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, the Investigator of Record (IoR) and delegated study staff are responsible for continuous monitoring of participant safety as well as the quality of study conduct and study data.
- As network sponsors, National Institute of Allergy and Infectious Diseases (NIAID) and National Institute of Child Health and Human Development (NICHD) contract with clinical site monitors who conduct on-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 and other team members monitor the quality of study implementation to identify emerging issues and address these with study sites as needed.
- The IMPAACT 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) may also review 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) policy on Requirements for Clinical Quality Management Plans, 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 policy at:
http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/ClinicalSite.aspx.

13.2 On-Site Monitoring

As the sponsor of IMPAACT studies, the NIH has a regulatory responsibility for oversight of IMPAACT studies under the US Code of Federal Regulations (CFR) Title 45, Parts 46, 160, and 164; Title 21, Parts 11, 50, 54, 56, and 312; and International Conference on Harmonization (ICH) Guidelines E6. As part of fulfilling these responsibilities, NIAID and NICHD contract with clinical site monitors to perform on-site monitoring at the IMPAACT sites that they fund. Contracted monitors visit study sites to inspect study facilities and review participant study records including consent forms, paper-based case report forms (CRF, if used), electronic case report forms (eCRFs, if used), medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the Institutional Review Boards/Ethics Committees (IRB/EC) approved protocol, and accuracy and completeness of records. Monitors also review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators must make study facilities and documents available for inspection by the monitors.

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, and 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 including problems with adverse event reporting. Quality indicators typically include participant accrual and retention, adherence to study regimen/intervention, endpoint evaluability, specimen availability, and data quality and completeness.

Monitoring at the protocol team level is typically accomplished through review of study-specific reports generated by the Statistical and Data Management Center (SDMC) as defined in the study monitoring plan. In addition, the protocol chair and protocol team members from the Operations Center, Data Management Center (DMC), and Laboratory Center (LC) may visit sites to assess study implementation and/or provide training and other technical assistance to site staff. As needed, issues or problems identified during such visits are brought to the attention of the protocol team for discussion and development of corrective action plans. If issues cannot be resolved at the protocol team level, or if the protocol team determines that corrective action plans may require additional network resources, the protocol chair or other protocol team members may refer the issues to the MOG for further review, guidance, and decision-making.

In addition to the above, IMPAACT protocol chairs, vice chairs, and other team members (or designated subsets of protocol team members) are responsible for monitoring participant safety. Each IMPAACT protocol, and corresponding study monitoring plan, specifies the roles and responsibilities of protocol team members for monitoring participant safety. The roles and responsibilities may differ, for example, based on the phase of the study and whether the study involves comparative groups. Protocol teams are generally expected to review safety data every 1-3 months and more frequently, if specified by the protocol. Protocol teams may also review other study data (e.g., pharmacokinetic parameters) in a similar manner. For some studies, again depending on protocol specifications, protocol team members are also responsible for identifying when the criteria for pausing a study are met. If at any time a safety issue or concern is identified, the medical officers (MO) are notified and the protocol team is responsible for taking appropriate action to address that concern. Such actions may include, for example, requesting

additional review of study data by the SMC or DSMB, modifying the dosing of study agents, and 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.

Importantly, 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, for recording clinical and laboratory data on case report forms, and key entering these data in a timely manner, so that current data are available for review at the protocol team level. Site staff are also responsible for alerting the protocol team or the designated subset to any safety-related issues or concerns that may arise.

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 toxicity reports for team review, generating interim analysis reports for independent review committee review and identifying when study pause or stopping rules specified in the protocol have been met.

Designated protocol team members typically review study data and progress during conference calls, although reviews may also take place during in-person meetings or by email. When team member assessments are required for the study database, these are recorded by the study 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, as noted above, sites are notified if a safety issue is identified that necessitates a change in study conduct; such notifications also address notification of IRBs/ECs and other relevant review bodies. Similar notifications may also be provided following safety reviews in studies with multiple sequential cohorts of participants, if specified in the study protocol. 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 trial specialist (CTS). During the ongoing conduct of a study, available information will be limited, particularly if the study involves comparative groups.

