CHANGE SUMMARY NOTE: This policy has been reviewed for accuracy and updated to meet 508 compliance guidelines.

1.0 PURPOSE

This policy describes the requirements for study progress, data, and safety monitoring plans (SPDSMP) for National Institute of Allergy and Infectious Diseases (NIAID) Division of Acquired Immunodeficiency Syndrome (DAIDS) supported and/or sponsored clinical trials.

2.0 SCOPE

This policy applies to all NIAID (DAIDS) supported and/or sponsored clinical trials that are conducted outside of the HIV/AIDS Clinical Trials Networks.

3.0 BACKGROUND

Study progress, data, and safety monitoring is required for all interventional studies, in order to ensure the safety of participants and the validity, integrity, and timeliness of the data. The type of monitoring should be commensurate with risks and with the size and complexity of the clinical trial. DAIDS ensures that the study team appropriately plans and executes data and safety monitoring and that the team communicates the results to DAIDS. Note that clinical on-site monitoring is outside the scope of this policy and is addressed in a separate DAIDS policy.

All NIAID (DAIDS) supported and/or sponsored clinical trials are subject to and must adhere to the most stringent of any applicable laws, regulations, guidelines, policies, terms of award, or other requirements for study progress, data, and safety monitoring including:

NIAID Clinical Terms of Award, and any additional study-specific terms of award required by DAIDS;

International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (ICH E6);

National Institutes of Health (NIH) Policy for Data and Safety Monitoring;

NIH, Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials;

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1 45 CFR 46.111(a)(6) & 21 CFR 56.111(a)(6)
Clinical trials which are subject to the U.S. Food and Drug Administration (FDA) regulations for evaluating drugs or biologics (i.e., 21 CFR 312) and/or devices (i.e., 21 CFR 800-892); and

**FDA Guidance for Clinical Trial Sponsors, Establishment of Operation of Clinical Trial Data Monitoring Committees.**

### 4.0 DEFINITIONS

Note: For purposes of the SPDSMP policy documents, 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).

For additional definitions, see [DAIDS glossary.](#)

### 5.0 RESPONSIBILITIES

**DAIDS Program Officer (PO)**

The DAIDS PO or designee is responsible for ensuring and documenting that the study progress, data, and safety monitoring are done in accordance with the Terms of Award for the grant, and that all DAIDS requirements for study progress, data, and safety monitoring as described in this policy have been met. The DAIDS PO works closely with the DAIDS Medical Officer (MO) for a trial. The DAIDS PO and MO share responsibility to maintain communication between them regarding the SPDSMP.

**DAIDS Medical Officer/Medical Monitor/Clinical Representative (MO/MM/CR)**

For purposes of this policy, the DAIDS MO is: the designated DAIDS Medical Officer, DAIDS Medical Monitor, or DAIDS Clinical Representative. The **DAIDS MO/MM/CR**, is responsible for reviewing the protocol for all aspects of progress, data and safety monitoring, approving the Study Progress, Data, and Safety Monitoring Plan (SPDSMP), and participating in the monitoring of study progress, timely data collection and participant safety, to the extent specified in the Terms of Award for the grant and in the protocol/SPDSMP. The MO will work together in collaboration with the DAIDS PO to ensure that this policy is followed, the SPDSMP is in accord with
the terms of the Award and that the SPDSMP is followed during the course of the study.

Protocol Chair/Study Principal Investigator (PI)

The Protocol Chair/Study PI is responsible for ensuring that all DAIDS requirements for study progress, data, and safety monitoring are met, and that appropriate documentation is kept and available for DAIDS site monitors and program staff review.

DAIDS Director or designee

The DAIDS Director or designee is responsible for reviewing and approving or disapproving any alternative proposal for study progress, data, and safety monitoring, including the use of a non-DAIDS DSMB.

6.0 POLICY

6.1 Study Progress, Data, and Safety Monitoring Plan

All clinical trials supported and/or sponsored by NIAID (DAIDS) must have a SPDSMP which describes the type and frequency of planned study progress, data, and safety monitoring reviews. The SPDSMP may either be included in the relevant sections of the protocol document (e.g., Data and Safety Monitoring, Appendix), or in a separate document. If a separate document is used for the SPDSMP, the protocol must still include a basic study monitoring plan that describes the frequency of monitoring, key parameters for assessment of study progress, feasibility, safety, and efficacy, and pause rules as appropriate. If safety or efficacy monitoring criteria are apt to change during the clinical trial (e.g., due to the monitoring body recommendation), the protocol may include a general description of the plan, with details described in a separate SPDSMP document. All NIAID (DAIDS) supported and/or sponsored clinical trials must have a study progress, data, and safety review at least once a year for as long as participants continue on study follow-up.

