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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

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). Throughout the course of the study, the protocol team may survey study sites for updated accrual projections to assist with decisions related to study implementation (e.g., following the issuance of a full version amendment or to determine the need for study expansion to other sites).

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 and/or other aspects of 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 protocol 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. Note that over-enrollment is not permitted as a means to make up for participant loss-to-follow-up unless the protocol wording permits over-enrollment.

Enrollment into each IMPAACT study is open to all sites that are selected to conduct the study. However, some sites may not be able to enroll any participants into studies for which they are selected. For example, sites may not be able identify participants who meet the study eligibility criteria. In addition, sites with protracted timelines for obtaining ethical and regulatory approval of the study protocols may not be able to initiate screening and enrollment activities before the study enrollment target has been met.

For studies in which enrollment targets are shifted across sites, sites should 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, typically on a monthly basis. 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. A study is considered to have met the [DAIDS status](#) of “enrolling” on the date that the first participant is enrolled.

Unless otherwise specified, the study-specific enrollment period begins on the day the first participant enrolled at any participating study site; site-specific enrollment periods are considered to begin on the day that the first participant enrolled 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.

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 in consultation with Network leadership, screening for each study is tracked using the Data Management Center (DMC) Study Enrollment System (SES), and reasons for screening failures are recorded or entered on Screening Failure electronic case report forms (eCRFs). 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 \(DAIDS\)](#) guidelines on essential documents 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. The DAIDS guidelines 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. Additional information is available in the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual.

12.2 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. Failure to conduct study-specific procedures within the protocol-specified visit window is a deviation from the protocol and should be documented appropriately (see Section 12.5).

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 documented in the participant's study record; 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.

12.2.1 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 eCRFs 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 any paper-based CRFs):
 - Original source documents — including original CRFs that serve as source documents — are retained at the originating site; certified copies are provided to the receiving site.
 - Original paper-based CRFs (excluding those that serve as source documents) are provided to the receiving site; certified copies are retained at the originating site.
 - eCRFs must be signed off by the originating site IoR in Rave prior to the participant transfer; the DMC will work with the originating and receiving sites to make the eCRFs available to the receiving 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.
- The originating site should consult with the protocol team regarding the handling of specimens (e.g., when and where to ship specimens).

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.

12.2.2 Investigator-Initiated Early 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 an individual's IMPAACT study participation prior to the protocol-specified completion of follow-up should occur only under extraordinary circumstances. For instance, termination may be considered if there is potential for harm to the participant or 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. 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 documents and provides 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.

12.2.3 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 included in Appendix I, Unblinding Procedures, must be explicitly stated in the protocol; such "non-standard" unblinding procedures are reviewed and approved by the Statistical and Data Analysis Center and the IMPAACT Multidisciplinary Protocol Review Group prior to protocol finalization. Additional details describing the background on blinding, procedures for unblinding during study conduct for safety or per-protocol, and procedures for unblinding following study closure can be found in Appendix I.

12.2.4 Closing to Accrual

A study is considered to have met the DAIDS status of "closed to accrual" on the date when no more study participants will be enrolled in the study. Participant follow-up (including assessments, data collection, etc.) typically continues past the closed to accrual date. The closed to accrual date may occur once the protocol-specific accrual targets have been met or when the SMC or DSMB recommends, and the MOG or DAIDS, respectively, accepts the decision that the study should discontinue enrollment.

For studies that are projected to close to accrual following successfully meeting the protocol accrual targets, the protocol team should begin planning for study closing to accrual approximately three months prior to the anticipated date. For studies that are closed to accrual following an SMC or DSMB review, such planning may not be possible.

Planning activities may include determining requirements for laboratory sample shipments; communicating with sites on accrual trends, communicating with site stakeholders, communicating with potential participants during the informed consent process about their potential to enroll, and/or planning for potential participants in the screening process when the protocol-specific accrual target is met.

As needed, the SDMC will provide the protocol team with information on the projected primary completion date for the study, which is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. The SDMC will also provide information on the projected date for closing to follow-up (i.e., the projected study completion date), and the date range during which the final follow-up study visits should occur. Initial projections are typically updated upon completion of accrual into the study. Thereafter, projections are updated as needed depending on the study design and planned duration of participant follow-up.