13.4 IMPAACT Leadership Oversight

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

Routine MOG oversight includes evaluation of study progress with respect to key implementation milestones as well as resource allocation and use across studies. In support of the MOG's oversight function, a Study Operations Report is generated each month with updates on the status of each study, participant accrual and retention, and study implementation issues and problems. Other data reports required by the MOG are generated 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 for discussion. The MOG reviews proposals from protocol teams to modify protocols and/or study implementations plans (e.g., to expand to additional sites). 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 also supported in its oversight role by independent SMC reviews of selected studies, as described in Section 13.5 below.

13.5 IMPAACT Study Monitoring Committee Review

In support of the management and oversight functions of the MOG and for designated studies, a SMC monitors participant safety, the progress and quality of IMPAACT study conduct and makes recommendations related to study continuation, including cohort progression and dose escalation/dose selection when applicable. The scope of SMC reviews varies across studies, depending on protocol specifications for SMC oversight and the specifications of each individual study monitoring plan.

13.5.1 SMC Membership

For each study that is subject to SMC review, SMC membership will include:

- SMC chair
- IMPAACT network chair or vice chair
- IMPAACT Scientific Committee (SC) chair or vice chair
- Representatives of the IMPAACT Operations Center, LC, and SDAC
- DAIDS and NICHD representatives
- As needed, relevant content area reviewers (e.g., pharmacology, immunology, virology reviewer)

In addition to the above, other reviewers may be added as needed.

The SMC chair and representatives of the IMPAACT Operations Center, LC, and SDAC are considered standing members and will take part in all SMCs unless they are not independent of the study under review. All SMCs will also include either the network chair or vice chair, and either the chair or vice chair of the relevant SC. While SMC membership may vary across studies, every effort will be made to maintain consistent composition for each study over time. In the event that voting is required among SMC members, all members comprising the SMC for a given study, except the DAIDS and NICHD representatives, will be considered voting members.

SMC members will be 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. When standing members are not independent of a study under review, replacement reviewers will be designated. For example, if the standing Operations Center representative is a member of the protocol team, the Operations Center will designate an alternate reviewer.

13.5.2 SMC Review Process

SMC reviews will typically take place via conference call, although in-person reviews may also occur. The Operations Center will schedule and coordinate all reviews. In the event that an SMC member is not available to take part in a scheduled review, he or she may be given the option to provide written review comments in advance of the scheduled review.

For each review, the protocol chair, CTS, and other team members may attend an open session of the review, at the discretion of the SMC. The protocol statistician attends open and closed sessions.

The required timing of SMC reviews will be coordinated by the Operations Center and the SDAC, specifically the protocol statistician assigned to each study. SMC review requirements are identified in the Study Operations Reports generated each month by the Operations Center and will serve as a general reference for when reviews may be required. In addition, the protocol statistician will proactively coordinate with the Operations Center to identify potential review dates and establish timelines for when

review materials will be provided for each review. The statistician is responsible for preparing and distributing these materials, using secure means when analysis results are included.

A summary of roles, responsibilities, and timelines associated with SMC reviews is provided in Table 13-1, with additional description provided below.

Table 13-1. Summary of SMC Roles and Responsibilities

Person Responsible	Role/Responsibility	Timeline
SMC chair	• 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 finalize review reports	• Ideally within 3 working days after each review
	• Coordinate with Operations Center representative to receive and review protocol team responses to review reports (as applicable)	• Following each review
	• As needed, liaise with the IMPAACT MOG regarding SMC operations, review findings and recommendations	• As needed
SMC members	• Review data reports	• Prior to each review
	• As needed, request clarification of report contents via email (copying other SMC members)	• Prior to each review (as needed)
	• Provide review comments and recommendations	• During each review
	• When applicable, coordinate with the Operations Center representative to finalize review reports	• Ideally within 3 working days after each review
Operations Center representative to the SMC	• Coordinate with protocol statisticians and protocol CTS to schedule SMC reviews	• Ongoing based on study-specific needs
	• Coordinate review conference calls; distribute administrative information in support of each review	• Approximate 2-4 weeks prior to each review
	• Draft review reports and coordinate with the SMC chair and other SMC members (when applicable) to finalize review reports	• Following each review
	• Distribute final review reports to IMPAACT MOG and protocol teams	• Ideally within 3 working days after each review
	• Coordinate with SMC chair to receive and review protocol team responses to review reports (as applicable)	• Following each review
	• 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 to schedule SMC reviews • Prepare and distribute data reports for review • Take part in open and closed review sessions; provide an overview of the closed data report during closed review sessions	• Ongoing based on study-specific review needs • At least one week prior to each review • During each review (open and closed sessions)
Protocol chair	• Take part in open review sessions when applicable; 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	• During open review sessions
Other protocol team members including the protocol medical officers	• Take part in open review sessions when applicable; respond to SMC questions when applicable	• During open review sessions