Discussions regarding development of the SPDSMP should be initiated with the DAIDS MO and PO as early as possible. The study team must adequately address changes and additions requested by DAIDS. The DAIDS MO assigned to the clinical trial must give final written approval for the SPDSMP before clinical trial initiation.
The SPDSMP may require revisions during the conduct of the trial as issues arise. All revisions to the SPDSMP must be approved in writing by DAIDS.

6.1.1 Regardless of whether located in the protocol or a separate document, key elements of the SPDSMP must include:

6.1.1.1 The designated reviewer(s)/review committee for each type of data report that will be reviewed.

6.1.1.2 The schedule for submission to reviewer(s)/review committees for each type of data report.

6.1.1.3 The types of study progress, data, and safety monitoring reports. Examples of these data reports include:

1. Interim safety reports for DSMB or Study Monitoring Committee (SMC) review

2. Periodic data quality reports for study team review

3. Periodic enrollment reports for independent safety monitor review

6.1.1.4 The parameters to be included in each report type planned, such as, :

Study progress,

Feasibility,

Timeliness and quality of data submission,

Safety,

Futility,

Efficacy, and

Other outcomes, as appropriate.
See the [DAIDS Protocol Documents Manual](#) for details to consider in the planned interim analyses and stopping guidelines sections of the SPDSMP, including interim safety review and interim efficacy.

The [DAIDS Protocol Documents Template](#) provides a template for data and safety monitoring information to include in clinical trial protocol documents. The [Study Progress, Data, and Safety Monitoring Plan Considerations](#) document provides additional information on considerations for development of SPDSMP documents. DAIDS does not require the use of a standard protocol or SPDSMP format.

### 6.2 Types of SPDSMPs

There are four types of SPDSMP review: DSMB, SMC, Study Team Review, and Independent Safety Monitor (ISM). Sections 6.2.1-6.2.4 contain a description of these review types and conditions under which each is used. The choice of the type of SPDSMP will be guided primarily by study phase and must be specified in the SPDSMP. DAIDS will determine which type of safety monitoring is appropriate for the clinical trial based on the characteristics of the trial and the NIH and NIAID DSMB policy requirements. Persons involved in any type of clinical trial review must maintain the confidentiality of the internal discussions, activities and the content of data reports, as well as be free of any real or perceived conflict of interest.

#### 6.2.1 Data and Safety Monitoring Board

A DSMB is an independent group of experts that advises DAIDS and the study investigators on protection of study participants and study conduct. Additional responsibilities include periodically reviewing and evaluating the accumulated study data for safety, quality of trial conduct, progress, feasibility, futility, and, when appropriate, efficacy. Based on these reviews, the DSMB makes recommendations to DAIDS concerning the continuation, modification, or termination of the clinical trial.

All clinical trials monitored by a DSMB must be reviewed by the Board at a minimum of once a year as mandated in the [DAIDS DSMB Charter](#). All annual reviews will include data reports addressing...
study progress, data quality, and safety parameters. The DSMB must continue to review the clinical trial for at least as long as any interventions continue to be compared. The study team or a SMC may assume responsibilities for interim safety monitoring if follow-up continues after all trial comparisons have been terminated.

### 6.2.1.1 DAIDS-appointed DSMBs

DAIDS appoints and supports several standing DSMBs to perform interim review of clinical trials. New clinical trials will be assigned for monitoring to the most appropriate DSMB by DAIDS at the time of protocol review by a DAIDS scientific review committee. On a trial-specific basis, DAIDS may add *ad hoc* members as needed to a standing DSMB in order to address special aspects of the clinical trial.

The list of the DAIDS standing DSMBs (hyperlink) and [DAIDS DSMB Charter](#) may be accessed online. The charter addresses the DSMB’s scope of responsibilities, membership and appointment procedures, meeting planning conduct and data reports, and DSMB recommendations.

### 6.2.1.2 Non-DAIDS appointed DSMBs

The use of a non-DAIDS appointed DSMB must be approved in writing by the DAIDS Director or designee. Non-DAIDS appointed DSMBs must comply with the [NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations](#).

