# 13 STUDY OVERSIGHT

Oversight of IMPAACT studies occurs at many levels, consistent with US and international regulations, policies, and guidelines applicable to human subjects research funded by the National Institutes of Health (NIH):

- At each clinical research site (CRS), the Investigator of Record (IoR) and delegated study staff are responsible for continuous monitoring of participant safety. The IoR and delegated staff are also responsible for continuous monitoring of the quality of study conduct and study data.
- The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development (NICHD) contract with clinical site monitors to conduct site monitoring activities and have established procedures to ensure that monitoring findings are addressed as needed at each site.
- For each study, the protocol chair, DAIDS Medical Officer (MO), NICHD Medical Officer, and other team members routinely monitor study progress and the quality of study conduct; any emerging issues identified through this monitoring are addressed with study sites and elevated to IMPAACT Network leadership, as needed.
- The IMPAACT Network leadership has established oversight procedures that are continuously carried out for all studies by the Management Oversight Group (MOG).
- An independent IMPAACT Study Monitoring Committee (SMC) or NIAID Data and Safety Monitoring Board (DSMB) also provides oversight of IMPAACT studies when applicable.

Each of these levels of oversight is further described in this section.

## 13.1 On-Site Clinical Quality Management

Per the Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual, all sites conducting or participating in DAIDS-supported and/or DAIDS-sponsored clinical research must develop and implement a clinical quality management plan (CQMP). The CQMP must describe the

quality assurance (QA) and quality control (QC) activities that will be performed at the site for each study and describe the types of tools and checklists that will be used in the QA and QC processes. The CQMP must also state the frequency with which QA and QC activities will be performed. Further details can be found in the DAIDS SCORE Manual at https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

## 13.2 Clinical Site Monitoring

As the sponsor of IMPAACT studies, the NIH has a regulatory responsibility for oversight of IMPAACT studies per the US Code of Federal Regulations (CFR; Title 45, Parts 46, 160, and 164; Title 21, Parts 11, 50, 54, 56, and 312) and per the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). As part of fulfilling these responsibilities, NIAID and NICHD contract with clinical site monitors to conduct site monitoring activities. Contracted monitors inspect study site facilities and review participant study records – including informed consent forms, paper-based case report forms (CRFs, if used), electronic case report forms (eCRFs), laboratory records, and pharmacy records – to ensure protection of study participants, compliance with IRB/EC approved protocols, and accuracy and completeness of study records. Site investigators will make study facilities and documents available for inspection by monitors.

Remote monitoring may be performed to supplement or reduce the frequency and extent of on-site monitoring. Site investigators must make study documents available for remote monitoring utilizing a secure platform that is 21 CFR Part 11 compliant and HIPAA compliant (for sites in the US). The DMC has configured Medidata Remote Source Review (RSR) to be available to all sites. If Medidata RSR is not utilized, other secure platforms that are 21 CFR Part 11 compliant and HIPAA compliant (for sites in the US) may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.

All sites are monitored at least once annually. The extent and frequency of monitoring will depend on the size, risk, and complexity of studies conducted at the site and may change over time depending on study status and performance of the site. Monitoring reports are prepared following each visit and provided to the sponsor (NIAID or NICHD) and the site. Sites are required to respond to monitoring findings in a timely manner and in accordance with sponsor-specific (NIAID or NICHD) procedures.

## 13.3 Protocol Team Monitoring

IMPAACT protocol teams are responsible for actively monitoring both participant safety and the quality of study conduct, and for working with sites to address any issues or concerns that may arise. Quality indicators monitored by protocol teams typically include participant accrual and retention, compliance with the study protocol, adherence to the study intervention, endpoint evaluability, data and specimen availability, and data quality and completeness.

Monitoring by the protocol team is typically accomplished through review of study-specific reports generated by the Statistical and Data Management Center (SDMC) per the Study Progress, Data, and Safety Monitoring Plan (SPDSMP); additional monitoring plans may also be developed as needed for individual studies (e.g., pharmacology data management plans or qualitative monitoring plans). The protocol chair and protocol team members from the Operations Center, Data Management Center (DMC), and Laboratory Center (LC) may visit sites or hold virtual meetings to assess study implementation and/or provide training and other technical assistance to site staff.

