ATTACHMENT III

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

INDEPENDENT SAFETY MONITOR (ISM) GUIDELINES

I. Roles and Responsibilities

The Independent Safety Monitor (ISM) is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

An ISM could be the sole monitor for the study or may perform this role as a member of a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC). An ISM is appropriate as the sole independent safety monitor for small, early phase studies considered to be low risk, such as some pharmacokinetics or immunogenicity studies, or other studies of short duration. DSMBs and SMCs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events (SAEs) rather than all adverse events (AEs).

II. Selection and Invitation to Participate

The ISM should be selected based on relevant study-related expertise. Participation is for the duration of the study. The ISM should be able to readily access participant records in real time. He/she is generally a member of the participating institution's staff. The ISM should not be under the direct supervision of the investigator and should preferably be from a different organizational group.

Conflict of Interest

No ISM should have direct involvement in the conduct of the study. Furthermore, no ISM should have certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. Letters of invitation to prospective ISMs should include the following: "Acceptance of this invitation to serve as the xxx ISM 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 ISMs will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Appendix III).

If the ISM performs this role as a member of a DSMB or SMC, DMID program staff or the DSMB or SMC Chair (as appropriate) will reconfirm that no conflict of interest exists for the ISM at the beginning of every DSMB or SMC meeting. Interests that may create a potential conflict of interest should be disclosed to the DSMB or SMC prior to any discussion. The DSMB or SMC will determine how to handle such potential conflict. The DSMB or SMC can require that an ISM with a potential conflict not vote or take other means deemed appropriate.

If the ISM is acting as the sole independent monitor, the DMID Program/Project Officer (PO) will reconfirm prior to any review of data or at least annually that no conflict of interest exists. Interests that may create a potential conflict of interest should be disclosed to the DMID PO prior to any review of data.

The DMID PO, in consultation with the Chief, Office of Clinical Research Affairs (OCRA), will determine if the relationship is in conflict or gives the appearance of a conflict such that the individual should not serve as the ISM. DMID will determine how to handle such potential conflict. DMID can require that an ISM with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss an ISM in the event of unmanageable potential conflict.

III. Study Materials for ISM Review

The primary focus of the ISM is to independently review all adverse events and thoroughly investigate those considered serious and unexpected. As the sole monitor, the ISM accomplishes this by evaluating all adverse events against the known safety profile of the study product. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. If necessary, special reports are prepared by the investigator or study statistician.

It is the responsibility of the PI to ensure that the ISM is apprised of all new safety information relevant to the study product and the study. This includes providing the ISM with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all CIB revisions and all safety reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the ISM. The ISM should receive all protocol revisions and may receive other documents relating to the study.

IV. Reports from the ISM

The following reports are submitted by the ISM when acting as the sole independent monitor; otherwise the ISM operates under the guidelines of the DSMB or SMC).

A. Review Report
According to pre-specified criteria agreed upon by the DMID Program or Project Officer (PO), the ISM should communicate in writing his/her findings, any concerns and recommendations to DMID representatives and, subsequently, the study investigators.

Unless otherwise specified, the written report will be forwarded through the DMID PO to a designated study team representative (usually the Principal Investigator) and to other appropriate DMID staff including the Chief, Office of Clinical Research Affairs (OCRA) and the Chief, Office of Regulatory Affairs (ORA). The study team representative is responsible for disseminating the ISM summary report to any other site investigators and each investigator must, in turn, submit the report as per local IRB policy. If under an IND, the sponsor will forward the summary report to the FDA and to any other industrial collaborators.

B. Immediate Action Report
The ISM will notify the PO of any findings of a serious and immediate nature including any recommendations to discontinue all or part of the trial, and the PO will immediately inform the Chief, OCRA, the Chief, ORA, and Deputy Director of DMID or designate. 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 ISM review. This written, confidential report may contain unmasked supporting data and include the ISM's rationale for the recommendations. The report 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.