The major components of the data reports for scheduled interim reviews are specified in the SPDSMP. These data reports must be sufficiently detailed to give all the necessary information for review by the committee to assess study progress, feasibility, futility, data quality, safety, and efficacy as appropriate. The overall interim monitoring plan and a template for this monitoring data report should be discussed with the monitoring committee before the first scheduled study review, and preferably before clinical trial initiation. For additional information, see the [NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations](#).
6.2.2 Study Monitoring Committee

A SMC is an independent group of experts that advises DAIDS and the study investigators. The primary responsibility of the SMC is to monitor study progress, data, and participant safety. Typically, a SMC advises DAIDS for clinical trials that do not require DMSB monitoring, but require more than study team review. SMCs are most commonly used for phase II and some Phase I clinical trials. SMCs may be used in conjunction with a DSMB. Roles and responsibilities are similar to those of a DSMB. However, SMCs have fewer members and perform more frequent interim reviews. A SMC must be able to convene on an ad hoc basis when immediate safety concerns arise. Investigators and DAIDS POs and MOs may consider having at least one member of the SMC serve as an ISM. Membership qualifications are fully described in Appendix 1, DAIDS SMC Guidelines. A SMC may also include one or two members of a standing DAIDS DSMB.

Generally, interim reviews for Phase II clinical trials are performed by a DAIDS-approved SMC. However, DSMB review may be more appropriate for some randomized Phase II trials, e.g., clinical trials that are large/multi-center, are blinded, are of particularly high risk or long duration, and/or involve vulnerable populations. Also, reviews by study teams may be acceptable for small Phase II trials in the early stage of study agent evaluation, but this must be specifically approved in writing by DAIDS before trial initiation.

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.

The major components of the data reports for scheduled interim reviews are specified in the SPDSMP. The overall interim monitoring
plan and a template for this monitoring data report should be discussed with the SMC before the first scheduled study review, and preferably before clinical trial initiation. For additional information, see Appendix 1, DAIDS SMC Guidelines.

6.2.3 Study (Protocol) Team Review

For the purpose of this policy, the study team may function as the study progress, data, and safety monitoring entity for Phase I and other small-scale clinical trials. The study team may also consider appointing an ISM. A list of the designated safety reviewers from the study team (sometimes called the Protocol Safety Review Team or PSRT) must be submitted to DAIDS before trial initiation. DAIDS will review this list and may require the addition of an ISM.

Periodic data reports for study team review include administrative, study progress, data quality, and aggregated adverse event frequencies and are reviewed by the study team at a frequency specified in the SPDSMP. The study team should not review unblinded data.

6.2.4 Independent Safety Monitor

The ISM is a physician or other appropriate independent expert who is available to review serious adverse events (SAEs), selected individual participant data, and cumulative safety data in a timely fashion. The ISM recommends appropriate actions regarding safe continuation of the trial to the study team and DAIDS. The ISM should work closely with the DAIDS MO when performing these reviews.

For Phase II and III/IV clinical trials, in addition to DSMB or SMC review, a study team may consider appointing an ISM. DSMBs and/or SMCs may consider designating one or more members to review select SAE cases on a continuous basis and/or more frequently review cumulative data safety reports between the scheduled full committee reviews.

Contents of the periodic data reports for ISM review should be
detailed in the SPDSMP, including whether or not data will be provided by study arm. For additional information, see Appendix 2, for DAIDS ISM Guidelines.

6.2.4.1 Responsibilities for Selection or Designation of ISM

DAIDS may retain the responsibility to identify the ISM. Alternatively, DAIDS may delegate nomination of the ISM to the study 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 study initiation to facilitate this approval. DAIDS must provide written approval for the ISM(s) recommended by the study PI and his/her role, before the clinical trial is initiated.

6.3 Submission of SPDSMP Summary Reports to DAIDS

A written summary of the results of each independent interim study progress, data, and safety monitoring review must be submitted to DAIDS within 30 days after completion of the review. At a minimum, these summary reports will be provided to DAIDS at the frequency of each review as specified in the SPDSMP. For studies where safety monitoring is performed by study teams without an ISM, the study PI is responsible for generating a study progress, data, and safety monitoring summary report at the frequency specified in the SPDSMP (no more than six-months apart), and whenever significant safety issues arise. The PI submits this summary report to the DAIDS MO and PO for review and approval before any further distribution to site investigators, industry collaborators, or regulatory agencies as appropriate.

6.4 Study Reviewer/Committee Summary Report Recommendations

The DAIDS DSMB Charter includes information on distributing DSMB summary reports. DSMB recommendations and subsequent actions that may be taken by the study sponsor are described fully in the DSMB charter.

