Note that this Appendix applies to all National Institute of Allergy and Infectious Diseases (NIAID) (Division of Acquired Immunodeficiency Syndrome (DAIDS)) supported and/or sponsored clinical trials with a SMC that are conducted outside of the HIV/AIDS Clinical Trials networks.

Note: For purposes of this document, the terms data reports and summary reports are defined as follows:

Data reports are documents containing data related to study progress, data, and safety monitoring generated for the review by the designated monitor(s).

Summary reports are the synopsis of the observations and recommendations of the designated monitor(s).

1. Roles and Responsibilities

A Study Monitoring Committee (SMC) is an independent group of experts that advises the DAIDS and the study investigators. The primary responsibility of the SMC is to monitor study progress and participant safety. The SMC considers study-specific data as well as relevant background information about the disease, study agent, and target population under study. The contents and schedule of data reports to be reviewed by the SMC will be specified in the study progress, data, and safety monitoring plan (SPDSMP) with input from the SMC. A member of a SMC may be designated to serve as an Independent Safety Monitor (ISM) and review selected individual case adverse event reports and/or periodic cumulative adverse event reports in addition to those reviewed by the entire SMC.

The SMC should review the protocol and the SPDSMP, and identify any major concerns prior to implementation. The SMC should define its deliberative processes prior to clinical trial initiation. These processes may include event triggers that would call for an unscheduled review, guidelines for stopping administration of study product and accrual or unblinding (unmasking), and voting procedures. The SMC must maintain the confidentiality of its internal discussions and activities, as well as the contents of data reports provided.

During the trial the SMC should review:

- Study progress and safety data
- Adherence to the protocol
- Factors that might affect the clinical trial outcome or feasibility or compromise the trial data (such as slow accrual, poor data quality or timeliness, protocol violations,
losses to follow-up, etc.)

- Data relevant to proceeding to the next stage of the clinical trial, if applicable
- If appropriate, effectiveness outcomes/endpoints

Other relevant issues, such as endpoint evaluability, pharmacokinetics and/or immunogenicity data, site performance, and factors external to the clinical trial may also need to be considered, as specified in the SPDSMP.

The SMC should conclude each review with the committee’s recommendation to DAIDS as to whether the clinical trial should continue, be modified, or be terminated. Recommendations regarding modification of the design and conduct of the clinical trial may include corrective actions when performance is unsatisfactory, or recommendations to advance to the next dose in a dose escalation clinical trial, for example, or to the next stage in product testing.

Confidentiality must always be maintained during all phases of SMC review and deliberations. Only members of the SMC and the study biostatistician should have access to the emerging study data sorted by treatment group (even if the group identities are masked). Exceptions may be made when the SMC deems it appropriate. Whenever blinded data are presented to the SMC, the key to the group coding must be available for immediate unblinding.

2. Membership

The membership of the SMC should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The SMC generally consists of at least three voting members. Membership may include an ISM with expertise in the clinical aspects of the disease/patient population being studied, and expertise in current clinical trials conduct and methodology. An SMC may also include one or two members of a standing DAIDS Data and Safety Monitoring Board (DSMB) and this may be required by DAIDS.

Strong consideration should be given to including an independent biostatistician if statistical analysis of the data will be evaluated. A biostatistician, as well as other specialists, may be invited to participate as non-voting members on an ad hoc basis at any time if additional expertise is desired. SMC and ad hoc members may be from the principal investigator’s institution or from other participating sites but cannot be directly involved with the trial or under the supervision of a trial investigator. Furthermore, the SMC members should generally be in a different organizational group than the Principal Investigator (PI).
Appendix 1
Study Progress, Data, and Safety Monitoring
STUDY MONITORING COMMITTEE (SMC) GUIDELINES

DAIDS and other National Institutes of Health (NIH) staff who are not involved in the clinical trial may also participate as voting members. However, members of the sponsoring DAIDS Branch are discouraged from having voting privileges. Medical Officers/Medical Monitors/Clinical Representatives or other NIH staff involved in the clinical trial may participate as ex officio, non-voting members, in selected cases. Representatives of the manufacturer (industry collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the clinical trial are not eligible to serve on the SMC as ad hoc, ex officio or voting members.

