DMID SAFETY INFORMATION SHEET

Regulatory requirements including the Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), and European Union (EU) Clinical Trials Directive set forth safety monitoring and reporting responsibilities of sponsors and investigators to ensure the safety and protection of human subjects participating in clinical trials. NIH also requires safety monitoring of clinical trials. DMID utilizes Safety Oversight Committees and SAE reporting to monitor subject safety in DMID supported clinical trials.

Safety Oversight Structures

Committees

NIAID requires **Data and Safety Monitoring Board (DSMB)** oversight for, at a minimum, all randomized clinical trials of any phase that involve both investigator-masked interventions and enrollment of greater than 100 subjects.

DSMB refers to a committee of experts, independent of the trial investigators, pharmaceutical sponsor (if any), and funding agency, that periodically reviews the conduct and results of the clinical trial and recommends continuation without change, continuation with change, or termination of the trial.

DMID utilizes another type of committee, a **Safety Monitoring Committee (SMC)**, which is an independent group of experts that advises DMID and the study investigators for many Phase I and smaller Phase II trials.

The DSMB or SMC is convened by authority of the DMID and is advisory to DMID and the study team.

The DSMB/SMC consists of at least three voting Members. A DSMB will include a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise; although not required, a biostatistician may also be included in the SMC.

Individuals who are directly involved in the conduct of the clinical trial will not be Members. Members will not be under the supervision of any of the investigators involved in the conduct of the clinical trial.

Membership in DMID DSMBs and SMCs is strictly voluntary as these positions do not receive compensation.

Safety Charters

The DSMB/SMC Charter serves as the Standard Operating Procedure and defines the primary responsibilities of the DSMB/SMC, its membership, the purpose and timing of its meetings, reports and data to be reviewed, and procedures for ensuring confidentiality and proper communication.

Independent Safety Monitors

DMID also utilizes Independent Safety Monitors (ISMs) at each clinical trial site to assist in safety oversight.

An ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in real time. The ISM should have immediate access to the subjects and the subject's medical and research records.

If a clinical trial meets certain criteria, a waiver of the ISM requirement may be requested.

DMID-CROMS Safety Oversight Committee Support

The Safety Oversight Committee Support (SOCS) group is the DMID-Clinical Research Operations and Management Support (CROMS) contractor that facilitates DSMB/SMC meetings and related activities. SOCS serves as the executive secretary for the DSMB/SMC and supports the DSMB/SMC Chair with meeting conduct and documentation.

Safety Oversight Roles and Responsibilities

Investigators

- Protocol Principal Investigator (PI) participates in the Open session of meetings by providing overview/status of the study and responds to questions from Committee Members regarding study design and implementation.
- Site investigator participates in the Open session of meetings by providing information regarding specific safety events under review and responds to questions from committee members.
- Contract PI may attend the Open session of meetings to provide oversight for site investigator.
- Must not communicate with the DSMB/SMC directly. Communicate with DMID Medical Monitor (MM) and Clinical Project Manager (CPM). Communications with the DSMB/SMC are sent from DMID through the contractor (SOCS).
- Receive meeting notifications, access to Open session report on secure website, DSMB/SMC recommendations and minutes, and charter from SOCS.
- Submit DSMB/SMC recommendations to the Institutional Review Board (IRB) as required
- Other site personnel may attend the Open session with the investigator but will not have access to the secure website or be on the distribution list as they do not have a role in the meetings. Recommendations and the charter will be made available with other study documents as designated.
- Identifies ISM for the investigator's site that meets the NIAID conflict of interest (COI) policy requirements.

Independent Safety Monitor

- Receives reports of serious adverse events (SAEs) by email when DMID is notified of the event.
- Communicates with the investigator at the participating site as needed.
- Evaluates the SAE and reports the clinical assessment to DMID, through DMID-CROMS SOCS, in writing in a timely manner.
- Reviews additional safety-related events at the request of DMID.
- Provides additional information to DMID and/or the DSMB/SMC by teleconference as requested.