Designated protocol team members are responsible for monitoring participant safety. Specific roles and responsibilities are specified in the SPDSMP. These roles and responsibilities may differ based on the phase of the study and whether the study involves comparative groups. Team members are generally

expected to review safety data at least monthly; more frequent reviews may occur if specified by the study protocol or at the discretion of the team. For some studies, again depending on protocol specifications, team members are also responsible for identifying when criteria for pausing a study or convening a safety review have been met. If at any time a safety issue or concern is identified, designated protocol team members are responsible for taking appropriate action to address the issue or concern. Such actions may include requesting additional review of study data by the SMC or DSMB, modifying the dosing of study agents, or modifying other protocol specifications. The protocol team is also responsible for informing study sites in the event that any changes in study conduct are required.

The data upon which protocol team and other study oversight reviews are based are generated at the site level, based on evaluations performed by site clinicians and other study site staff. Site staff are responsible for monitoring the safety of each study participant and entering clinical and laboratory data into eCRFs in a timely manner, so that current data are available for review by the protocol team and other oversight bodies. Site staff are also responsible for alerting designated protocol team members to any safety-related issues or concerns that may arise; all protocol specifications for notification or consultation with the team must be followed.

SDMC staff also play a key role in monitoring participant safety, through their roles in reviewing and coding safety data, querying sites as needed to ensure that accurate and complete data are available for review, generating safety data reports for review, generating interim analysis reports for SMC or DSMB review, and identifying when study pause or stopping rules have been met.

Designated protocol team members typically review study monitoring reports during conference calls, although reviews may also take place during in-person meetings or by email; refer to Section 12 for detailed information on quorum requirements for these reviews. When team member assessments are required for the study database, these are recorded by the protocol data manager following standard DMC procedures. Otherwise, reviews are documented in the form of conference call or meeting summaries. Documentation of these reviews is not typically provided to study sites. However, sites are notified of any issues that may necessitate a change in study conduct; such notifications also provide instructions to sites regarding notification of Institutional Review Boards/Ethics Committees (IRBs/ECs) and other applicable review bodies. Similar notifications may also be provided following safety reviews in studies with multiple sequential cohorts of participants. Should a study site require a safety-related summary in order to meet IRB/EC requirements for continuing review, this may be requested from the protocol team, with the request emailed to the clinical research manager (CRM). During the ongoing conduct of a study, available information will be limited.

## 13.4 IMPAACT Leadership Oversight

The IMPAACT MOG monitors network studies with regard to protocol development, study implementation, analysis, and reporting.

Routine MOG oversight includes evaluation of study progress with respect to key milestones; the MOG also monitors resource allocation and use across studies. In support of the MOG's oversight function, a Study Operations Report is generated each month by the Operations Center with updates on the status of each study and any study implementation issues and problems; similar information is included in the report for protocols in development. Other data reports are generated for the MOG by the SDMC as needed. Members of the MOG who represent the SDMC, LC, and Operations Center may also bring issues to the attention of the MOG. The MOG reviews proposals from protocol teams to modify protocols and/or study implementations plans (e.g., to expand to additional sites) as needed (see Sections 9 and 10). MOG discussion and decision-making is documented in conference call and meeting summaries, and decisions and recommendations are formally communicated to protocol teams when applicable. Also,

when applicable, the MOG coordinates with NIH to assess and respond to needs for additional resources, for example, because of unexpected costs associated with planned study procedures or to support additional sites or ancillary studies.

The MOG is supported in its oversight role by independent SMC reviews of selected studies, as described in Section 13.5.

## 13.5 IMPAACT Study Monitoring Committee Review

In support of the management and oversight functions of the MOG, for designated studies, an IMPAACT SMC monitors participant safety and the progress and quality of IMPAACT study conduct. Based on its reviews, the SMC makes recommendations related to study continuation, including cohort progression and dose selection, when applicable. The scope of SMC reviews varies across studies, depending on protocol specifications. The policies and procedures included in this section are followed for all IMPAACT studies subject to SMC oversight, in lieu of study-specific SMC charters; these procedures may be supplemented or amended if needed for individual studies, consistent with protocol specifications.

### 13.5.1 SMC Membership

For each study that is subject to SMC oversight, SMC membership includes:

- SMC chair
- IMPAACT Network chair or vice chair
- IMPAACT Scientific Committee (SC) representative
- IMPAACT Operations Center representative
- IMPAACT Statistical and Data Analysis Center (SDAC) representative
- IMPAACT Laboratory Center (LC) representative
- DAIDS representative
- NICHD representative

In addition to the above, other relevant content area reviewers (e.g., pharmacology reviewer) may be added as needed. When applicable, SMC members may fill multiple roles; for example, when the SMC chair is a member of the relevant SC, they may serve as both the SMC chair and SC representative. While SMC membership may vary across studies, every effort is made to maintain consistent composition for each study over time.