13.5.2.1 Open Review Sessions

SMC reviews may include an optional 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, protocol team members are provided an open report containing relevant monitoring data as defined in the study monitoring plan. For reviews that include both 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. Open reports may be distributed to all protocol team members.

During open review sessions, protocol chairs are not expected to provide a formal presentation to the SMC, but should be prepared to 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 that the protocol team would like to bring to the SMC's attention for targeted consultation and feedback. SMC members may ask questions of the protocol chair (and other team members who attend open review sessions if applicable), requesting their insights into data presented into open reports and further clarifying issues, problems, and strategies to address these.

13.5.2.2 Closed Review Sessions

In closed sessions, SMC members assess the quality of study conduct, participant safety, and other key issues as specified in the study protocol and study monitoring plan, such as participant accrual, participant retention, data quality, adverse events, intervention adherence, endpoint evaluability, and selected efficacy data. When relevant, the SMC may also review pharmacokinetic and dose finding data. The

review considers the ongoing safety and feasibility of the study as designed and evaluates whether modification may be required to minimize risks to study participants or meet the study objectives.

As indicated above, data are presented by study arm in closed reports. Where applicable, the study arms are coded to avoid unnecessary unblinding, but coding keys are provided in the event that 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, it is essential that the SMC Chair first confirms that all members of the SMC agree to being unblinded.

Participation in closed review sessions is limited to SMC members and the protocol statistician, unless exceptions are specified in the study monitoring plan. Closed data reports are considered confidential, to be distributed only to designated SMC members and destroyed following each review. However, distribution to others may be permitted on a case-by-case basis in consultation with the SMC Chair and the IMPAACT 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 do not include the study statistician(s).

13.5.3 Types of SMC Review

13.5.3.1 Protocol Initiation Review

Studies subject to SMC review will undergo an initial review in which the near-final draft study monitoring plan will be reviewed and discussed in detail with the protocol statistician and protocol team leadership. This review is expected to take place before or soon after the protocol is finalized, and prior to the enrollment of any study participants. The purpose of this review is to agree upon key specifications of the study monitoring plan, the required frequency of SMC reviews for the study, and the data to be presented in interim analysis reports. The protocol statistician will finalize the study monitoring plan after this initial SMC review takes place.

13.5.3.2 Reviews During Study Implementation

Routine Reviews

For most studies, the primary purpose of SMC review is to assess whether the study is proceeding as expected with respect to issues such as participant accrual, participant retention, data quality, adherence to intervention, endpoint evaluability, and adverse events. Routine reviews should occur at least annually, or more frequently per the study protocol or as requested by the SMC or IMPAACT MOG.

Event-Driven Reviews

Some study protocols and monitoring plans may specify more limited SMC review, (e.g., to review data relevant to cohort progression or dose escalation). Other studies may require SMC review only if certain safety triggers or other pre-specified criteria are met. For this type of review, timelines for scheduling, preparation and distribution of data reports, and documentation of review findings and recommendations may be truncated.

Critical emergent safety issues may also require SMC review. These reviews generally take place on short notice and are limited in scope to the emergent issue that required review. For this type of review, timelines for scheduling, preparation and distribution of data reports, and documentation of review findings and recommendations will be truncated.

