivity, and administrative reports, are available to sites; some reports are available within the DMC portal or in Medidata Rave. Studies that are migrated from eData to Medidata Rave will continue to use the reports available on the DMC portal.

Site staff should use completion guides developed and distributed by the DMC. These guides provide the framework for collecting the necessary study data based on the schedules of evaluation in the study protocol and aid in scheduling participant visits and specimen collection.

12.2.2.3 Data Management Procedures for Studies using either eData or Medidata Rave

Sites use the Subject Enrollment System on the DMC portal for submission of screening checklists and eligibility checklists for both new and subsequent steps for participant enrollments. Requests for participant transfers to new sites, eligibility corrections, and unblinding requests are managed through the appropriate utilities on the DMC portal. Any questions on available reports should be sent to the protocol data manager.

Site staff should utilize daily and monthly reports provided by the DMC for error resolution, resolving data delinquencies, and responding to data queries, and select web utilities on the DMC portal provide additional data QA/QC reports for site staff to review participant data.

The assigned protocol data managers and other DMC staff answer questions about data management and system issues. If the protocol data manager is unavailable, sites should contact the Chief Data Manager or Coordinating Data Manager, who have overall responsibility for central data management in IMPAACT.

Hardware and software computing requirements as well as procedures for enrolling participants, submitting participant data, and other areas of central DMC requirements can be obtained by contacting FSTRF User Support and from the Computer Manual, accessible by the FSTRF website: https://www.frontierscience.org/. Information regarding DMC training programs is also available at this website as well.

12.3 Study Team Communications

After initial release of a study protocol, several types of study-related communications may be used to report on study progress or provide further clarification of protocol-specified procedures and study documentation requirements. Such communications may include, but are not limited to, the following:

Table 12-1. Study Team Communications

Conference calls and meetings	Protocol teams (including site representatives), and designated subgroups, take part in routine meetings and conference calls throughout the period of study implementation. Summaries of these meetings and conference calls, which often document key protocol-related and study implementation decisions and action items, are prepared and distributed as described in Section 6.
Protocol clarification memoranda, letters of amendment, and full amendments with an attendant summary of revisions	These documents are developed and issued as described in Section 9. Development of these documents is coordinated by the protocol CTS, and final versions are distributed to all protocol team members and study sites. Final versions also are posted on the IMPAACT website.
Study-specific MOP updates	These updates are developed and issued as described in Section 11. As with the initial MOP version, development of the updated version is coordinated by the CTS and final versions are posted on the IMPAACT website.
Reports	Data reports on study progress, protocol adherence, data quality, etc., are developed and issued by the SDMC in accordance with the study monitoring plan (Section 11).
Study implementation questions	These questions may be related to protocol interpretation as well as administrative, ethical, regulatory, clinical, counseling, data, and laboratory operations. Any such questions that are not answered by the protocol or other operational guidance documents should be emailed to the protocol team or designated subgroup (e.g., study-specific Clinical Management Committee), as per protocol. As described in Section 12.4, protocol deviations are submitted to the protocol deviation email list (IMPAACT.deviation@fstrf.org).
Conference calls and refresher training sessions with site staff	Refresher trainings and conference calls for study coordinators and other site staff with the study clinical trials specialist, data manager, laboratory representative and other protocol team members are held as needed, and for some studies on a routine basis. These sessions provide a forum for discussion of study implementation challenges, clarification of operational aspects, review of protocol updates (i.e., associated with amendments and clarification memoranda) and other topics suggested by site staff.

12.3.1 Confidentiality of Study Data

Unless otherwise specified in the study protocol, discussion of study post-entry data during an ongoing study should be limited to designated committees (e.g., Data and Safety Monitoring Board) to avoid bias in study conduct and/or interpretation of data.

12.3.2 Clinical Management Committee

For studies with a biomedical intervention, a Clinical Management Committee (CMC), or analogous group, is typically instituted, composed of appropriate protocol team clinicians (and external clinicians as appropriate) and other team members. This committee provides support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations). No aggregate data are provided to this committee, unless otherwise designated in the protocol, and no treatment assignment information is provided for the individual participant discussion(s) unless essential to ensure participant safety.

12.3.3 DMC Queries and QC Reports

The protocol data manager and designated DMC staff (e.g., medical coders) review CRF data submitted to the central study database and items that need verification or further clarification are sent as queries to the site data management staff.