The SMC chair and an alternate chair are appointed by the MOG; other SMC members are designated by the organization they represent. The appointed chair serves in this role unless they are conflicted due to study involvement (see below) or other potential conflicts of interest (see Section 7). When the appointed chair has a conflict, the appointed alternate serves as chair. Given conflict of interest and quorum requirements (described below), the Operations Center, LC, and SDAC may designate two representatives to the SMC; if this is done, the two members provide consensus input to SMC recommendations. For regulatory purposes, all SMC members must provide updates of their resumes to the Operations Center approximately every three years.

SMC members are independent of each study under review. They may not be members of the protocol team or directly involved in the conduct of the study at a study site. If affiliated with a study site, SMC members should have no expected involvement in study or participant management at the site. In addition, all SMC members must comply with the financial disclosure requirements and responsibilities described in Section 7.

The following SMC members comprise the quorum for SMC decision-making: SMC chair (or alternate chair), DAIDS representative, and one representative each from the Operations Center and SDAC. These members must take part in each review. For reviews that take place via conference call, these members must attend the call or provide written review comments in advance if they cannot attend the call. In the latter scenario, an alternate representative of the IMPAACT Operations Center, SDAC, and DAIDS may be designated to attend the call (written review comments must still be provided in advance by the SMC member). Alternatively, the NICHD representative may serve in place of the DAIDS representative. In the event the SMC chair cannot attend the call, another SMC member may be designated to serve as chair during the call; the SMC chair must provide written review comments in advance. If quorum requirements are not met, the review will be postponed.

### 13.5.2 SMC Review Process

SMC reviews typically take place via conference call; in-person or email reviews may also occur. Convened conference call reviews typically include open and closed review sessions and may include executive sessions as described in Sections 13.5.2.1–13.5.2.3. The Operations Center schedules and coordinates all reviews. In the event that an SMC member is not available to take part in a review, they may provide written review comments in advance of the review (see Section 13.5.1 for quorum requirements).

Protocol team members, including the protocol chair(s), protocol pharmacologist(s) (as applicable), NIH medical and program officers, and CRMs generally attend open review sessions. Protocol statisticians attend both open and closed sessions. Other team members who are designated in the SPDSMP to receive SMC data reports may attend open sessions at the discretion of the protocol chair.

The scheduling of SMC reviews is coordinated by the Operations Center. SMC review requirements are noted in the Study Operations Reports generated each month and these notations may serve as a guide for when reviews are required. Protocol teams are responsible for awareness of when reviews are expected to take place and proactively planning for all scheduled reviews. Protocol statisticians should lead planning efforts within the team, including but not limited to establishing timelines for drafting and finalizing data reports and other materials for review, and should coordinate with the Operations Center to identify potential review dates and timelines for distributing materials to the SMC. Materials prepared for SMC review must adhere to good documentation practices and are distributed using secure methods when individual participant data or analysis results are included.

A summary of roles, responsibilities, and timelines associated with SMC reviews is provided in Table 13-1, with additional description below. For each study, roles, responsibilities, and the scope of SMC oversight are directed by the protocol and the SPDSMP. The SMC typically monitors the quality of study conduct, participant safety, and other key issues through review of indicators such as participant accrual, participant retention, compliance with/deviations from the study protocol, adherence to the study intervention, data quality, data completeness, specimen availability, endpoint evaluability, and adverse events as indicated in the SPDSMP; pharmacokinetics (PK) findings and other study outcome measures may also be reviewed if specified in the protocol and/or SPDSMP. Reviews may evaluate the safety, efficacy, and/or feasibility of the study as designed and determine whether modification may be required to minimize risks to study participants or meet study objectives.

