National Institute of Allergy and Infectious Diseases NIAID Bethesda, MD USA	**POLICY**	Version No: 6 Date: 27June2024 Page 1 of 11
	Release Date: 27June2024 Effective Date: 27June2024	

Title: NIAID POLICY ON DATA AND SAFETY MONITORING BOARD (DSMB) OPERATIONS

APPROVAL	**Approving Entity**	**Date**
Approval Mechanism:	NIAID Division Directors	27June2024

1.0 PURPOSE

This policy establishes requirements for the operations of Data and Safety Monitoring Boards (DSMBs) utilized to monitor NIAID supported trials.

2.0 BACKGROUND

The "NIH Policy for Data and Safety Monitoring" (1998)[1] 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 size and scope and lies on a continuum. Specifically, NIAID Divisions may utilize the principal investigator, NIAID Program Staff, an independent safety monitor (ISM), a safety monitoring committee (SMC), a data and safety monitoring board (DSMB) or more than one of these for the same trial.

Additionally, federal regulations require an "independent data monitoring committee for research studies in emergency settings in which the informed consent requirement is excepted [21 CFR 50.24(a)(7)(iv)][2].

NIAID Divisions each established policies, procedures, and guidelines to implement and comply with the policy and with NIH's "Further Guidance on Data and Safety Monitoring for Phase I And Phase II Trials" (2000)[3]. Although some program variances may be appropriate/necessary, this NIAID policy specifies a minimum requirement for DSMBs that are mandatory across the Institute. Divisions may have policies/SOPS that require a DSMB for studies not specified in this document. There is not a central DSMB for NIAID.

This policy addresses only committee structures that are classified as "Data and Safety Monitoring Boards". Divisions should establish a policy or SOP for other safety monitoring methods.

3.0 DEFINITIONS

3.1 Data and Safety Monitoring Board (DSMB)

"Data and safety monitoring board" 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 trial and recommends continuation without change, continuation with change, or termination of the trial.

4.0 POLICY

4.1 Trials Requiring a DSMB

NIAID operationalizes the NIH Data and Safety Monitoring policy and guidance by requiring DSMB oversight for, at a minimum, any of the following:

- 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).

Additional factors that must be considered for designating other trials for DSMB oversight are long duration, complex design, high-risk interventions (e.g. gene therapy), vulnerable populations, and significant public health impact or high public interest and concern. Each Division will have policies/SOPs that describe types of trials requiring a DSMB, as well as DSMB membership and operations. The FDA "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees"[4] and revision (currently in draft)[5] may be relevant in how divisions determine the need for DSMB oversight.

All divisions must use a DSMB for new studies that meet the above criteria. Existing studies (or studies beginning before June 27, 2024 (6 months after the amended policy)) that use Safety Monitoring Committees (SMC) with statisticians may be considered as fulfilling the requirements of this policy.

4.2 Convener of the DSMB

- For trials where NIAID is the regulatory sponsor (or otherwise responsible for the oversight and implementation of a trial), NIAID will convene the DSMB (which may be delegated to contractors and grantees).
- For NIAID funded trials where the sponsor is not NIAID, the sponsor generally organizes the DSMB. As funder, NIAID retains the right to organize the DSMB for the trial instead of the sponsor.
- In certain circumstances, and with concurrence of the corresponding NIAID Division Director, NIAID may organize the DSMB for another IC or agency even if NIAID is not involved in funding or conducting the trial.
- DSMB convening arrangements other than those above may be permitted if covered by the division policies/SOP and agreed to by both the NIAID Division Director and the NIAID Deputy Director for Clinical Research and Special Projects.