2.1. Conflict of Interest

SMC voting members cannot have any other involvement in the conduct of the clinical trial. Furthermore, no member may have financial, proprietary, professional, or other interests that could affect impartial, independent decision-making by the SMC. Letters of invitation to prospective SMC and ad hoc members should include the following: "Acceptance of this invitation to serve on the SMC for this study confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all SMC voting and ad hoc members will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Attachment A). At the beginning of every SMC meeting, DAIDS Program staff or the SMC Chair will reconfirm that no conflict of interest exists for SMC members. Interests that may create a potential conflict of interest must be disclosed to the SMC prior to any discussion. The SMC will determine how to handle such potential conflict. The SMC can require that a member with a potential conflict not vote or take other means deemed appropriate. DAIDS may dismiss a member of the SMC in the event of unmanageable potential conflict.

2.2. Selection and Invitation to Participate

DAIDS may retain the primary responsibility for selection of the members and chairperson and for organizing the SMC, or DAIDS may delegate this responsibility to the study PI. If delegated to the study PI, the proposed description, charter, operating procedures (including meeting/review schedule and venues), and roster (with curriculum vitaes (CVs) for each member) must be submitted at least 30 days before the projected date of clinical trial initiation and approved in writing by DAIDS before the clinical trial may be initiated. In some cases, SMC voting members may select the Chair.

3. Meetings or Teleconferences

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The structure and operating procedures for a SMC are usually less formal than that of a DSMB. The initial SMC meeting or teleconference should occur before the start of the trial or as soon thereafter as possible. DAIDS staff may discuss DAIDS's perspective on and expectations for the clinical trial at this time. At this session, the SMC should discuss the protocol and the suggested triggers for data review, define a quorum, and establish guidelines for monitoring the clinical trial. The SMC should decide whether any member(s) should serve as an ISM and receive individual case reports of serious adverse events (SAEs) and/or cumulative adverse event (AE) reports at specified intervals between the scheduled interim SMC reviews. Guidelines for stopping the clinical trial for safety concerns should be established. At this meeting, the SMC should also develop procedures for conducting business (e.g., data required for review, voting rules, attendance, etc.). Teleconference calls are usually the most appropriate means for conducting meetings.

Based on initial discussions, the SMC should decide whether to have additional ad hoc meetings based on the occurrence of certain types or frequencies of adverse events. Ad hoc meetings may also be triggered by study progress, or data quality events, or by external data that would impact the clinical trial. Scheduling of meetings should be based on the magnitude of the perceived risks, decision points in the protocol (e.g., the decision to move to a higher dose), rate of enrollment, or problems that occur during the progress of the clinical trial. The SMC may be asked for advice at the conclusion of the clinical trial about whether to proceed with the next phase of development of the study product.

DAIDS is responsible to convene conference calls/meetings unless this has been delegated in writing to the grantee. However, for cause meetings may be requested by any member of the SMC, the PI, an Institutional Review Board (IRB)/Ethics Committee (EC), an industry sponsor, or DAIDS. The study statistical team preparing the SMC data reports will be responsible for ensuring the distribution of materials for review to SMC members and other meeting participants.

3.1. SMC Meeting Format

The recommended meeting format may consist of the following sessions: Open Session, Closed Session, and Closed Executive Session (optional).

3.1.1. Open Session

Occurrences of adverse events and toxicity issues are reviewed. Issues relating to the general conduct and progress of the clinical trial should also be considered. Efficacy outcome results must not be discussed during this session and, for comparative trials, no study group-specific data will be reviewed or discussed.
SMC members (voting and ex officio), DAIDS staff members, and any ad hoc experts may attend and participate in this session. The PI and study statistician, if applicable, should attend and participate to present results and respond to questions. This session is open to study investigators, coordinating center staff, representatives for industry collaborators, representatives from the U.S. Food and Drug Administration (FDA), and NIH program and regulatory staff.

3.1.2. Closed Session

Study group-specific data including all relevant efficacy outcome measures, masked if so specified, are presented at this session. This session is normally attended only by voting members, non-voting (ex officio and ad hoc) members, and the study statistician. The voting members can choose as a group to make decisions and formulate recommendations either during this session or during a Closed Executive Session.

3.1.3. Closed Executive Session (optional)

This final session involves only voting members to ensure complete independence for making decisions and formulating independent recommendations. The SMC may unmask the data during this session based on procedures identified in advance.