**Table 13-1. Summary of SMC Roles and Responsibilities**

| Person Responsible | Role/Responsibility | Timeline |
|---|---|---|
| **SMC chair** | • Review data reports and other submitted materials | • Prior to each review |
| | • Request clarification of materials submitted for review via email (copying other SMC members) | • Prior to each review (as needed) |
| | • Lead all review sessions, ensuring input and discussion as needed from all SMC members | • During each review |
| | • Ensure that findings, recommendations, action items, and next steps are agreed upon prior to the close of each review | • During each review |
| | • Coordinate with Operations Center representative to draft summary review reports for review by SMC members and then finalize these reports | • Ideally within 3-5 working days after each review |
| | • Coordinate with Operations Center representative to receive and review protocol team responses to review reports | • Following each review (as applicable) |
| | • Coordinate with Operations Center representative to finalize a memorandum documenting the review for study sites | • Ideally within 7 working days after the final outcome of each review |
| | • Liaise with the IMPAACT MOG regarding SMC operations, review findings, and recommendations | • As needed |
| **SMC members** | • Review data reports and other submitted materials | • Prior to each review |
| | • Request clarification of materials submitted for review via email (copying other SMC members) | • Prior to each review (as needed) |
| | • Provide review comments and recommendations | • During each review |
| | • Optionally review and provide feedback on draft summary review reports | • Typically within 2 working days after receipt of draft review report |
| **Operations Center representative to the SMC (in addition to other SMC member roles and responsibilities)** | • Coordinate with protocol statistician and CRM to schedule SMC reviews | • Ongoing based on study-specific needs |
| | • Coordinate review conference calls; distribute administrative information in support of each review | • Approximately 2-4 weeks prior to each review |
| | • Coordinate with SMC chair to draft summary review reports for review by SMC members and then finalize these reports | • Following each review |
| | • Distribute final summary review reports to protocol teams | • Ideally within 3-5 working days after each review |
| | • Coordinate with SMC chair to receive and review protocol team responses to summary review reports | • Following each review (as applicable) |
| | • Coordinate with SMC chair to prepare a memorandum documenting the review for study sites and coordinate with the CRM to distribute the memorandum to participating sites | • Ideally within 7 working days after the final outcome of each review |
| | • Coordinate with the CRM to include relevant information in Study Operations Reports | • Monthly when applicable |

**Table 13-1. Summary of SMC Roles and Responsibilities**

| Person Responsible | Role/Responsibility | Timeline |
|---|---|---|
| **Protocol statistician** | • Coordinate with the Operations Center and the protocol pharmacologist when applicable to schedule SMC reviews<br>• Prepare and distribute draft open data reports for selected protocol team member review<br>• Finalize and distribute data reports and other materials for SMC review***<br>• Take part in open and closed review sessions; provide an overview of the data report during review sessions; respond to SMC questions | • Ongoing based on study-specific review needs<br>• At least 9 working days prior to each review*<br>• At least 4 working days prior to each review**<br>• During each review (open and closed sessions) |
| **Protocol Data Manager** | • Notify sites of upcoming SMC review and timelines for data keying and query responses, noting critical data for review<br>• Review targeted data for SMC and issue queries, as needed<br>• Generate reports and/or datasets for protocol statistician per the SPDSMP | • Prior to each review<br>• Prior to each review<br>• Prior to each review* |
| **Laboratory Data Manager** | • Review targeted data for SMC and issue queries, as needed<br>• Generate reports and/or datasets for protocol statistician per the SPDSMP | • Prior to each review<br>• Prior to each review* |
| **Protocol chair** | • Review draft data reports and other materials to be submitted for SMC review<br>• Take part in open review sessions; during these sessions, provide a brief synopsis of study status, key issues and problems (if any), and strategies undertaken or planned to address these; identify issues that the protocol team would like to bring to the SMC's attention for consultation and feedback; respond to SMC questions | • 7-9 working days prior to each review<br>• During open review sessions |
| **Protocol pharmacologist (as needed for SMC reviews of pharmacology data)** | • Coordinate with the protocol statistician and Operations Center to schedule SMC reviews<br>• Prepare and distribute draft data reports for protocol team member review<br>• Coordinate with protocol statisticians to finalize and distribute data reports and other materials for SMC review***<br>• Take part in open review sessions; provide an overview of the pharmacology data report during review sessions; respond to SMC questions | • Ongoing based on study-specific review needs<br>• At least 9 working days prior to each review*<br>• At least 4 working days prior to each review**<br>• During open review sessions |
| **Medical Officers** | • Review draft data reports prepared by the protocol statistician and other materials to be submitted for review when applicable<br>• Take part in open review sessions; respond to SMC questions when applicable | • 7-9 days working days prior to each review<br>• During open review sessions |

**Table 13-1. Summary of SMC Roles and Responsibilities**

| Person Responsible | Role/Responsibility | Timeline |
|---|---|---|
| **Other protocol team members, as applicable based upon the content of the review** | • Review draft data reports prepared by the protocol statistician and other materials to be submitted for review when applicable<br>• Take part in open review sessions; respond to SMC questions when applicable | • 7-9 days working days prior to each review<br>• During open review sessions |

*Sufficient time should be allowed for applicable team members to review data reports and other materials to enable distribution of final materials to the SMC at least three working days prior to each review. If timeline is unlikely to be met, SDAC will inform the protocol team.
**For example, for SMC reviews scheduled on a Friday, materials should be distributed to the SMC on the preceding Monday.
***All materials submitted for SMC review must comply with good documentation practices.