4.3 DSMB Reporting

- For trials where NIAID is the regulatory sponsor (or otherwise responsible for the oversight and implementation of a trial) the DSMB recommendations will be reported to NIAID. Major recommendations (e.g. stopping a trial) will first be reported to NIAID leadership (as specified in the division SOP) for approval or rejection. NIAID may consult with the trial leadership and/or relevant staff before making the final decision regarding the recommendations. DSMBs are advisory to the IND/regulatory sponsor (and NIAID if not the sponsor). While the committee recommendations are generally followed, NIAID may choose to deviate from the recommendations. If recommendations are not followed an explanation must be sent to the DSMB with

appropriate rationale.

- Where NIAID is not the sponsor, and the sponsor organizes the DSMB, recommendations are reported to the sponsor and must be shared with NIAID (the process of submission will be outlined in division procedural documents).
- Where NIAID is not the sponsor, and NIAID organizes the DSMB, the DSMB recommendations will be reported to both the sponsor and NIAID. In this case, major recommendations (e.g. stopping a trial) will be reported to both the sponsor and NIAID leadership for approval or rejection.

The final approved DSMB recommendations must be distributed to Site investigators, Institutional Review Boards (IRBs)/Ethics Committees (ECs) of record, and any regulatory authorities as applicable[7].

5.0 RESPONSIBILITIES

5.1 Policy Dissemination and Compliance

Division Directors are responsible for the dissemination of this policy to all staff and outside collaborators, if applicable, involved in DSMB oversight and operations. Division Directors must also have designated staff and procedures in place within their Divisions to ensure compliance with this policy.

5.2 Policy Revisions /Update

The Division of Clinical Research (DCR), in coordination with the NIAID Clinical Research Subcommittee (NCRS), will be responsible to review and propose revisions to this policy as needed based on new/revised NIH policy or federal regulations. Section 12 of this policy establishes the frequency for mandatory review intervals. The NIAID Executive Committee or Division Directors must approve any revisions to this policy for them to take effect.

5.3 Policy Exceptions

The NIAID Division Director and the NIAID Deputy Director for Clinical Research and Special Projects must approve any exceptions to this policy.

6.0 OPERATIONS

6.1 DSMB Charter

Each DSMB must operate according to the provisions of a formal charter, agreed to in advance by NIAID and DSMB members and provided to study leadership. Charters should address appointment and responsibilities of members, roles, and responsibilities of NIAID staff and contractors, unrestricted DSMB access to and management of unblinded trial data, terms of appointment, scheduling and format of meetings**,** quorum requirements, distribution and disposition of meeting materials, preparation of meeting summaries and written recommendations, management of conflict of interest, voting rights, and other procedural

matters.

6.2 DSMB Membership

DSMBs must consist of at least three voting members including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise and that are independent from the protocol. Representatives of other clinical or laboratory specialties, bioethics, and the affected community are often critically important. Selection of DSMB members should include consideration of clinical trials experience, relevant expertise, prior DSMB service and absence of significant conflict of interest.

For assessing potential conflicts of interest (COI) for DSMBs that NIAID establishes, refer to the "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" [6].

NIAID employees or contractors may not serve as voting DSMB members (NIAID employees or contractors may serve as the unblinded study statisticians and/or executive secretary as needed). Each Division should have policies and/or procedures regarding the appointment of DSMB members. DSMB membership should reflect NIAID's commitment to diversity.

6.3 DSMB Review Procedures

DSMB members must review the protocol(s), charter(s), and other pertinent documents related to DSMB oversight of the trial(s). The DSMB must understand prior to its first data review and preferably prior to protocol enrollment how the investigators intend to approach: (1) timing and conditions for data reviews; and (2) possible early stopping for safety, futility, efficacy, and/or ethical reasons. DSMB members must have the opportunity to discuss any significant concerns with NIAID and protocol team leadership.

In addition, NIAID staff must inform the DSMB that it is the DSMB's responsibility and prerogative to review unblinded data to render any safety, planned efficacy, and planned futility recommendations. The DSMB may decide to defer unblinding while interim results permit that. However, the mechanics for immediate unblinding must be clearly established before the DSMB reviews any grouped data. The DSMB may access any available trial data needed to carry out its primary responsibilities.

