ATTACHMENT II

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)

SAFETY MONITORING COMMITTEE (SMC) GUIDELINES

I. Roles and Responsibilities

The Safety Monitoring Committee (SMC) is an independent group of experts that advises DMID and the study investigators for Phase I and some Phase II trials. ***The primary responsibility of the SMC is to monitor participant safety.*** The SMC considers study-specific data as well as relevant background information about the disease, test agent, and target population under study.

Prior to the first data review and preferably prior to study initiation, the SMC should define its deliberative processes. These may include event triggers that would call for an unscheduled review, guidelines for stopping or unmasking (unblinding), and voting procedures. The SMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The SMC should review the protocol, including the safety monitoring plan, and identify any major concerns prior to implementation. During the trial the SMC should review:

- Real-time and cumulative safety data for evidence of study-related adverse events;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the trial data (such as protocol violations, losses to follow-up, etc.); and,
- Data relevant to proceeding to the next stage of the study, if applicable.

Other relevant issues, such as pharmacokinetics and/or immunogenicity data, data quality, site performance, recruitment and retention, and factors external to the study may also need to be considered.

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

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

II. 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 should include an Independent Safety Monitor (ISM) from one or more participating sites, expertise in the clinical aspects of the disease/patient population being studied, and expertise in current clinical trials conduct and methodology.

Consideration should be given to including a biostatistician if statistical tests 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 should not be directly involved with the trial or under the supervision of the trial investigator. Furthermore, the SMC members should generally be in a different organizational group than the Principal Investigator (PI).

DMID and other NIH staff who are not involved in the study may also participate as voting members. However, members of the sponsoring DMID Branch are discouraged from having voting privileges. Project Officers or other NIH staff involved in the study may participate as *ex officio*, non-voting members. Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are <u>not</u> eligible to serve on the SMC as *ex officio* or voting members.

<u>Conflict of Interest</u>

No member of the SMC should have direct involvement in the conduct of the study. Furthermore, no member should have certain financial, proprietary, professional, or other interests that may 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 xxx SMC 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 and *ad hoc* members will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Appendix II). At the beginning of every SMC meeting, DMID 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 should 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. NIAID may dismiss a member of the SMC in the event of unmanageable potential conflict.

<u>Selection and Invitation to Participate</u>

The NIAID Program or Project Officer (PO) holds primary responsibility for the formation of the SMC, unless the Clinical Terms of Award for a grant specifically identifies this as the responsibility of the grantee. The PO (or grantee as specified) is responsible for developing the roster of potential SMC members. Recommendations for proposed members may be solicited from many sources. The proposed roster of members must be submitted to the Chief, Office of Clinical Research Affairs (OCRA) or designee for review and approval before invitations are issued.

The PO (or grantee as specified) is responsible for identifying the SMC Chair. He/she may either select the Chair directly or ask SMC voting members to select the Chair.

III. Meetings

The structure and operating procedures for a SMC are usually less formal than that of a DSMB. The initial SMC meeting should occur before the start of the trial or as soon thereafter as possible. DMID staff may discuss DMID's perspective on and expectations for the study at this initial meeting. At this meeting the SMC should discuss the protocol, set triggers for data review, define a quorum, and establish guidelines for monitoring the study. The SMC should decide which member(s) should receive reports of serious adverse events in real time and determine if on-site review of clinical records might be needed. Guidelines for stopping the study 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 may often be an appropriate means for conducting meetings.

Based on initial discussions, the SMC should decide whether to meet on a regular basis or only with the occurrence of adverse events. In many cases, it may be appropriate for meetings to be convened on an *ad hoc* basis based on the occurrence of adverse events. 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 study. The SMC may be asked for advice at the conclusion of the study about whether to proceed with the next phase of development of the study product.

The PO or designee is responsible for convening meetings or conference calls as needed unless the Clinical Terms of Award for a grant specifically identifies this as the responsibility of the grantee. However, meetings may be requested for cause by any member of the SMC, the investigator, IRB, the manufacturer, or DMID. The investigator will be responsible for ensuring the distribution of materials for review to SMC members and other meeting participants.

A. SMC meeting format

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

1. Open Session
   Occurrences of adverse events and toxicity issues are reviewed. Issues relating to the general conduct and progress of the study may also be considered. Outcome results must not be discussed during this session and, if the study is masked, no study group-specific data should be reviewed or discussed.

   SMC members, voting and *ex officio* members, NIAID staff members, and *ad hoc* experts attend and participate in this session. The lead investigator 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 industrial collaborators, representatives from the Food and Drug Administration (FDA), and NIH program and regulatory staff.

2. Closed Session (optional; generally only required if the study is masked)
   Study group-specific data, masked if so specified, are presented at this session. This session is normally attended only by voting members, study statistician, and *ex officio* members.

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

B. Voting

A quorum, as defined by the SMC in the initial meeting, must be present either in person or by conference call. After a thorough discussion of SMC members' opinions and rationale and a joint attempt to reach clarity regarding individual recommendations, the final recommendations of each SMC member should be solicited in Closed Executive Session (e*x officio* members shall not vote and shall not be present at this voting session). The final recommendations are recorded and either identified as majority or minority positions or are accompanied by actual vote tallies for each divergent recommendation, i.e., as number of votes for or against a particular action, e.g., continue study, terminate study, etc.

IV. Study 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 study. This includes providing the SMC with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all IB revisions and all safety reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the SMC. The SMC should receive all protocol revisions and may receive other documents relating to the study.

Reports are prepared by the study statistician or else the investigator. The general content for reports to the SMC is as determined by the SMC at the initial meeting. The SMC and DMID must also review and approve the actual data elements to be presented. At each meeting, additions or modifications to these reports may be directed by the SMC on a one-time or continuing basis. Distribution of written reports should allow sufficient time for review.

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

V. Other Reports of Study Progress

Safety and enrollment data should be forwarded periodically to all SMC members. The SMC should also receive all protocol revisions and may receive other documents relating to the study, such as annual reports, manuscripts, and newsletters.

VI. Reports from the SMC

A. Verbal Report

At the conclusion of a SMC meeting, the SMC should discuss its findings and recommendations with DMID representatives and the study investigators. If DMID is not represented at the meeting, the SMC Chair should contact DMID immediately after the meeting to debrief the PO.

B. Summary Report

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

Unless otherwise specified, the summary report will be forwarded through the DMID PO to a designated study team representative (usually the Principal Investigator) and to other appropriate DMID staff. The study team representative is responsible for disseminating the SMC summary report to site investigators and IND sponsors and industrial collaborators, if any. Site investigators must, in turn, submit the reports to their respective IRBs in accordance with local IRB policy and other industrial collaborators. If under an IND, the sponsor (IND holder) will forward the summary report to the FDA.

C. Closed Session Minutes (optional)

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

D. Immediate Action Report

The SMC Chair will notify the PO of any findings of a serious and immediate nature, such as if the SMC recommends that all or part of the trial be discontinued. The PO will immediately inform appropriate DMID staff, including: the Chief, Office of Clinical Research Affairs (OCRA), the Chief, Office of Regulatory Affairs (ORA), and the Deputy Director of DMID or designee. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to DMID in writing on the day of the SMC meeting. This written, confidential briefing may contain unmasked supporting data and should include the SMC members' rationale for its recommendations. The written briefing should be submitted to OCRA and ORA for submission to the FDA, if under an IND.

See Appendix IV for the DMID sign-off sheet for the above reports.