#### 13.5.2.1 Open Review Sessions

SMC reviews typically include an open session to provide an opportunity for the protocol chair and other protocol team members, if applicable, to discuss the study with the SMC. For such sessions, the SMC and designated protocol team members are provided with an open report containing relevant monitoring data as defined in the SPDSMP. For reviews that include separate data reports for open and closed sessions, the data contained in open and closed reports are based on the same dataset, but open reports present data pooled across study arms.

During open review sessions, protocol chairs are not expected to provide a formal presentation to the SMC but should provide a brief synopsis of study status, key issues and problems (if any) with respect to study implementation, and strategies undertaken or planned to address these. With respect to safety and PK data (when applicable), the protocol chair may summarize the team's overall assessment of currently available data. The protocol chair may also identify issues the protocol team would like to bring to the SMC's attention for targeted consultation and feedback. In addition to the protocol chair's synopsis, the protocol statistician will provide an overview of the data report that serves as the basis for the review; the protocol pharmacologist may likewise provide an overview of any PK reports provided for review. The protocol statistician is generally expected to present the report on screen, displaying the key data highlighted in their overview. Slide presentations are not expected unless requested by the SMC. These overviews and presentations are expected to be brief and typically no longer 20 minutes. SMC members may ask questions of the protocol chair, statistician, and other team members, requesting their insights into data presented in open reports and further clarifying issues, problems, and strategies to address these.

For non-comparative studies, SMC members may provide assessments of the quality of study conduct, participant safety, and other key issues during open sessions or they may choose to further discuss these assessments in closed review sessions before providing consensus findings and recommendations to the protocol team.

#### 13.5.2.2 Closed Review Sessions

SMC reviews typically include a closed session in which SMC members assess the quality of study conduct, participant safety, and other key issues and agree upon consensus findings and recommendations. For comparative studies, closed sessions may include review of closed reports with data presented by study arm. Study arms are typically coded to avoid unnecessary unblinding, but coding keys are provided in the event the SMC determines that unblinding is necessary to protect participant

safety or evaluate study integrity. If an SMC member wishes to discuss results by unblinded study arm, the SMC chair must first confirm that all members of the SMC agree to being unblinded.

Participation in closed review sessions is limited to SMC members and the protocol statisticians unless exceptions are requested by the SMC or specified in the SPDSMP. Closed data reports are considered confidential, to be distributed only to designated SMC members. However, distribution to others may be permitted on a case-by-case basis in consultation with the SMC chair and the MOG.

#### 13.5.2.3 Executive Review Sessions

SMC reviews may include an optional executive session, attended only by SMC members, to review selected data or otherwise take part in discussions that are limited to SMC members only. These sessions differ from closed sessions in that the protocol statisticians are not included.

### 13.5.3 Types of SMC Review

#### 13.5.3.1 Initial Review

Studies subject to SMC review undergo an initial SMC review in which a draft SPDSMP is reviewed, along with the draft protocol (unless already finalized and posted on the study website), and discussed in detail with the protocol chair, statistician, CRM, MOs, and other team members. CRMs, in close coordination with statisticians, will coordinate scheduling of the initial SMC review. Typically, the protocol statistician distributes the draft SPDSMP and any other documents (e.g., draft Pharmacology Data Management Plan), which are expected to describe key aspects of study monitoring or are otherwise referenced in the SPDSMP, to the SMC no later than four working days prior to the review date (for example, for SMC reviews scheduled on a Friday, materials should be distributed to the SMC on the preceding Monday). Protocol team members should not be copied on submissions to the SMC; however, they may be notified once submission is complete.

This initial review should ideally take place in the late stages of protocol development to enable the SPDSMP and other relevant documents to be finalized prior to opening the study to accrual. The purpose of this review is to orient SMC members to the study protocol, agree upon key specifications of the SPDSMP, the required frequency of SMC reviews for the study, criteria for triggered SMC reviews, if applicable, and the data to be presented in reports prepared for SMC review. The SPDSMP and any other applicable documents are finalized after the initial SMC review takes place and SMC review comments are addressed.

The protocol chair should work with the protocol statistician and other team members as needed to prepare a presentation for the initial review. The protocol chair or protocol statistician distributes the presentation to the SMC, no later than the day prior to the scheduled review. During the open review session, the protocol chair should present a brief overview of the study, focusing on the rationale, objectives, and design. The protocol chair may also highlight key issues the protocol team would like to emphasize for consideration by the SMC. This presentation should be completed in no more than ten minutes. Following this introduction, the protocol statistician may briefly highlight the statistical design of the study and present key aspects of the SPDSMP, including an overview of the types of monitoring data reports that will be provided to the study team and to the SMC. Any protocol-specified triggers for *ad hoc* SMC reviews should also be noted. This presentation should be completed in no more than 15 minutes.