Upon confirmation of last enrollment:

- Notify protocol team and sites of last enrollment – protocol data manager (PDM)
- Notify the DAIDS Regulatory Support Center Clinical Study Information Office (RSC CSIO) of study status change to closed to accrual – CTS

12.3 Data Collection

The DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual specifies the essential documents that study sites must maintain for DAIDS-sponsored studies.

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. Additional information is available in the DAIDS SCORE Manual, which is available at <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations>.

12.3.1 Participant Research Records

The United States Code of Federal Regulations and International Council for Harmonisation (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.

12.3.1.1 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, all protocol deviations involving participants should be documented in participants’ study records, along with reasons for the deviation and attempts to prevent or correct the deviations, if applicable. More information regarding DAIDS requirements can be found in the SCORE Manual. See Section 12.3 regarding IMPAACT requirements for reporting protocol deviations.

12.3.1.2 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 SCORE Manual and the DAIDS policy on [Electronic Information Systems](#). In cases where DAIDS guidance 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 data collection instruments 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

12.3.1.3 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.

12.3.1.4 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 each of 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.

12.3.2 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 using eData, the formats include:

- 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 using Medidata Rave, the formats include:

- Electronic CRF (eCRF) completion guide: PDF versions of the eCRFs with instructions for preparation of collection of the study data and with data collection forms schedules 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
- Annotated print matrix: PDF versions of forms as they appear in the CTDMS, with annotated fields that may be used for data retrieval, which may be downloaded by site personnel from the DMC portal
- eCRFs for Participant Interviews or Questionnaires: PDF versions of these CRFs are furnished to sites through the Forms Management Utility on the DMC portal and sites are 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 were implemented using eData may continue to use eData, while other studies were converted to Medidata Rave. All new studies utilize Medidata Rave. Refer to the protocol and associated documents for the CTDMS to be used. In addition, the LPC and MOP should be used in scheduling participant visits and specimen collection.

12.3.2.1 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 remote data entry 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 made available 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.

12.3.2.2 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 overdue forms. 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.

Site staff should use completion guides developed and made available 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.

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

Sites use the SES 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 and within Medidata Rave 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 Computing Manual, accessible by the FSTRF website: <https://www.frontierscience.org/>. Information regarding DMC training programs is also available at this website.

12.4 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 those listed in Table 12-1. Unless otherwise specified in a study protocol, quorum and sign-off requirements included in Table 12-1 should be considered minimum standards; protocol teams may specify additional requirements, beyond those specified in the table, if applicable. Further guidance on expectations and procedures for meeting quorum requirements is provided below the table.

Table 12-1. Study Team Communications

Communication Type	Description
<p>Conference calls and meetings</p>	<p>Protocol teams (including site representatives), and designated subgroups (e.g., Clinical Management Committee), take part in routine meetings and conference calls throughout the period of study implementation. Summaries of these meetings and conference calls are typically prepared and distributed by the protocol CTS. Refer to Table 12-2 and Figure 12-1 for requirements related to quorum and for alternative procedures to be followed for study-specific groups that function — in whole or in part — independent of the protocol team (e.g., safety or endpoint review groups).</p> <p>Meeting and conference call summaries will list all participants, designate participants who are members of designated subgroups, and state whether relevant quorum requirements were met.</p> <p>When protocol-specified or other important study implementation decisions require review and/or recommendations from a Study Monitoring Committee or Data and Safety Monitoring Board, these will be documented per the procedures described in Section 13 of this manual.</p>
<p>All-site email messages and memoranda</p>	<p>Protocol teams typically provide key study-related updates to site representatives via email. For example, updates on participant accrual and achievement of study milestones (e.g., completion of accrual, closure of follow-up) are often provided by email.</p> <p>When protocol-specified or other important study implementation decisions require communication to sites (e.g., study drug dose-finding or cohort progression decisions), these are communicated in a memorandum that is reviewed by the protocol team or designated subgroup and then distributed to all sites via email. Prior to distribution of any such memorandum, sign-off must be obtained from one protocol chair (chair, co-chair, or vice chair), one protocol statistician, one protocol data manager, and the DAIDS medical officer; when a memorandum involves PK issues, sign-off must also be obtained from a protocol pharmacologist. The process of preparing, obtaining review and sign-off, and distributing this type of memorandum is coordinated by the protocol CTS.</p>