Medical Monitor

- Monitors safety and prompts review by committee when indicated, such as halting rule requiring ad hoc meeting.
- Consults with investigator, ISM, or committee chair as needed for assessment of safety events.
- Reviews and approves the DSMB/SMC Charter.
- Determines the purpose for each meeting and ensures appropriate review materials are prepared for the DSMB/SMC for each meeting.
- Reviews and approves Open session reports intended for all meeting participants.
- Participates in Open sessions of meetings as DMID representative.
- Reviews the DSMB/SMC Recommendations and recommend actions for implementation by the study team, as applicable.
- Reviews and approves Open session meeting summaries.

For Ad Hoc Meetings, in collaboration with the CPM:

- Recommends required attendees.
- Identifies date for meeting at time when safety data will be available for review.
- Ensures safety data and MM report to Committee for review is approved and provided to SOCS to be posted/distributed to committee.
- Provides list of questions for Committee consideration.

DMID-CROMS Safety Oversight Committee Support group

- Serves as executive secretary.
- Communicates with members, DMID Office of Clinical Research Affairs (OCRA) Safety, CPM, MM, data collection entities (DCEs), Investigators, ISMs, and Pharmacovigilance

(PVG). (NOTE: does not communicate directly with other site/study personnel).

- Facilitates communications between DMID/study team and Committee members.
- Assists with Committee start-up activities.
- Facilitates meetings and electronic reviews.
- Drafts and distributes Committee documents.
- Facilitates access and posts meeting materials to the DMID-CROMS secure website.

Serious Adverse Event Reporting

DMID relies on investigative sites to provide accurate and thorough initial assessments of adverse events (AEs) and follow-up secondary to initial reports of these events. DMID has centralized SAE reporting through its CROMS contract. Criteria and reporting procedures are detailed in the clinical protocol. For Investigational New Drug Application (IND)/Investigational Device Exemption (IDE) studies, all reporting must comply with 21 CFR 312 and 812.50. Studies conducted outside of the U.S. must also comply with any local regulations.

The PVG group is the DMID-CROMS contractor that receives and processes SAE reports.

SAE Reporting Roles and Responsibilities

Investigator

- Identify and report SAEs to DMID.
- Notify the ISM of SAEs.
- Provide assessment if SAE was related or not related to study product and update the assessment if needed when additional information becomes available.
- Provide additional information on SAE to DMID upon request.
- Submit SAE and MedWatch reports to IRB as required.
- Assess if the SAE met protocol dose escalation or halting criteria.

Independent Safety Monitor

- Evaluates SAEs and provides assessment to DMID through SOCS.
- May recommend an ad hoc meeting of the DSMB/SMC.

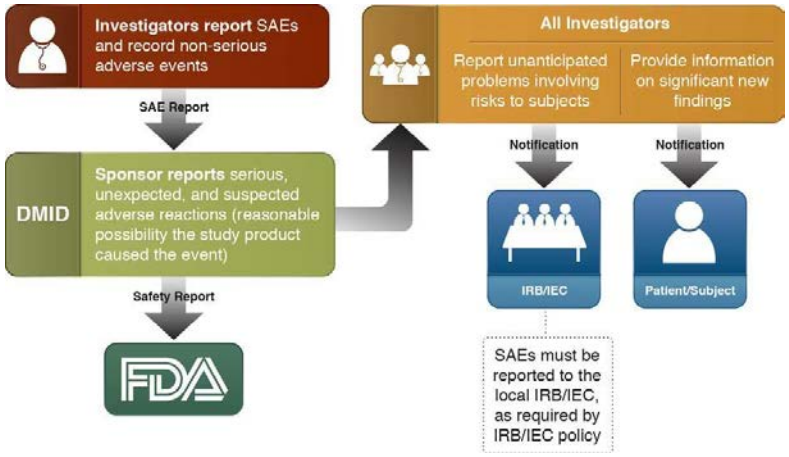
Medical Monitor

- Promptly reviews SAE notifications and SAE reports received from PVG.
- Assess SAEs regarding halting rules and whether requires MedWatch report (for DMID held IND studies only).
- Consults with investigator and ISM as needed to assess SAEs.
- Responsible for DMID assessment and content of MedWatch report.
- Notifies OCRA Director, OCRA Safety, and CPM of SAE that may meet halting rules, may require ad hoc SMC/DSMB review, or may require MedWatch report as required.