3.2. Voting

A quorum, as defined by the SMC in the initial meeting, must be present either in person or by teleconference. After a thorough discussion of SMC members' opinions and rationale, the final recommendations of each SMC member should be solicited in either Closed Session or Closed Executive Session. The final recommendations are recorded and either identified as majority or minority positions (if a general consensus is achieved) or followed by a vote for recommendations without an achievable consensus.

4. Study-related information and Data Reports for SMC Review

It is the responsibility of the PI to ensure that the SMC is apprised of all new safety information relevant to the study product and the clinical trial. If applicable, this includes providing the SMC with a copy of the Investigator's Brochure (IB) or package insert in advance of the first SMC session, as well as promptly providing all IB or package insert revisions and all data safety reports issued by the industry sponsor. Summary safety and enrollment data must be forwarded periodically to the SMC as directed by the SPDSMP. The
SMC must receive all protocol revisions and may receive other documents relating to the clinical trial, such as annual data reports, manuscripts, and newsletters. Other relevant new information (e.g., results from studies of the same or similar agents or important preclinical testing results) must also be provided on a timely basis.

The SMC will review the SPDSMP and the proposed general content of the SMC monitoring data reports at the initial meeting. The SMC may request changes or additions to the actual data elements to be presented and to the proposed review schedule. At each meeting, further additions or modifications to these data reports may be directed by the SMC on a one-time or continuing basis. Distribution of written data reports must allow sufficient time for review.

Data reports for meetings of the SMC will consist of the Open Session Data Report and, as required, a Closed Session Data Report. Open Session Data Reports are distributed to all SMC members, selected DAIDS staff, and other appropriate persons as directed by the SMC. Closed Session Data Reports are distributed only to SMC members and others as designated by the SMC. The Closed Session Data Report may contain study group-specific outcome data and should be marked confidential and handled accordingly.

5. Summary Reports From the SMC

5.1. Verbal Summary Report

At the conclusion of a SMC meeting, the SMC should discuss its findings and recommendations with DAIDS representatives and the study investigators. If DAIDS is not represented at the meeting, the SMC Chair should contact the DAIDS Program Officer (PO) and Medical Officer (MO) immediately after the meeting for debriefing.

5.2. Summary Report

The SMC will issue a written summary report summarizing topics discussed by the SMC and describing their findings, overall safety assessment, and recommendations. This generally occurs after each meeting but SMCs that meet on a very frequent basis may summarize more than one meeting in a single summary report. The rationale for recommendations will be included when appropriate. This summary report will not include confidential information. The SMC Chair or designee is responsible for preparing and distributing the summary report.

Unless otherwise specified, the summary report will be submitted by the SMC chair to the DAIDS PO and MO. The DAIDS PO will forward the summary report to a designated study team representative (usually the PI) and to other appropriate DAIDS staff. The study team representative is responsible for disseminating the SMC
study report to site investigators, and any Investigational New Drug Application (IND) sponsors and industry collaborators. Site investigators must, in turn, submit the summary reports to their respective IRBs/ECs in accordance with the reviewing IRB/EC policy. If the trial is being conducted under an IND, the IND holder will forward the summary report to the FDA.

5.3. Closed Session Minutes (optional)

The SMC may also prepare confidential minutes that include details of discussions in the closed session(s). Meeting minutes are to be held in strict confidence, accessible only to voting members of the SMC until a) such time when the clinical trial is closed, b) DAIDS accepts a SMC recommendation for early termination, or c) if the minutes are requested by the FDA or DAIDS for patient safety or regulatory purposes.

5.4. Immediate Action Summary Report

The SMC Chair will notify the DAIDS PO and MO of any findings of a serious and immediate nature, such as if the SMC recommends substantial clinical trial modifications or that all or part of the trial be discontinued. The PO and MO will immediately inform appropriate Program staff, including their Branch Chiefs and others as determined by their Program. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a clinical trial must be conveyed to DAIDS in writing within 48 hours of the SMC meeting. This written, confidential briefing may contain study group-specific and/or unmasked supporting data and should include the SMC members’ rationale for its recommendations.

The SMC provides recommendations concerning continuation or major changes in study conduct to DAIDS. After consultation with the investigators, all final decisions regarding these recommendations are made by DAIDS.