Table 12-1. Study Team Communications

Communication Type	Description
Communications to Network leadership and oversight groups	Protocol teams may need to provide study-related communications to IMPAACT leadership and/or oversight groups. For example, teams may need to provide study-related updates or request consultation on study design or study implementation issues. When this type of communication is needed, relevant team members will prepare a memorandum or other applicable document for review by the protocol team or designated subgroup. Prior to distribution to the Network leadership or oversight group, sign-off must be obtained from one protocol chair (chair, co-chair, or vice chair), one protocol statistician, one protocol data manager, and the DAIDS medical officer; when the document involves PK issues, sign-off must also be obtained from a protocol pharmacologist. The process of preparing, obtaining review and sign-off, and distributing this type of memorandum is coordinated by the protocol CTS.
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 are also posted on the IMPAACT website.
Study reports	Data reports on study progress, protocol adherence, data quality, etc., are developed and issued by the SDMC in accordance with the study progress, data, and safety monitoring plan (SPDSMP, see 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 12.5, reportable protocol deviations are submitted to the protocol deviation email list (IMPAACT.deviation@fstrf.org).
Site-specific conference calls and refresher training sessions	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.

The quorum requirements specified in Table 12-2 should routinely be met through active real-time participation in meetings and conference calls. Quorum members should proactively identify any meetings or conference calls for which they are not available and provide written review comments or other required input in advance of the meeting or call; receipt of such input in advance will be considered sufficient to meet quorum requirements.

Table 12-2. Quorum Requirements

Quorum Type	Required Members to Meet Quorum
When protocol-specified or other important study implementation decisions are made via conference call, the following team members, who comprise the quorum for decision-making, must take part in the call:	<ul style="list-style-type: none"> • One protocol chair (chair, co-chair, or vice chair) • One protocol statistician • One protocol data manager • One CTS • DAIDS medical officer or designee* • When decisions involve pharmacokinetic (PK) issues, the quorum also includes one protocol pharmacologist.
When reviews of study data for purposes of monitoring participant safety are conducted via conference call, the following team or subgroup members, who comprise the quorum for this type of review, must take part in the call:	<ul style="list-style-type: none"> • One protocol chair (chair, co-chair, or vice chair) • One protocol statistician • One protocol data manager • One CTS • DAIDS medical officer or designee* • When reviews involve PK data and/or considerations for individual study drug dosing, the quorum also includes one protocol pharmacologist.
When reviews of study data for purposes of monitoring study progress and/or the quality of study conduct are conducted via conference call, the following team or subgroup members who comprise the quorum for this type of review, must take part in the call:	<ul style="list-style-type: none"> • One protocol chair (chair, co-chair, or vice chair) • One protocol statistician • One protocol data manager • One CTS • DAIDS medical officer or designee*
<p>*The assigned DAIDS medical officer should ideally take part in all reviews and decisions. If the assigned DAIDS medical officer is not available, the assigned NICHD medical officer or an alternate DAIDS representative designated by the assigned DAIDS medical officer may take part in the place of the assigned DAIDS medical officer.</p>	

When quorum requirements are not met, the decision to be made or the review to be performed should be deferred to a later date while still meeting protocol requirements for timeliness and frequency of review; in particular, safety data reviews should occur within protocol-specified timelines. When it is not possible to re-schedule in a timely manner, the following procedures may be followed to complete the required decision-making or perform the required review:

- All available team members will take part in the scheduled call or meeting; the CTS will prepare a summary of the call or meeting, listing all participants and stating that quorum requirements were not met.
- A protocol chair will provide a summary of the relevant discussion to the absent quorum member via email (copied to the CTS) and request that the absent member reply via email to confirm his or her review and indicate whether he or she concurs with the discussion that took place in his or her absence (copied to the CTS).
- If the absent quorum member does not concur, the protocol chair will determine next steps (e.g., further email communication, convening an ad hoc conference call, deferral to the next scheduled conference call).
- Once consensus is achieved, the CTS will document the discussion and inform all relevant team members of the outcome.

Use of the above-listed procedures is expected to be infrequent within a given protocol team or sub-group. Should any team or sub-group identify that quorum requirements are frequently not being met,

action should be taken by the team to address this; when resolution cannot be achieved within the team, action may be taken by the IMPAACT MOG.

