1. PURPOSE

1.1 The purpose of this Policy (POL) is to describe the requirements for independent data and safety monitoring for DMID clinical research to ensure the protection of participants and compliance with NIH and NIAID policies. This is inclusive of Data and Safety Monitoring Boards (DSMB), Safety Monitoring Committees (SMC), and Independent Safety Monitors (ISM).

1.1.1 This policy is in addition to the policy for general safety oversight - as described in policy DMID-SF-POL-00001.

2. SCOPE

2.1 This document applies to all clinical research funded by NIAID DMID.

3. DEFINITIONS

3.1 Clinical Trials – NIH's Definition of a Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

For additional definitions, see DMID glossary.

4. RESPONSIBILITIES

4.1 As defined under Policy.

5. POLICY

5.1 Policy and Regulatory Considerations:

5.1.1 The *NIH Policy for Data and Safety Monitoring*" (1998) requires data and safety monitoring for all NIH supported clinical trials to ensure the safety of participants and the validity and integrity of the data. The NIH policy notes that data and safety oversight may be conducted in various ways and by various individuals or groups depending on study nature, size, and scope, and lies on a continuum. Specifically, institute divisions may utilize the principal investigator, program staff, an ISM, a SMC, a DSMB, or more than one of these for the same trial.

5.1.2 The *NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations* specifies requirements for DSMBs for certain types of clinical trials that apply across NIAID divisions but defers other safety monitoring structures and decision to the division policies.

5.1.3 The US FDA's *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees* notes "All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors, and investigators."

5.1.4 Additionally, federal regulations require "establishment of an independent data monitoring committee to exercise oversight of the clinical investigation" for research studies in emergency settings in which the informed consent requirement is excepted [21 CFR 50.24(a)(7)(iv)].

5.2 Decision making authority:

5.2.1 Activities that are funded by grants including cooperative agreements must comply with the NIH Grants Policy Statement (NIHGPS), the NIAID Clinical Terms of Award, and any terms and conditions in the Notice of Award (NoA).

5.2.2 Activities that are funded by contracts must comply with the contract statement of work (SOW), the NIAID Clinical Terms of Award, and any other conditions specified in the award/contract.

5.2.3 All funding from the NIH require compliance with NIH policies including the NIH Policy for Data and Safety Monitoring

5.2.4 In the event the policy below contradicts the terms of the grant or contract, the grant or contract will take precedence.

5.3 The type of trial and funding mechanism determines who is responsible for deciding the need and type of independent data and safety monitoring (see matrix below) while adhering to the absolute requirements noted in this policy (Section 5.4).

IND/IDE Clinical Trials

Type of Trial	**Grant**	**Cooperative Agreement**	**Contract**
IND/IDE held by DMID	See 5.3.1	See 5.3.1	See 5.3.1
IND/IDE held by another entity	See 5.3.2	See 5.3.2	See 5.3.3

Non-IND/IDE Clinical Trials and Clinical Studies

Type of Trial/Study	**Grant**	**Cooperative Agreement**	**Contract**
Clinical Trial: High Resource	See 5.3.4	See 5.3.4	See 5.3.5
Clinical Trial: Low Resource	See 5.3.4	See 5.3.4	See 5.3.5
Clinical Study (not a trial): Higher Risk Procedure	See 5.3.6	See 5.3.6	See 5.3.7
Clinical Study (not a trial): Not High Risk	See 5.3.8	See 5.3.8	See 5.3.8

5.3.1 For an IND (or equivalent) clinical trial where the IND holder is DMID, regardless of the type of funding, the DMID protocol team will determine the need and type of independent data and safety monitoring. Any disagreement on the independent safety oversight plan should be brought to the Director of OCRA who will determine the independent safety oversight to be used in the trial.

5.3.2 For an IND (or equivalent) clinical trial funded by grant or cooperative agreement where the IND holder is not DMID, the sponsor will determine the need and type of independent data and safety monitoring. Per NIAID clinical terms of award, final decisions regarding the type of independent monitoring to be used must be made jointly by NIAID and the awardee before enrollment starts.