Following the presentations, the SMC will discuss the SPDSMP and other materials submitted for review. A written report documenting the review discussion and delineating SMC feedback on the team's materials will be provided following the review (see Section 13.5.4). It is generally expected that the protocol team will be asked to revise the SPDSMP and other materials submitted for review based on SMC feedback; the statisticians will then submit the revised documents to the SMC for additional review. A response document is not typically required; however, in some cases, the SMC may ask for specific responses or clarifications from the protocol team. The process of preparing and submitting the response is typically coordinated by the CRM. Protocol teams should review and provide feedback on the response, though sign-off is not required. The SMC will provide a final memorandum to the protocol team, documenting any further comments, or to confirm no further comments. Unless otherwise specified, this additional review is expected to be completed via email.

#### 13.5.3.2 Reviews During Study Implementation

If memoranda are prepared by the protocol team during study implementation for routine, event-driven, or interim analysis reviews, either in response to prior reviews or in advance of an upcoming review, the CRM coordinates preparation, review, sign-off (see Section 13.5.5), and submission. Scheduling and other administrative questions and clarifications, regardless of format, do not require sign-off. Due to their urgent nature, materials shared with the SMC in advance of triggered or emergent safety reviews do not require sign-off. Data reports developed and finalized by the SDMC or protocol pharmacologists must be reviewed following the processes above (see Section 13.5.2) but do not require sign-off.

##### *Routine Reviews*

For most studies, the primary purpose of SMC reviews is to routinely assess whether the study is proceeding as expected with respect to participant safety and the timeliness and quality of study conduct. Routine reviews should occur at least annually. More frequent reviews may be conducted per protocol or as requested by the SMC or MOG.

##### *Event-Driven and Interim Analysis Reviews*

For some studies, the protocol and SPDSMP may require SMC review of interim analyses or when certain pre-specified criteria are met (e.g., when sufficient data have been accumulated to support decision-making on cohort progression or dose confirmation or comparing data across arms). The timing of these reviews may be periodic, event-driven, or upon request by the protocol team, SMC, or MOG.

##### *Triggered or Emergent Safety Reviews*

Protocols may also specify SMC review when certain safety triggers are met. Emergent safety issues not otherwise specified in a study protocol may also require SMC review. For triggered or emergent safety reviews, timelines for scheduling, preparation and distribution of data reports, and documentation of review findings and recommendations may be truncated.

### 13.5.4 Documentation and Response to SMC Reviews

As part of each review, the SMC will agree upon consensus findings, recommendations, action items, and next steps. With respect to ongoing conduct of the study, recommendations will typically be made within the following categories:

(A) Continue as currently designed
(B) Continue with recommended modifications
(C) Discontinue study implementation

Review findings, recommendations, action items, and next steps will be documented in a summary review report drafted by the Operations Center and reviewed by the SMC chair prior to distribution. Other SMC members who took part in the review will be provided an opportunity to review the draft report prior to finalization; however, review by all SMC members is not required prior to finalization. Every effort will be made to finalize and distribute the review report to protocol team members within three to five working days after the review; the final report will also be provided to all SMC members. The MOG will be informed of review outcomes and recommendations at the time of their next scheduled call or meeting unless a more immediate notification is required (e.g., when recommendations involve significant protocol modifications or discontinuation of study implementation). Memoranda documenting SMC reviews that occur during study implementation will also be provided to participating study sites by the Operations Center for submission to IRBs/ECs and other applicable review bodies within approximately one week after the final summary to the team. Summary review reports, memoranda, and other communications from the SMC will adhere to good documentation practices.

When requested by the SMC, protocol teams will respond to SMC findings and recommendations. Responses will be reviewed for adequacy and completeness by the SMC chair, with support from the Operations Center and other SMC members as needed. In the event that the SMC chair assesses that the team's response is not adequate or complete, communication with the team will continue until satisfactory resolution. Completion of this process will be documented in a memorandum to the protocol team and in the monthly Study Operations Report.

### 13.5.5 Protocol Team Review and Sign-Off

Protocol team members are expected to review materials for submission to the SMC within agreed-upon timelines. For materials other than data reports prepared by the SDMC or pharmacologist and when sign-off is required, the CRM requests sign-off from one protocol chair (chair, co-chair, or vice chair), one statistician/epidemiologist, one PDM, and one DAIDS MO; when the materials involve PK considerations, sign-off must also be obtained from one protocol pharmacologist.