The DAIDS SMC Guidelines and ISM Guidelines include information on distributing summary reports. Recommendations from SMCs and independent
6.5 Support for SMC and ISM Activities

Financial support for the SMC or ISM activities must be obtained from the clinical trial grant funding, unless another arrangement is reached with NIAID.

6.6 International Clinical Trials and Local Requirement

For international clinical trials, all requirements for study progress, data, and safety monitoring imposed by in-country regulatory and other applicable regulatory authorities must be met by either the study team or clinical site investigators, as appropriate. DAIDS may require submission of a plan for adherence with in-country regulations from the study PI or from the Investigator of Record (IoR) for a clinical site, as applicable.

6.7 Relationship Between Study Progress, Data, and Safety Monitoring Reviews and Institutional Review Boards (IRBs) and/or Ethics Committees (ECs)

6.7.1 Once a study progress, data, and safety monitoring review is established for a clinical trial, each of the relevant IRBs and/or ECs should be informed of the operating procedures with regard to study progress, data, and safety monitoring (i.e., who, what, when, and how safety monitoring will take place). This will provide the IRB/EC the assurance that adequate provisions for monitoring the data collected to ensure participant safety is met, as required under the U.S. Department of Health and Human Services (HHS) and U.S. Food and Drug Administration (FDA) regulations, Criteria for IRB/EC approval of research. If the IRB/EC is not satisfied with these procedures, the study team should work with the IRB/EC to resolve any concerns.

6.7.2 Implementation procedures are provided in the NIH Guidance on Reporting Adverse Events to IRBs for NIH-supported Multicenter Studies.
Clinical Trials. While this policy applies specifically to DSMBs, study teams should consider implementing similar procedures as discussed in this guidance for non-DSMB studies.

6.7.3 When a DAIDS DSMB monitors a clinical trial, DAIDS will distribute a summary report of DSMB reviews to all participating investigators for submission to the reviewing IRBs/EC(s). Distribution of summary reports for SMC and appropriate ISM or study team reviews to site investigators will be the responsibility of the study PI or designee, unless another arrangement is approved in writing by DAIDS.

6.8 Reporting Serious Adverse Events

The US Code of Federal Regulations (CFR) defines procedures and requirements for the monitoring and reporting of serious adverse events (21 CFR 312) and is outside the scope of this policy. DAIDS is responsible for ensuring that NIAID (DAIDS) supported and/or sponsored research is conducted in accordance with the above regulation, other applicable CFRs, and both the FDA and ICH guidance documents. However, DAIDS may delegate these responsibilities, including expedited adverse event (EAE) reporting and submission of annual reports to the FDA and pharmaceutical collaborators, to the IND holder or non-NIAID (DAIDS) sponsor.

See the DAIDS Expedited Adverse Events Reporting Policy and Manual for information on reporting adverse events to DAIDS.

7.0 REFERENCES

HHS regulations for the Protection of Human Subjects at 45 CFR 46

FDA regulations on Institutional Review Boards at 21 CFR 56

FDA regulations on Investigational New Drug Application at 21 CFR 312

FDA regulations on Devices at 21 CFR 800-892

Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

FDA Guidance for Clinical Trial Sponsors, Establishment of Operation of Clinical Trial Data Monitoring Committees
NIH Policy for Data and Safety Monitoring

NIH Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials

NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multicenter Clinical Trials

NIAID Clinical Terms of Award

NIAID Policy for Identifying Potential Conflict of Interest for Individuals Serving on Advisory Committees or Independent Safety Monitors Responsible for Data and Safety Monitoring of Clinical Trials

NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations

Charter for the Data and Safety Monitoring Boards of the Division of AIDS National Institute of Allergy and Infectious Diseases

DAIDS Policy Expedited Adverse Events Reporting

Manual for Expedited Reporting of Adverse Events to DAIDS

DAIDS Policy Requirements for On-Site Monitoring

DAIDS Protocol Documents Manual

DAIDS Protocol Documents Template

8.0 INQUIRIES

Questions and comments regarding this SOP may be directed to the OPCRO Policy Group.

9.0 AVAILABILITY

This policy is available electronically on the Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures webpage.

10.0 APPENDICES AND RELATED DOCUMENTS

Appendix 1 - DAIDS SMC Guidelines

Appendix 2 - DAIDS ISM Guidelines
Study Progress, Data, and Safety Monitoring Plan Considerations

11.0 APPROVAL