1. PURPOSE

1.1 This policy describes the safety oversight and reporting requirements for clinical trials conducted under an Investigational New Drug or Investigational Device Exemption (IND/IDE) held by Division of Microbiology and Infectious Diseases (DMID).

1.1.1 The Policy for general safety oversight and reporting is described in DMID-SF-POL-00001.

1.1.2 The Policy for independent data and safety oversight is described in DMID-SF-POL-00002.

2. SCOPE

2.1 This document applies to all clinical trials conducted under an Investigational New Drug or IND/IDE held by DMID.

3. DEFINITIONS

For other definitions, see DMID glossary.

4. RESPONSIBILITIES

4.1 Responsibilities are delineated in the policy.

5. PROCEDURE

5.1 While safety oversight is a joint responsibility of DMID, the investigator(s), the investigational product manufacturer, and any safety oversight committee, DMID as the trial Sponsor is ultimately responsible for safety oversight and regulatory reporting.

- DMID may delegate safety oversight and reporting to a vendor (e.g., contractor or grantee).

5.2 Safety oversight activities should be commensurate with the nature, size, and complexity of the trial and the risk to the study participant from the investigational product and study activities.

5.3 A description of safety oversight and reporting must be provided in the clinical protocol.

5.3.1 The protocol must address roles and responsibilities in safety oversight and reporting to the Institutional Review Board(s)/Ethics Committees (IRB/EC), regulatory authorities, and DMID.

5.3.2 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE) cannot be changed from the standard language found in the DMID protocol template.

- Adverse events include not only symptoms, but also laboratory findings and vital signs.
- Clinical trial protocols in populations with underlying diseases (e.g. those hospitalized with COVID-19) may be written to exclude some grades or relatedness of AEs and SAEs from being collected in the database if similar findings are encountered in the underlying disease.
- Controlled human infection (challenge) trials may be written to exclude symptoms associated with the infection from being collected in the database.

5.4 Toxicity Grading Scale

5.4.1 Clinical trial protocols for adults must use a published and commonly used toxicity grading scale (e.g., FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials). Pediatric trials must use a commonly used toxicity grading scale if available for the population.

- The toxicity table must reflect the population being studied (i.e. healthy vs. sick population).
- A protocol must use one toxicity table for all populations in the trial where comparisons between populations is likely to occur (prespecified or implied).
- Modifications of the toxicity grading scale are not permitted.
  - If there are areas of overlap between a site normal range and the toxicity table, the protocol may specify that these are not to be captured as AEs.
  - Gaps from the site normal range to grade 1 on the toxicity table are not adverse events.
- The toxicity table including versions must not change during the trial.
- If there are events expected during a trial that are not listed in the toxicity scale, the protocol may develop grading criteria/table to be used in addition to the standard toxicity table.

5.5 Safety monitoring

5.5.1 A DMID Medical Monitor (MM) must review any SAE individual case safety reports (ICSR) that are reported, and will determine if it is a serious unexpected suspected adverse reaction (SUSAR) and meets regulatory reporting criteria.

5.5.2 The DMID MM must review other events such as Adverse Event of Special Interest (AESI), Medically Attended Adverse Event (MAAE), and will determine if they meet reporting criteria.

5.5.3 There must be periodic and regular review of study safety data, distinct from any independent data and safety monitoring or other committees.

5.6 Regulatory reporting

5.6.1 DMID is responsible for safety reporting to regulatory authorities for DMID held IND/IDE studies.

- DMID and a product manufacturer may decide to report safety information in a Development Safety Update Report (DSUR) from the manufacturer rather than have the safety information submitted to the FDA by DMID.

5.7 Independent data and safety oversight

5.7.1 The type of independent data and safety oversight in a trial will follow DMID-SF-POL-00002.

5.7.2 If an independent data and safety oversight committee is used, the protocol must contain:

- The type of safety oversight committee.
- The committee's responsibilities for reviewing trial and safety data.
- The frequency of review - based on time, protocol milestones, and/or events.
- A high-level description of the data to be provided to the committee for review.

5.7.3 DMID staff must propose members for the independent data and safety oversight committees.

5.7.4 DMID staff may not be members of the independent data and safety oversight committee for DMID held IND trials.
- Staff from other NIAID divisions may be members of SMCs.
- NIAID employees or contractors may not serve as voting DSMB members (per NIAID policy) but may serve as the unblinded study statisticians as needed.

5.7.5 Independent data and safety oversight committee members must disclose conflicts of interest (COI) and provide curriculum vitae. The OCRA Director or designee will evaluate any COI disclosed and determine whether a COI exists. COI forms and CVs of members must be stored.

5.7.6 The meetings must be documented in the form of minutes and include meeting participants, data reviewed, and a summary of the review with recommendations.

5.7.7 The meeting minutes, data reviewed, and recommendations must be stored in the CROMS committee management system, document library or TMF.

5.7.8 All meeting summaries must be distributed to the site investigators.

5.7.9 Independent safety oversight committees are advisory to DMID. While the committee recommendations are generally followed, DMID may deviate from the recommendations. If recommendations are not followed, an explanation must be sent to the committee with a copy to the Director of OCRA.

5.8 Protocol Safety Review Team (PSRT)

PSRTs are advisory groups internal to a specific protocol that may be used when a protocol has a decision step based on safety data or other factors that require team input and deliberation.
- *Note - the term Safety Review Committee (SRC) may be used to describe this group, but this term is less preferred as it may be conflated with Safety Monitoring Committee (SMC).*

5.8.1 If a PSRT is used, the protocol must contain the following:
- The responsibilities for PSRT members in reviewing trial safety data.
- The frequency of review - based on time, protocol milestones, and/or events.
- A high-level description of the data to be reviewed.

5.8.2 DMID staff can be members of the PSRTs, as can staff from other divisions.

5.8.3 PSRT members are not required to disclose COI or provide CV.

5.8.4 The PSRT reviews must be documented, and must include:
- PSRT members.
- The safety data reviewed (e.g. pdfs or other record of the data reviewed).
- The summary and the decision of the review and impact on protocol execution.

5.8.5 The PSRT meeting summary, conclusions, and data reviewed must be stored in the CROMS Committee Management System, document library, or TMF.

5.8.6 The outcome of the review must be communicated to the investigators.

6. REFERENCES

6.1 FDA Guidance: Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies, June 2021 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sponsor-responsibilities-safety-reporting-requirements-and-safety-assessment-ind-and

6.2 FDA Guidance: Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices, September 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-safety-reporting-investigational-drugs-and-devices

6.3 21 CFR 312.64 and 312.32.

7. APPENDICES

Not applicable

8. REVISION HISTORY

8.1 DMID-SF-POL-00003 revision 01 is the original version of this procedure within the eQMS.

9. ADDITIONAL INFORMATION

9.1 Document Lead: OCRA Director

9.2 Posting externally: Yes