DMID-CROMS Pharmacovigilance Group

- Maintains DMID central safety database.
- Processes SAE reports and prepares narratives.
- Notifies DMID and SOCS of SAE reports.
- PVG Medical Monitor assesses SAEs.
- Gathers information requested by DMID from investigator.
- Prepares IND safety reports (MedWatch) for regulatory submission.
- Distributes IND safety reports to DMID and investigators.

Overview of SAE Reporting flow



DEFINITIONS

CHARTER

The Committee Charter serves as the Standard Operating Procedure and defines the primary responsibilities of the DSMB/SMC, its membership, the purpose and timing of its meetings, data to be reviewed, and procedures for ensuring confidentiality and proper communication. The Charter is drafted based on the final protocol and is finalized upon the review and approval by the DSMB/SMC during the Organizational meeting. The Charter is updated when the protocol is amended regarding safety oversight and/or when the DSMB/SMC requests an additional safety related activity. Revisions to the Charter will be reviewed and approved by the DSMB/SMC and DMID. The Charter cannot override the protocol.

CLINICAL PROJECT MANAGER (CPM)

The Program Staff responsible for the planning, coordination and management of DMID-supported clinical research studies and clinical trials.

CLOSED REPORT

The Closed session report will be posted to the DMID-CROMS Document Library, but will be accessible to DSMB/SMC Members only and will only be discussed during the Closed session. The Closed session report may include data that could reveal treatment assignments for individuals or groups, otherwise described as unblinded data, for review by Members only. This Closed session report is not reviewed and approved by the DMID CPM and MM prior to posting.

DATA COLLECTION ENTITY (DCE)

The entity responsible for clinical trial data collection. In large multi-centered studies, this is separate from other study personnel.

DATA COORDINATING CENTER (DCC)

A non-governmental organization funded by the NIAID which receives, reviews, and performs data management tasks on the Human Subject Case Report Forms completed for the clinical trial. Also, may be referred to as the Data Collection Entity (DCE).

MEDICAL MONITOR (MM)

Physician responsible for monitoring the safety of participants in DMID-supported clinical research.

MEDICAL OFFICER (MO)

Physician primarily responsible for protocol development, inclusion/exclusion criteria, and eligibility questions.

OCRA SAFETY

Group within Office of Clinical Research Affairs (OCRA) responsible for providing oversight of the safety of human subjects participating in DMID-sponsored clinical research, through a centralized pharmacovigilance and safety monitoring program. On the DMID-CROMS contract, OCRA Safety is also responsible for providing direction to SOCS and PVG staff for DSMB/SMC-related activities.

OPEN REPORT

The Open session report (previously referred to as the blinded report) will generally consist of

aggregate data only and be available for review by all meeting participants during the Open session of the meeting. The Open session report will describe the design and progress of the study, including data regarding recruitment and baseline characteristics, and pooled data regarding adverse events, eligibility violations, completeness of follow-up, and compliance.

References

- NIAID DSMB policy and FDA Guidance on Establishment and Operation of Clinical Trial Data Monitoring Committees
- 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 DSMB training module
- DMID Safety Oversight
- EMA Guideline on Requirements for first-in-man clinical trials for potential high-risk medicinal products
  - Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (10 November 2016)
  - Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (19 July 2007)

Questions: Contact your DMID protocol-specific Point of Contact or email the DMID Office of Clinical Research Affairs, OCRA Help.