For studies using eData, on a daily or monthly basis, the DMC sends a number of QA/QC reports (e.g., the UPD8 and monthly quality assurance reports) to site staff to identify data that are inconsistent, missing, or contain out-of-range values. Additionally, QA/QC reports are available on the DMC portal and may be run as needed by site staff. Site staff should review and respond to QC reports sent by the DMC.

For studies using Medidata Rave, reports to review queries, overdue forms, and other quality assurance reports are available within Medidata Rave and may be run as needed by sites. Data management staff at the sites should routinely review the reports and correct or clarify the data items in question. Site staff should routinely check within Rave to ensure QC issues, such as overdue forms or queries, are addressed.

For all studies, queries may also be sent in preparation for interim analyses and these should be addressed as soon as possible. If the site has questions about any queried items that show up repeatedly on QC reports, they should contact the protocol data manager for further explanation. Any issues should be addressed as soon as possible, generally within seven to ten working days of receipt.

12.3.4 Data Management Quality Summary Reports

The SDMC routinely generates reports on site-specific and protocol-specific data management performance.

For studies using eData, the reports include:

- Total number of records expected versus submitted
- QC rate (the number of errors per 100 transactions)
- Percentage of QCs resolved
- Timeliness of submitted data (mean/median number of weeks)

For studies using Medidata Rave, these reports are in development and this section of the MOP will be updated as those reports become available.

If there are concerns about a site's data management quality, the data manager and protocol team work with the site to help develop strategies for improving performance.

12.4 Protocol Deviations

This section outlines the process by which protocol deviations are defined, classified, reported, and documented for IMPAACT studies. These guidelines apply to all IMPAACT studies and may be augmented by additional sponsor requirements or any protocol specifications.

Investigators of Record (IoRs), and by delegation all study staff, are responsible for conducting IMPAACT studies in compliance with the IRB-approved protocol; applicable US laws and regulations; ICH Guidelines on Good Clinical Practice; applicable local laws, regulations, and guidelines; and standards of professional conduct and practice. Any non-compliance with the IRB-approved protocol is a protocol deviation. Deviations may be incurred by study participants, protocol team members, IoRs, sub-investigators, coordinators, physicians, nurses, counselors, data managers, pharmacy staff, laboratory staff, and/or additional supervisory, oversight, or support staff.

Note: Throughout this section, reference is made to the "IRB-approved protocol." This terminology refers to the study protocol that has been approved by site institutional review boards, ethics committees, drug regulatory authorities, and all other applicable regulatory entities.

12.4.1 Applicable Regulatory Requirements and Guidance

United States Code of Federal Regulations (U.S. CFR)

- **21 CFR 312.60:** states that "an investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and the applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation…"
- **21 CFR 56.108:** states that investigators must "(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval."
- **45 CFR 46.113:** authorizes the IRB to suspend or terminate approval of research that is not being conducted in accordance with IRB's requirements or that has been associated with unexpected or serious harm to subjects.
- **45 CFR 46.103(b)(4)(iii):** states that institutions must have written procedures (which investigators must follow) for ensuring the prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
- **45 CFR 46.103 (b) (5):** states that institutions must have written procedures (which investigators must follow) for prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of any unanticipated problems involving risks to subjects or other**s**, or any serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval.

The full U.S. CFR may be found at www.ecfr.gov/.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- **ICH Guideline 4.5:** states that the investigator should not implement any deviation from or changes of the protocol without prior review and documented approval from the IRB except where it is necessary to eliminate an immediate hazard(s) to a study subject or when the change(s) involve only logistical or administrative aspects of the study.
- **ICH 4.5.3:** states that the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The full ICH guidelines may be found at http://ichgcp.net/.

United States Food and Drug Administration (U.S. FDA)

Guidance, compliance, and regulatory information from the US Food and Drug Administration (FDA) may be found at http://www.fda.gov/drugs/default.htm. The FDA considers protocol deviations as acts contrary to the written protocol.