## 13.6 Sponsor Oversight

As sponsor of IMPAACT studies, the NIH has regulatory responsibility for oversight and monitoring of IMPAACT studies. As part of fulfilling these responsibilities, NIAID requires IMPAACT sites to develop and implement a CQMP, and NIAID and NICHD contract with clinical site monitors to perform on-site monitoring at the IMPAACT-affiliated sites that they fund, as described in Sections 13.1 and 13.2. NIAID and NICHD staff (or their contractors) work with study sites as needed to address monitoring findings and other study implementation issues or problems. When issues or problems necessitate suspension of study implementation at a site, procedures described in Section 13.7 are followed.

NIH medical and program officers are also active in overseeing study implementation as part of protocol teams and as members of the IMPAACT leadership (see Sections 13.3 and 13.4).

For some IMPAACT studies, NIAID convenes DSMB reviews as part of its study oversight responsibilities, as described in Section 13.8.

## 13.7 IMPAACT Network Issue Escalation

### 13.7.1 Overview

Issues or problems identified by any protocol team member or Network entity (including other central resource members or site and laboratory staff) during review of study-specific reports, site visits, or other means, should be raised for discussion to the protocol team. The protocol team will determine follow-up and requested corrective actions, as needed. If any issues arise during the study that are site-specific, the relevant IoR should also be informed, and the site's issue-escalation procedures should be followed.

The Network leadership (including the chair and content-specific leadership members [e.g., LC PI or SDMC PIs]) should be notified by the protocol chair and/or relevant protocol team members, as appropriate, if any issues arise during a study that could:

- Significantly compromise study outcomes or integrity
- Require additional time or Network/sponsor resources to investigate and resolve
- Affect other Network studies, and/or
- Require specific communications with pharmaceutical collaborators

Such matters may be referred to the MOG for further review, guidance, and decision-making.

### 13.7.2 Site Suspension Process

Serious and/or persistent non-compliance with protocol, regulatory, or grant requirements may result in temporary or permanent suspension of study-specific activities, network-specific activities, or all DAIDS-sponsored research being conducted at a site. Concerns with site conduct may be identified at multiple levels, including by the sponsor, clinical site monitors, protocol teams, and IMPAACT Network central resources (i.e., Operations Center, LC, SDMC).

If any of these individuals become aware of significant concerns about a site's implementation of a study, they should ensure that the organization escalation pathways are followed; these generally should include ensuring that the protocol chair(s), MOs, site IoR, and other site leadership are aware of emerging concerns. This may include site team consultation with the study protocol team and/or Clinical Management Committee. It is also generally expected that the IoR will ensure that the CRS leaders, Clinical Trials Unit (CTU) leaders, and other relevant site staff are aware as per site escalation procedures.

The concerns should also be shared with IMPAACT leadership through communication to the MOG. The MOG, in close consultation with DAIDS and NICHD representatives on the MOG, makes a determination on whether a suspension (e.g., enrollment pause) should be recommended and whether study-specific nuances should be specified. The OCSO Network Liaison, OCSO Program Officer (PO), or Westat manager should be informed of this recommendation.

Regardless of who identifies the concern, the site suspension communications and process will be managed by the DAIDS OCSO for NIAID-funded sites and by Westat for NICHD-funded sites, unless an urgent safety concern is identified requiring immediate notification (e.g., of a pause in enrollment) by the Network.

### 13.7.3 Communication of Site Suspensions and Resolution

The OCSO PO (or Westat manager) and relevant stakeholders will review concerns and make a determination on whether a suspension should be enacted. The OCSO PO (or Westat manager) notifies the site leadership, including the CRS leader, CRS coordinator, and (if applicable) CTU leaders, as well as IMPAACT.SiteActions@fstrf.org, which includes the Network Chairs and key contacts within Operations Center, SDMC, and LC. The IMPAACT Operations Center will also notify the relevant protocol chair(s) and team members. The relevant Network central resource group representatives on the MOG will further circulate the suspension notification to relevant central resource group members, as needed.

In rare but urgent cases when it may not be possible to notify OCSO or Westat manager in advance, such as an immediate safety concern, the MOG may issue a site suspension notification to the site directly, copying the OCSO PO and OCSO Network Liaison or the Westat manager.

At the time of site notification of the suspension, Network members will complete any necessary follow-up actions (e.g., closing enrollment screens by the DMC). The site will complete corrective and preventive actions (CAPA) and forward responses to OCSO or Westat, IMPAACT leadership, and applicable central resource group members. IMPAACT leadership and central resource group members will work with OCSO/Westat to review the CAPA and determine when the suspension should be lifted. Once concerns are resolved and OCSO/Westat, in consultation with the MOG, agrees that the suspension can be lifted, the OCSO PO/Westat communicates the decision to the site.