The above-listed procedures generally apply to decisions made or reviews performed via meeting or conference call. In some cases, decisions may be made and reviews may be performed via email. In such cases, all protocol team or subgroup members should ideally provide input via email and an email response must be obtained from the applicable quorum members (as listed in Table 12-2). A protocol chair will coordinate with the CTS to confirm the outcome of the decision or the review and, if consensus is not reached, to determine next steps. Once consensus is achieved, the CTS will inform all relevant team members of the outcome.

Figure 12-1. Alternative procedures to be followed for study-specific groups that function independent of protocol teams

For some IMPAACT studies, groups designated to fulfill key responsibilities may function — in whole or in part — independently of the protocol team (e.g., safety or endpoint review groups). In some cases, protocol team members (e.g., protocol chair, medical officer) are members of the group. In most cases, protocol data managers and/or statisticians work directly with the group (e.g., by providing data reports to be reviewed by the group and documenting review outcomes). For any such group, the requirements of this MOP section are generally expected to apply, and the following should be described in the SPDSMP:

- Quorum requirements for the group’s key functions must be defined. Group members may or may not choose to designate a chair of the group, but regardless of this designation, a quorum must be defined.
- An individual must be designated to fulfill the documentation requirements specified in this section. This individual may be a protocol chair, chair of the group, protocol data manager, protocol statistician, or other designee.

See Section 4 for additional details related to study-specific groups.

12.4.1 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.

12.4.2 Clinical Management Committee (CMC)

Note: This section describes CMC responsibilities in support of participant management. CMCs may also be involved in study data reviews and decision-making; refer to Table 12-1 for more information on those topics. Typically, the CMC consists of the protocol chair(s), Medical Officers, statisticians, data managers, and CTSs. Other study investigators/clinicians may be added to the CMC, dependent on the protocol design and safety considerations and membership should be defined in each IMPAACT protocol.

Each IMPAACT protocol will specify if a CMC or analogous group composed of appropriate protocol team members is designated to provide support to site investigators and clinicians regarding clinical

management of participants and any adverse events, management of study drug regimens, and other clinical considerations. The CMC may also respond to site requests for guidance related to eligibility and co-enrollment in IMPAACT and other studies. Separate from information that may be provided to the CMC as part of notifications or queries from sites, distribution of study data to the CMC (or not) is directed by protocol specifications and the study monitoring plan. For comparative studies, treatment assignment information should not be provided to the CMC unless necessary for participant safety.

Site personnel should submit queries directly to the CMC based on the template included in the study-specific MOP (if available), or other standardized guidance, to ensure complete background information is provided. This should at a minimum include site number/contact, study number, PID, duration of time on study, and case description. The study number and PID should be included in the subject line of the email for ease of tracking. Attachments should only be included if necessary, and site personnel should include relevant clinical information from the attachment(s) in the case description to provide a detailed summary.

In general, designated members of the CMC, as decided by the protocol chair(s), will respond to queries received from sites as soon as possible and generally within 24 hours of receipt. When a complete response cannot be provided within 24 hours, a reply will be emailed to the site confirming receipt and indicating that a full response is in process.

When fielding site queries, designated CMC members are encouraged but not required to seek input from other CMC members before responding to the site to confirm the accuracy and completeness of a proposed response. However, internal CMC consultation should be done routinely in the first few months of study implementation to establish consensus among CMC members. When the CMC discusses a site query within the committee, the site personnel must be removed from the email messages. This will minimize confusion and/or misunderstanding at the site.

The designated CMC member should respond to the site, copying the CMC email group (generally, IMPAACT.####CMC@fstrf.org), and all site personnel included on the original query. The protocol team and site representative email groups (generally, IMPAACT.TEAM####@fstrf.org; IMPAACT.PROT####@fstrf.org) should not be copied (even if copied by the site in error). Responses should indicate when follow-up action and/or additional information is needed from the site and when a query or consultation is considered resolved or completed. Follow-up communications from the site and the CMC should be sent as replies to the original email message and “final response” should be included in the body of the CMC’s final email response to the site. The site will be instructed to file a copy of the final response (email exchange) in the participant’s study chart. For some studies, the CMC response may be archived with the DMC and available upon request.

Designated CMC members are permitted to respond to queries from the site with which they are affiliated, unless otherwise specified by the protocol or other operational guidance, such as the study-specific MOP. This should be done following the same process described above, with the CMC email group copied.