Further insight into the FDA's perspective on protocol deviations can be found at http://www.fda.gov. The website contains copies of warning letters issued by the FDA, as made available under the 1996 amended Freedom of Information Act. Examples of warning letters including protocol non-compliance issues include:

- Letter to JM Isner; 28 April 2000 (St. Elizabeth's Medical Center; Boston, Massachusetts): *Subject ___ was enrolled into study VEGF2-CAD-001 (cardiac arterial disease study); however, the subject met the protocol exclusion criteria.*
- Letter to EJ Kopp; 21 June 2000 (CARE Center, Raleigh, NC): *Two of 14 subjects did not meet protocol criteria regarding duration of _____.*

United States Health and Human Services

Regulations from the U.S. HHS may be found at http://www.hhs.gov/ohrp/.

12.4.2 Definitions Applicable to IMPAACT Research

Table 12-2. Definitions

Protocol deviations	Any departure from an IRB-approved protocol. This includes but is not limited to the following: • Administrative inconsistencies or minor errors in the implementation of the protocol (e.g., visit outside the window, lab off schedule, violation of inclusion/exclusion criteria) • Departure from specified treatment, examination, or data collection procedures in a study protocol Protocol deviations may or may not render a participant ineligible to participate in a study and may be considered significant or serious when they increase potential risk to participants or affect the integrity of study data. An isolated deviation may not be significant by itself but significance may increase with numerous deviations of the same nature.
<u>Reportable</u> protocol deviation	Deviations that require additional reporting by the IoR or designee as described in Section 12.4.3 below. Defined by IMPAACT as deviations that result in: • Significant increased risk to the study participants or others • Significant non-compliance with IRB-approved protocol requirements • Significant non-compliance with Good Clinical Practices or Good Clinical Laboratory Practices and all applicable regulations Examples of reportable protocol deviations include: • Enrollment of an ineligible participant • Failure to obtain informed consent or assent from the participant, legal guardian, or other or legally authorized representative prior to performing protocol-specified procedures • Performing procedures not specified in the IRB-approved protocol and not otherwise clinically indicated for the participant • Knowingly reporting of an inaccurate laboratory result • Failure to follow protocol-specified procedures for participant safety monitoring, management, or reporting (including failure to report expedited adverse events within three reporting days) • Breach of participant confidentiality The list of examples shown above is intended as a guide and is not all-inclusive. *Participant non-compliance (e.g., missed visits, missed doses of study drug) is considered a protocol deviation but is <u>not</u> considered a <u>reportable</u> protocol deviation. Participant non-compliance should be documented and reported per usual site procedures (and any applicable protocol requirements) but should not be reported as described in Section 12.4.3 below.*

Table 12-2. Definitions

Corrective action	Action taken to correct (when possible) or otherwise address a protocol deviation. Corrective actions are commonly specified in consultation with the relevant protocol team and/or IMPAACT leadership. In all cases, corrective action must include documentation of the deviation. Per the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*, all protocol departures/deviations/violations must be recorded in the participant's research record and, if pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation. Examples of corrective actions include (but are not limited to) notifying the affected participant(s), protocol team, and/or IRB; re-consenting the participant(s); completing missed procedures; repeating laboratory tests; completing additional participant monitoring or management procedures; and/or destroying specimens collected in error.
Preventive action	Action taken to prevent recurrence of a deviation. Preventive actions are commonly specified in consultation with the relevant protocol team and/or IMPAACT leadership. In all cases, preventive action must include documentation of the deviation. Per the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*, all protocol departures/deviations/violations must be recorded in the participant's research record and, if pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation. Examples of preventive actions include (but are not limited to) discussion of the deviation with relevant study staff, refresher training of study staff; review and/or revision of SOPs or other study implementation materials; development of new study implementation materials; implementation of additional communication, QC/QA, or oversight/supervisory procedures; changes in day-to-day workflow; and/or changes in general participant management or laboratory procedures.

NIAID and NICHD Clinical Site Monitors may identify protocol deviations in their monitoring reports and some of these may meet the definition of reportable protocol deviation. In the event that deviations identified by Clinical Site Monitors meet the definition of reportable, the IoR or designee must report the deviation as described in Section 12.4.3 below. Likewise, other network partners such as representatives of the Operations Center, DMC, or ILC may identify a reportable protocol deviation; these persons should notify the IoR as soon as possible (within 3 days of awareness) so that the IoR can then report the deviation.