5.3.3 For an IND (or equivalent) clinical trial funded by contract where the IND holder is not DMID, the sponsor will propose the need and type of independent data and safety monitoring. DMID must confirm the proposed plans for data and safety monitoring used in a trial. The COR will convey any independent data and safety monitoring that must be incorporated by the contractor.

5.3.4 For a non-IND clinical trial funded by grant or cooperative agreement, the grantee will propose the need and type of independent data and safety monitoring. Per NIAID clinical terms of award, final decisions regarding the type of independent monitoring to be used must be made jointly by NIAID and the awardee before enrollment starts.

5.3.5 For a non-IND clinical trial funded by contract, the DMID protocol team will determine the need and type of independent data and safety monitoring, which will be conveyed to the contractor by the DMID COR.

5.3.6 For a clinical study (not a clinical trial) that includes a higher risk procedure funded by grant or cooperative agreement, the grantee will propose the need and type of independent data and safety monitoring.

5.3.7 For a clinical study (not a clinical trial) that includes a higher risk procedure funded by contract, DMID will determine the need and type of independent data and safety monitoring which will be conveyed to the contractor by the DMID Contracting Officer Representative (COR).

5.3.8 For a clinical study (not a clinical trial) that is not high risk, independent data and safety monitoring is generally not needed.

5.4 DMID policy:

5.4.1 Safety oversight is primarily the function of the investigators and sponsor (if applicable) as detailed in DMID-SF-POL-00001.

5.4.2 DMID requires independent data and safety monitoring for the following:

- Any efficacy trial with a blinded intervention in children or other populations that may be viewed as potentially vulnerable.
- Any efficacy trial with a blinded intervention in a hospitalized population or a population with a control mortality exceeding 1% during the time of the trial.

- Adaptive trials where interim data is used for prespecified protocol modifications (e.g. dropping study arms, changing sample size, moving from phase 1 to phase 2, etc.).

DMID requires a DSMB for the following:

- Any efficacy trial with an interim efficacy analysis.
- Any efficacy trial with an interim statistical futility analysis.
  - Programmatic decisions about futility (i.e. a trial cannot be done because incidence is too low, the trial will take too long, etc.) do not require independent safety oversight committee input.
- Any randomized investigator-masked efficacy clinical trial that has a planned enrollment of greater than 100 participants, and in which one or more products that are used are under an US FDA Investigational New Drug (IND)/ Investigational Device Exemption (IDE) application (or foreign equivalent).*
- Any randomized efficacy clinical trial with a planned enrollment of greater than 200 participants.*
- Any phase 3 (or otherwise considered pivotal) clinical trial.*
- Any clinical research where informed consent is not obtained as a result of the severity and urgency of the subject's medical condition (as detailed in 21 CFR 50.24(a)(7)(iv).**

Note:

** These criteria are per the NIAID DSMB policy. The NIAID policy delineates a process to seek exemption from this policy, which involves approval in NIAID above division approvals.*

*** This criteria is federal law and there are no exemptions.*

5.4.3 Unless specific requirements are noted above in 5.4.2, the type of oversight (DSMB, SMC, or ISM) is determined by the party and process noted in 5.3.

5.5 Considerations (not policy statements, but added to the policy to help areas of interpretation and judgement):

5.5.1 Determining the need for an independent data and safety monitoring:

- Independent safety and data monitoring is needed when the factors about the trial design, investigational product, and study population preclude adequate data and safety monitoring by the investigators and sponsor (if applicable), or when more objective independent monitoring will enhance the protection of human participants and/or the validity and integrity of the data.
- Clinical studies that are not trials and clinical trials that do not meet the conditions above often do not need independent data and safety monitoring. Studies that have a higher risk procedure may benefit from an independent oversight, especially for safety assessments.
  - There are other unique circumstances where independent data and safety monitoring may be seen as added value, and this policy does not restrict the use of such committees.
- Independent data and safety monitoring is not needed for most phase 1 trials. The investigator(s), protocol teams (if applicable), and sponsor can adequately ensure the safety

of participants in these trials. The data and safety monitoring plan in the protocol or separate document (including the use of robust halting rules) must detail the data and safety monitoring that will be performed by the investigator, protocol teams (if applicable), and sponsor.