If an incomplete or incorrect response is inadvertently sent to a site, a correction or additional relevant guidance should be sent to the site as soon as possible. Sites should file any additional correspondence from the CMC in the participant’s chart along with the original response.

The study-specific CTSs who are members of the CMC will support the query response process by prompting for responses within 24 hours and by providing references to protocol and MOP sections that are relevant to a query. Upon request, the CTSs may also send responses on behalf of the designated CMC member. However, designated CMC members should generally plan to send all responses over

weekend and holiday periods. When responding to queries, the CMC is encouraged to review relevant prior correspondence, for example, to provide background information from a prior query for the same participant or provide a reminder of how similar queries were handled in the past.

Query responses must provide guidance to site staff that is consistent with protocol specifications. Responses cannot authorize or approve protocol deviations. In the event that a protocol deviation is identified in CMC communications with a site, the deviation should be acknowledged, and the site should be reminded to fully document the deviation, the reason why it occurred, and corrective and preventive actions taken, in accordance with DAIDS policies and good clinical practice guidelines. The CTSs can provide template wording when this type of response is necessary. The CTSs can also follow-up with sites as needed when deviations meeting IMPAACT criteria for network-level reporting occur (see Section 12.5).

12.4.3 DMC Queries and QC Reports

The protocol data manager and designated DMC staff (e.g., medical coders) review CRF data submitted to the clinical 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 in a timely manner.

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 task dashboards 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.

12.4.4 Data Management Quality Summary Reports

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

For studies using Medidata Rave, the reports include:

- Data completeness
- Timeliness of submitted data
- Query responsiveness
- Error responsiveness
- Regulatory (SAE timeliness)

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.

12.5 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.

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 (GCP); 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 IRBs, ECs, drug regulatory authorities, and all other applicable regulatory entities.

12.5.1 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 46.108(a)(3)(iii) and (4)(i):** 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 others, 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 Council for 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/>.

12.5.2 Definitions Applicable to IMPAACT Research

Table 12-3. Definitions

Term	Definition
<p>Protocol deviations</p>	<p>Any departure from an IRB-approved protocol. This includes but is not limited to the following:</p> <ul style="list-style-type: none"> • Administrative inconsistencies or minor errors in the implementation of the protocol (e.g., visit outside the window, lab assessed off schedule, violation of inclusion/exclusion criteria) • Departure from specified treatment, examination, or data collection procedures in a study protocol <p>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.</p>
<p><u>Reportable</u> protocol deviation</p>	<p>Deviations that require additional reporting by the IoR or designee as described in Section 12.5.3 below. Defined by IMPAACT as deviations that result in:</p> <ul style="list-style-type: none"> • 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 <p>Examples of reportable protocol deviations include:</p> <ul style="list-style-type: none"> • 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 <p>The list of examples shown above is intended as a guide and is not all-inclusive.</p> <p><i>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 12.5.3 below.</i></p>

Table 12-3. Definitions

Term	Definition
<p>Corrective action</p>	<p>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.</p> <p>In all cases, corrective action must include documentation of the deviation. 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.</p> <p>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.</p>
<p>Preventive action</p>	<p>Action taken to prevent recurrence of a deviation. Preventive actions are commonly specified in consultation with the relevant protocol team and/or IMPAACT leadership.</p> <p>In all cases, preventive action must include documentation of the deviation. 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.</p> <p>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.</p>

NIAID and NICHD Clinical Site Monitors may identify protocol deviations in their monitoring reports and some of these may meet the definition of a 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 12.5.3 below. Likewise, other network partners such as representatives of the Operations Center, DMC, or LC 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 12.5.3 describes procedures for reportable protocol deviations.

12.5.3 Procedures for Reportable Protocol Deviations

All reportable protocol deviations must be reported by site investigators within ten working days of site awareness (unless a shorter timeframe is otherwise specified in the protocol). If needed, consultation with the Operations Center, SDMC, LC, or respective protocol team is available. Of note, based on protocol-specific directions, protocol deviations are often communicated to protocol teams ahead of submission of the protocol deviation CRF (for example, through consultation with the study-specific Clinical Management Committee).