Note that there is not a one-to-one correlation between events reported by the Clinical Site Monitor and those to be reported through the IMPAACT protocol deviation reporting system. The Clinical Site Monitor may report protocol non-adherence events and violations that encompass every infraction of the protocol. For example, if a blood specimen is drawn for ALT, but is not processed by the laboratory, it is a non-adherence event according to the Clinical Site Monitor. This would not be a reportable protocol deviation because it is one missed collection and does not represent a systemic issue that would affect study data. If, however, an ALT is to be drawn at each participant visit and is not being done at all, this would be a reportable protocol deviation.

Section 12.4.3 describes procedures for **reportable protocol deviations**.

12.4.3 Procedures for Reportable Protocol Deviations

All reportable protocol deviations must be reported by site investigators within ten working days of site awareness. If needed, consultation with the Operations Center, SDMC, LC, or respective protocol team is available.

Reporting procedures require entry of a protocol deviation case report form (CRF) — so that the deviation is recorded in the study database — and distribution of the same information to members of the IMPAACT leadership and respective protocol team. To minimize reporting burden, sites should complete and enter the CRF per usual data management procedures, save a PDF version of the CRF, and email the PDF with any additional supplemental documents (e.g., IRB correspondence) to IMPAACT.Deviation@fstrf.org.

If a reportable deviation involves more than one participant, one protocol deviation CRF should be completed for each participant. If more than 25 participants are involved, or if the deviation does not involve specific participants, the deviation should be reported only via email to IMPAACT.Deviation@fstrf.org (i.e., a CRF should not be entered into the study database). If the deviation occurred over a period of time, the range of dates over which the deviation occurred should be indicated on the CRF.

The emailed report is tracked by the Operations Center and sent to the following distribution list within three working days:

- Protocol chair(s)
- Protocol medical officer(s)
- Protocol CTS(s)
- IMPAACT leadership (Network chair and vice-chair, as well as NIH and operational component representatives, including leadership of the SDMC, LC, and Operations Center)
- IMPAACT program officer(s)
- Site Office of Clinical Site Oversight (OCSO) program officer (NIAID sites only) or Westat site contact (NICHD sites only)
- Protocol pharmacist (if the deviation involves study product or prescribing issues)
- Protocol Laboratory Center representative (if the deviation involves laboratory issues)

This group works jointly to assess the deviation's severity and the appropriate corrective and preventive action plan. If revisions are incorporated following submission of the report into the database, the original protocol deviation CRF should be updated in the study database, and a PDF version of the revised CRF should be emailed to IMPAACT.Deviation@fstrf.org.

Figure 1: IMPAACT Protocol Deviation Reporting Form

(Note that the fields presented below are for reference only;
reportable deviations should be entered into CRFs as described in Section 12.4.3)

Date form submitted: ☐

Location of deviation:
CRS Name/Number (if applicable): ☐

Protocol Number: ☐

Participant Identification Number(s)
(if applicable): ☐

Site awareness date: ☐

Deviation date (or range): ☐ – ☐

Has or will this deviation be reported to the local IRB/EC?

- ☐ Yes
- ☐ No

Has or will this deviation be reported to DAIDS as a critical event?

- ☐ Yes
- ☐ No

Type of deviation (please check one):

- ☐ Inappropriate enrollment
- ☐ Failure to follow trial randomization or blinding procedures
- ☐ Study product management deviation
- ☐ Study product dispensing error
- ☐ Conduct of non-protocol procedure
- ☐ Breach of confidentiality
- ☐ Physical assessment deviation
- ☐ Lab assessment deviation
- ☐ Use of non-IRB/EC-approved materials
- ☐ Informed assent/consent process deviation
- ☐ Other

Please describe the deviation, explain the reason for the deviation, and how the deviation affected the:

- Risk/benefit ratio for the participant(s)
- Integrity of the research data
- Participant's willingness (or parent/legal guardian's willingness) to continue study participation

Figure 1: IMPAACT Protocol Deviation Reporting Form (continued)
(Note that the fields presented below are for reference only;
reportable deviations should be entered into CRFs as described above)

Describe any corrective actions taken to address this deviation:

_____
_____
_____
_____
_____

Describe any preventive actions taken to prevent recurrence:

_____
_____
_____
_____
_____

Deviation reported by (staff name): _____
Note the deviation should be reported by the responsible/communicating site staff member (IoR or other designee).

Please submit any additional supplementary materials to IMPAACT.Deviation@fstrf.org along with the PDF of the submitted CRF.