## 13.8 Data and Safety Monitoring Board Reviews

DSMB reviews are most commonly convened for large, randomized studies; however, other types of IMPAACT studies may be subject to DSMB review. NIAID decides which studies require DSMB review and coordinates all DSMB activities; for studies that are subject to DSMB review, reviews are conducted at least annually and in accordance with relevant NIAID standard operating procedures, which can be found at https://www.niaid.nih.gov/research/data-and-safety-monitoring-boards. DSMB members are independent of the studies they review, with no financial interest in the outcomes of the studies they review. Members include experts in the fields of HIV/AIDS, biostatistics, and medical ethics. Appointments to the DSMB are made by NIAID.

### 13.8.1 Preparation for and Participation in Reviews

The SDMC prepares data reports for DSMB review; other materials (e.g., memorandums, slide presentations) may also be prepared by the protocol team. Protocol team members designated in the SPDSMP to receive DSMB data reports are provided an opportunity to review draft reports and other materials planned to be discussed with the DSMB.

Representatives of the protocol team — including protocol chairs, statisticians, CRMs, and MOs — attend DSMB reviews in person or virtually. Similar to procedures described for SMC reviews, team members designated in the SPDSMP to receive open DSMB data reports typically attend open review sessions to discuss study progress, present blinded data (pooled across randomization arms), and respond

to questions from the DSMB. Statisticians also attend closed review sessions to present data by coded randomization arm and respond to questions from the DSMB.

Prior to each review, the Operations Center coordinates with the DAIDS Maternal, Adolescent and Pediatric Research Branch (MAPRB) Chief to schedule a conference call with IMPAACT leadership soon after the review date (typically within two days) to discuss any significant DSMB recommendations. If, based on the review findings and recommendations, the call is not required, it will be canceled. If the call is required, participants include:

- IMPAACT Network chair and vice chairs
- Relevant SC chair
- Protocol chair(s)
- Operations Center Director and protocol CRM
- SDMC principal investigator (PI) and protocol statistician
- LC principal investigator
- DAIDS Prevention Science Program Director
- DAIDS MAPRB Chief
- Protocol NIH medical and program officers
- Others as required

### 13.8.2 Review Findings and Recommendations

At the close of each review, the DSMB's findings and recommendations may be provided to team members who attended the review, depending on the nature of the recommendations (see Section 13.7.3). The findings and recommendations are communicated within DAIDS/NIAID and NIAID leadership has ultimate responsibility for determining whether to accept the recommendations. Recommendations may involve continuing a study as currently designed or modifying or stopping a study, for the following types of reasons:

- The study question has been answered
- The study question will not be answered
- The study question is no longer relevant
- Unacceptable risk to participant safety
- New information from other research is now available

Within approximately two weeks after each review, a summary of the review is distributed to the protocol team and participating study sites by DAIDS and its contractors. If requested in the summary report, the protocol team will submit a written response to the DSMB (with sign-off per Section 13.5.5); otherwise, the team response will be included in the data reports for the next DSMB review. Study sites must submit the summary of the review to their IRBs/ECs and other applicable review bodies; protocol teams may provide supplemental materials to sites for submission along with the summary.

### 13.8.3 Response to Significant Recommendations

If the DSMB recommends significant modifications of a study (e.g., early termination, closure of one or more randomized groups), this information will be immediately communicated to DAIDS/NIAID leadership, and NIAID leadership will determine whether to accept the recommendations. IMPAACT leadership and protocol team members will be informed of the recommendations and the NIAID decision during the conference call (described in Section 13.7.1) scheduled to take place soon after the review. During this call, immediate next steps, action items, and timelines will be agreed upon. Subsequent

communications among the protocol team and with study sites will be coordinated by the Operations Center in close collaboration with the protocol chair(s) and NIH medical and program officers; NIAID will assume primary responsibility for any public statements or press release associated with the DSMB recommendations.

In the event that a press release is planned, DSMB review findings and recommendations should remain confidential prior to the public release. Nonetheless, site investigators will be informed of the findings and recommendations with adequate advance notice to inform their IRBs/ECs and other review bodies in a timely and appropriate manner. In addition, priority will be given to informing study participants and other community stakeholders as soon as possible. To facilitate timely and appropriate communication, protocol teams should establish tentative communications plans (roles, responsibilities, timelines) in advance of DSMB reviews. See Section 12 for additional information on protocol team communications that may be applicable in this context.