Reporting procedures require that protocol deviations be entered either via CRF or into the Protocol Deviation Reporting System (PDRS) on the Frontier Science portal — so that the deviation is recorded in the study database — and that a copy of the deviation report be distributed to members of IMPAACT leadership and the respective protocol team, as listed below.

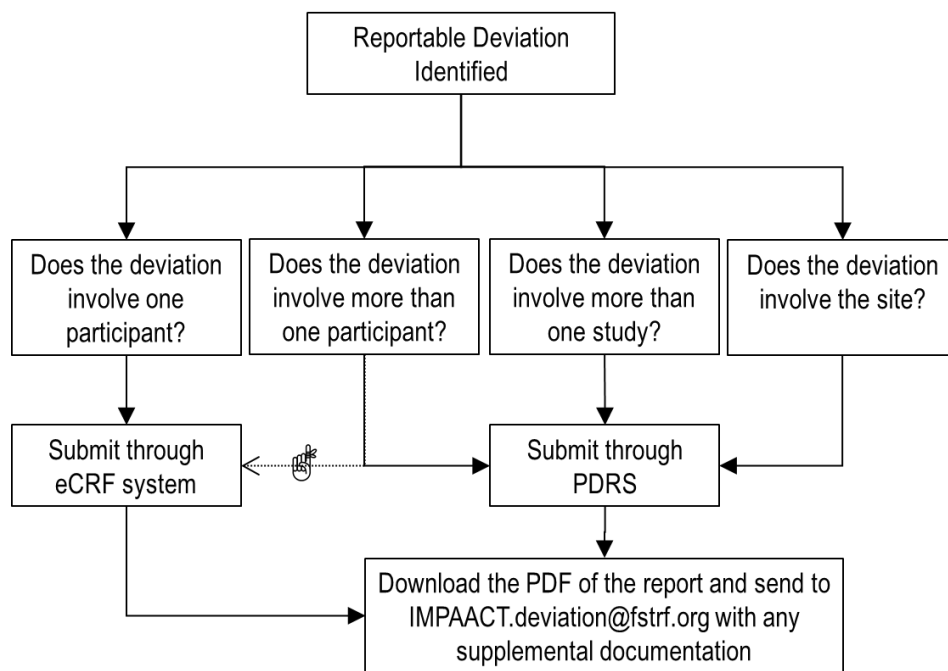
Protocol deviations that involve only one participant should generally be reported using the study protocol deviation CRF. Sites may also choose to report deviations involving more than one participant using the study protocol deviation CRF; however, in that case, one protocol deviation CRF should be completed for each impacted participant.


Protocol deviations that occurred at the study or site level (i.e., those that do not involve specific participants) should be reported using the PDRS. Sites may also choose to report deviations involving more than one participant using the PDRS; in that case, one submission documenting all impacted participants may be entered (i.e., individual submissions by participant need not be entered).

Sites should complete and enter the CRF or form on the PDRS per usual data management procedures, save a PDF version of the CRF or form, and email the PDF with any additional supplemental documents (e.g., IRB correspondence) to IMPAACT.Deviation@fstrf.org. If the deviation occurred over a period of time, the range of dates over which the deviation occurred should be indicated in the submission.

See Figure 12-2 for a visual representation of the reportable deviation process.

Figure 12-2. Reportable Protocol Deviation Process



 Sites may submit individual CRFs for one deviation involving multiple participants. However, sites should only submit deviations through one of the mechanisms (not both).

The Operations Center will review the emailed report(s) for completeness (e.g., all fields are completed, all pages are provided), comprehensiveness (e.g., the deviation and associated preventive and corrective actions are clearly described), and legibility (e.g., all fields are readable, pages and text are not cut off). In addition, if the reported deviation is unclear or incomplete, the Operations Center representative may consult with the protocol-specific CTS to work on next steps. Once any issues involving completeness, legibility, and comprehensiveness are resolved, the emailed report (completed deviation report and any supplementary materials) is sent to the following distribution list typically within five working days by the Operations Center:

- Protocol chair(s)
- Protocol medical officer(s)
- Protocol CTS(s)
- IMPAACT leadership (Network chair and vice chairs, 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)
- DAIDS Team Leader for the Office for Policy in Clinical Research Operations (OPCRO)
- 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; if requested, the updated PDF version of the revised CRF should be emailed to IMPAACT.Deviation@fstf.org.