Note that this Appendix applies to all National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) supported and/or sponsored clinical trials with an Independent Safety Monitor (ISM) 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).

An ISM is a physician or other health-care professional with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. There are two common circumstances in which an ISM functions, A) as the sole independent reviewer for a clinical trial or B) as a member of a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC) designated to perform interim safety reviews between DSMB and SMC meetings.

A. ISM as Sole Independent Reviewer

1. Role and Responsibilities

An ISM is appropriate as the sole independent reviewer for small, early phase studies, such as some pharmacokinetics, proof-of-concept, or immunogenicity studies, or other studies of short duration. The ISM will work with the study team and the DAIDS Medical Officer/Medical Monitor/Clinical Representative in review of safety data/reports, including both individual case adverse event (AE) data and periodic cumulative AE reports. Based on review of this safety data, the ISM will make recommendations regarding the safe continuation of the clinical trial.

DAIDS may retain the responsibility to identify the ISM and define his/her role. The ISM will be selected based on relevant study-related expertise. Participation will usually be for the duration of the clinical trial. In some cases, DAIDS may delegate nomination of the ISM to the study Principal Investigator (PI). If delegated, the study PI must submit to DAIDS the CV of the person(s) proposed to serve as the ISM and a detailed description of his/her role at least 30 days before the projected date of clinical trial initiation. DAIDS must provide written approval for the ISM(s) recommended by the study PI and his/her role, before the clinical trial is initiated.
2. Conflict of Interest

An ISM cannot have any other involvement in the conduct of the study. He/she may be a member of a participating institution's staff, but cannot be under the direct supervision of an investigator and should preferably be from a different organizational group. Furthermore, no ISM may have financial, proprietary, professional, or other interests that could affect impartial, independent decision-making. Letters of invitation to prospective ISMs should include the following: "Acceptance of this invitation to serve as the ISM 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 ISMs will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Attachment A).

The DAIDS Program/Project Officer (PO) will reconfirm at least annually that no conflict of interest exists. Interests that may create a potential conflict of interest must be disclosed to the DAIDS PO prior to any review of data. The DAIDS PO, in consultation with their Branch Chief, Program Director, or other appropriate staff, 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. DAIDS may replace an ISM in the event of unresolvable potential conflict.

3. Study Materials for ISM Review

The primary focus of the ISM is to independently review selected safety data as determined by the Study Progress, Data, and Safety Monitoring Plan (SPDSMP). This will include thorough evaluation of some or all individual SAEs and/or review of periodic cumulative AE reports. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. If necessary, special data reports are prepared by the investigator or study statistician.

It is the responsibility of the PI to ensure that the ISM is informed of all new safety information relevant to the study product. This includes providing the ISM with a copy of the current Investigator's Brochure (IB) or the study product's Package Insert before clinical trial initiation as well as promptly providing all IB revisions and all safety data 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 clinical trial.

4. Summary Reports From the ISM

The following summary reports are submitted by the ISM.
4.1. Summary Report

According to pre-specified criteria delineated in the SPDSMP, and as needed in response to study developments, the ISM will communicate in writing a summary of his/her findings, any concerns, and recommendations. The SPDSMP will include a communication pathway. Unless otherwise specified, the ISM will submit the summary report 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 designated DAIDS staff. The study team representative is responsible for disseminating the ISM summary report to any other study investigators, and relevant staff and each investigator must, in turn, submit the summary report as per the reviewing Institutional Review Board (IRB)/Ethics Committee (EC) policy. If under an Investigational New Drug Application (IND), the sponsor is responsible for submitting the summary report to the Food and Drug Administration (FDA) and to any industry collaborators as appropriate.

4.2. Immediate Action Summary Report

The ISM will immediately notify the DAIDS PO and MO of any findings of a serious nature including any recommendations to significantly modify or discontinue all or part of the clinical trial. The SPDSMP should state whether the PI will be informed simultaneously or after DAIDS has had an opportunity to discuss and formulate a plan. 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 one day of the ISM review. This written, confidential summary report may contain unblinded supporting data and include the ISM's rationale for the recommendations. The summary report will be submitted to the DAIDS PO and MO, who will determine further distribution. If under an Investigational New Drug Application (IND), the sponsor is responsible for submitting the summary report to the Food and Drug Administration (FDA) and to any industry collaborators as appropriate.

4.3. Recommendations and Actions

ISM recommendations concerning continuation or major changes in study conduct will be made directly to the DAIDS PO and MO. Final decisions regarding these recommendations will be made by DAIDS.

B. ISM as Member of a DSMB or SMC

1. Role and Responsibilities
DSMBs and SMCs may consider designating one or more members as ISM(s) to review serious adverse events (SAE) reports and/or review periodic cumulative adverse event reports between scheduled interim full committee reviews. Based on this review, the ISM may make recommendations for an ad hoc or urgent full committee review. The contents and schedule of data reports to be reviewed by the ISM will be specified in the SPDSMP with additional input from the DSMB or SMC.

2. Conflict of Interest

See Appendix 1, SMC Guidelines, section 2.1 for COI information on SMC members.

The ISM will confirm that he/she has no conflict of interest prior to performing the independent review. Interests that may create a potential conflict of interest must be disclosed to the DSMB or SMC Chair prior to the review. 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 be replaced or take other means deemed appropriate.

3. Study Materials for ISM Review

The primary focus of the ISM is to independently review selected safety data as guided by the DSMB or SMC. This may include thorough evaluation of some or all individual SAEs and/or review of periodic cumulative AE reports. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. If necessary, special data reports are prepared by the investigator or study statistician.

4. Summary Reports From the ISM

The ISM operates under the guidelines of the DSMB or SMC

4.1. Summary Report

According to pre-specified criteria delineated by the DSMB or SMC, and as needed in response to study developments, the ISM will communicate in writing a summary of his/her findings, any concerns, and recommendations. The ISM will submit the summary report to the DSMB or SMC and additional parties as specified in the SPDSMP. When appropriate, the ISM will recommend an urgent or ad hoc, for cause DSMB/SMC meeting.

4.2. Recommendations and Actions

The ISM will bring his/her concerns to the DSMB or SMC. The DSMB or SMC will be the body to make recommendations to DAIDS. See the DSMB Charter and Appendix
1, SMC Guidelines for information on the DSMB and SMC processes to communicate recommendations to DAIDS. Final decisions regarding these recommendations will be made by DAIDS.

For additional information on the DSMB, see the NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations. For additional information on the SMC, see the Appendix 1, SMC Guidelines.