Interim Analysis Reviews

For some, the protocol and monitoring plan may require interim analyses comparing study arms, for example, for purposes of determining whether the study should continue. The timing of these reviews may be periodic (e.g., at least annually), event-driven (e.g., when a certain number of person-years or endpoints has been accumulated), or upon request by the protocol team or IMPAACT MOG.

13.5.4 Documentation and Response to SMC Reviews

As part of each review, the SMC will agree upon consensus findings, recommendations for ongoing conduct of the study, 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; when indicated, other SMC members may also review the draft report prior to finalization. Every effort will be made to finalize and distribute the review report within three days after the review. When the SMC recommends that a study continue as currently designed, it is generally expected that the review report will be distributed concurrently to the protocol team and members of the IMPAACT MOG. When recommendations involve protocol modifications or discontinuation of study implementation conduct, the MOG members will immediately be informed and next steps will be coordinated with the MOG prior to communication with the protocol team. Summary SMC review reports will also be provided to participating study sites by the Operations Center for submission to their IRBs/ECs.

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

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 clinical quality management plans 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 above. 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 necessary, NIAID and NICHD may suspend or terminate site participation in an IMPAACT study, for example in response to serious and/or persistent non-compliance with protocol, regulatory, and/or contract or grant requirements.

NIAID, NICHD, and NIMH Medical Officers/Medical Monitors and Program Representatives 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 above).

For some IMPAACT studies, NIAID convenes DSMB reviews as part of its study oversight responsibilities, as described in Section 13.7 below.

13.7 Data and Safety Monitoring Board Reviews

DSMB reviews are most commonly convened for large-scale randomized controlled studies; however, other types of IMPAACT studies may be subject to DSMB review. For studies that are subject to DSMB review, reviews are conducted at least annually and in accordance with relevant NIAID standard operating procedures and DSMB charters. 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 biostatistics and medical ethics, clinicians, and other scientists who are experts in HIV transmission, plus ad hoc members. Appointments to the DSMB are made by NIAID.

13.7.1 Preparation for and Participation in Reviews

The SDMC prepares data reports for DSMB review; other materials may also be prepared for the DSMB by the protocol team (e.g., memos, slide presentations). Representatives of the protocol team — including the protocol chair, statistician, CTS, and MOs — attend DSMB reviews in person or via telephone. Similar to the procedures described above for SMC reviews, team members other than unblinded statisticians typically attend open review sessions to discuss study progress, present blinded (pooled across randomization arms) data, and respond to questions from the DSMB. Unblinded statisticians attend closed review sessions to present unblinded data and respond to additional 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 the IMPAACT leadership approximately 24-48 hours after the review date 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 will include:

- IMPAACT network chair and vice chair
- Relevant SC chair
- Protocol chair(s)
- Operations Center Director and protocol CTS
- SDMC principal investigator (PI) and protocol statistician
- LC PI
- DAIDS Prevention Science Program Director
- DAIDS MAPRB Chief
- DAIDS MO, NICHD MO, and NIMH Program Officer
- Others as required

13.7.2 Review Findings and Recommendations

At the close of each review, the DSMB's findings and recommendations are may be provided to team members who attended to review by the DSMB chair. The findings and recommendations are communicated within DAIDS/NIAID, with NIAID leadership having ultimate responsibility for determining whether to accept the recommendations. Recommendations may involve continuing a study as currently designed or may involve modifications of a study, for the following types of reasons:

- The study question has been answered (early termination of part of or the entire current protocol)
- The study question will not be answered (futility of part of or the entire current protocol)
- 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 report of the review is distributed to the protocol team and participating studies sites by DAIDS and its contractors. If requested in the summary report, the protocol team will submit a written response to the DSMB; otherwise, the team response will be included in the data reports for the next DSMB review. All study sites must submit a copy of the summary review report to their IRBs/ECs and other relevant review bodies; protocol teams may also provide supplemental materials for submission along with the summary report.

13.7.3 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. The IMPAACT leadership will be informed of the recommendations and the NIAID decision during the conference call (described in Section 13.7.1) scheduled to take place within 24-28 hours 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 generally be coordinated by the Operations Center in close collaboration with the Protocol Chair; however, 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 must 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 should 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).