- Independent data and safety oversight may be needed for clinical research studies (not trials) that include higher risk procedures. This can often be accomplished by an ISM and larger committees may not be needed.
- Factors that increase the need for independent safety oversight include (there is no one factor, but as the number of factors increase, there should be more consideration given to independent data and safety monitoring):
  - Blinded trials (where attribution of adverse events to a study intervention is obscured).
  - Situations where toxicities from the intervention may be seen in the population being studied (e.g. renal failure from a drug used in a hospitalized population already at risk of renal failure given the severity of underlying disease).
  - Situations where a trial with a highly favorable or unfavorable result at an interim analysis might ethically require termination of the study before its planned completion.
  - Trials performed in a population such as children, elderly in environments such as nursing homes, those who are terminally ill, or those with diminished mental capacity.
  - Trials being performed in a population with an elevated risk of death or other serious outcomes, where poor outcomes due to the intervention may be harder to detect.

5.5.2 Independent safety and data oversight structures include DSMB, SMC, and ISM. Other names may be used (as decided by the party in 5.3), but for DMID sponsored trials, the above terms will be used.

- The DSMB and SMCs independent group of experts that periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and make recommendations concerning the continuation, modification, or termination of the trial.
  - DSMBs differ from SMCs in that DSMBs have more stringent vetting of potential conflict of interest as well as a statistician as a member.
- DSMBs are not needed if the requirement is primarily safety oversight.
- DSMBs should be used instead of SMC when objectivity is paramount.
- DSMBs should be used when interpretation of interim findings may benefit from an objective statistician, i.e., trials with an interim efficacy analysis where the trial may be stopped early for efficacy.
- An ISM is a qualified clinician with relevant expertise whose primary responsibility is to provide independent safety monitoring.
  - ISM may be used when the oversight of one objective person is deemed sufficient.

5.5.3 If an independent safety and data oversight is needed, the following matrix delineates the organizer of the committee:

IND/IDE Clinical Trials

Type of Trial	Grant	Cooperative Agreement	Contract
IND/IDE held by DMID	DMID organizes	DMID organizes	DMID organizes
IND/IDE held by another entity	Sponsor organizes	Sponsor organizes	Sponsor organizes

Non-IND/IDE Clinical Trials and Clinical Studies

Type of Trial/Study	Grant	Cooperative Agreement	Contract
Clinical Trial: High Resource	Grantee organizes	Grantee organizes	DMID organizes
Clinical Trial: Low Resource	Grantee organizes	Grantee organizes	DMID organizes
Clinical Study (not a trial): Higher Risk Procedure	N/A	N/A	N/A
Clinical Study (not a trial): Not High Risk	N/A	N/A	N/A

- In unique circumstance, DMID may agree to organize oversight committees for investigators/grantees, other sponsors, and other institutions, but requires approval by the Director of OCRA.

6. REFERENCES

6.1 NIH Policy for Data and Safety Monitoring

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

6.3 FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees

6.4 NIAID Clinical Terms of Award

7. APPENDICES

Not applicable

8. REVISION HISTORY

8.1 DMID-SF-POL-00002 rev 01, Rewritten when included in the eQMS. Prior Policy: DMID Policy-010 - NCRS 1.2 v 2.0

8.2 DMID-SF-POL-00002 rev 02, Updated to reflect revised NIAID DSMB policy (v6), and formatting of tables for Section 508 compliance.

9. ADDITIONAL INFORMATION

9.1 Document Lead: OCRA Director

9.2 Posting externally: Yes