DSMB meetings generally include three types of sessions: (1) open; (2) closed; (3) closed executive.

(1) Open Session

The focus of the open session is on the general conduct and progress of the study. If any safety or efficacy data are presented during this session, the blinding, if present, must be preserved. In addition to DSMB members, this session may be attended by the protocol team, coordinating/data center staff, NIAID staff, collaborators, and representatives from other government agencies.

(2) Closed Session

During the closed session, grouped (e.g. Group A, Group B) safety and efficacy data are reviewed. Attendance at the closed session is typically limited to DSMB members,

the Executive Secretary and, as the Board authorizes, the unblinded biostatistician who prepared the closed data reports. Information contained in the closed reports is also limited to these individuals. In unusual circumstances, an NIAID Medical/Safety Officer or Monitor may attend for a defined portion of the closed session for a specific safety concern if authorized; see Section 6.4.

(3) Closed Executive Session
Only DSMB members and the Executive Secretary may attend the closed executive sessions, to ensure complete objectivity as members review outcome data and formulate recommendations regarding the protocol.

The DSMB at its discretion may invite any individual to participate in any type of session if it believes the individual has important information or knowledge that will assist the DSMB in fulfilling its responsibilities. Likewise, the DSMB always has the option to hold discussions involving only DSMB members.

6.4 NIAID Staff/Contractors Attending DSMB Closed Sessions and Closed Executive Sessions

A limited number of NIAID employees or contractors may attend DSMB closed sessions or closed executive sessions. These individuals and the DSMB should understand that NIAID staff roles and responsibilities are to uphold the public interest and support the work of the DSMB. NIAID employees or contractors may not vote nor attempt to influence DSMB deliberations or recommendations. Their roles and responsibilities are:

a) DSMB Executive Secretary: facilitates effective functioning, record keeping, and interactions between NIAID and the DSMB but may have no other direct or supervisory role in the conduct of the trial being reviewed.
b) Unblinded protocol biostatistician: clarifies the report(s) and answers questions regarding the analyses.
c) NIAID Medical /Safety Officer or Monitor: In rare circumstances, the Division Director (or designee), upon consultation with the DSMB chair, may authorize attendance and access to closed safety data – if information from ongoing review of individual adverse event reports and summaries, or emerging information external to the trial raises concern about safety of current or future trial participants. This Medical/Safety Officer or Monitor may share supplemental clinical information with the DSMB and gain DSMB perspective on safety issues relating to his/her safety oversight responsibilities. DSMB members should be notified of this authorization in advance of the meeting date with an adequate opportunity for the Division Director or designee to address any member's concerns. The DSMB may also request to talk to the NIAID Medical /Safety Officer or Monitor during the closed meeting about unblinded data and should do so only with concurrence of the Division Director or designee.
d) NIAID employees or contractors who support the operations and record keeping of the DSMB meeting itself. These staff may not have a role in the conduct of the trial(s) being discussed and may be recused from the session(s)at the discretion of the Executive Secretary of DSMB.

6.5 Record Retention

The DSMB Executive Secretary or equivalent authority must maintain DSMB meeting documentation, including closed data reports and the resulting DSMB recommendations, during the DSMB's oversight of a trial. When the trial has concluded, the convening authority will maintain those records for as long as is required for other key trial records.

7.0 PROFESSIONAL LIABILITY INSURANCE FOR DSMB MEMBERS

Members who choose to obtain liability insurance to cover their participation on an NIAID DSMB may be eligible for reimbursement for their premiums.
(Attachment A)

8.0 REFERENCES/LINKS

8.1 Supersedes: Policy Version 5.0 (September 4, 2014)

8.2 The below online information is current as of the effective date of this policy.

[1]NIH Policy for Data and Safety Monitoring (June 10, 1998)
http://grants.nih.gov/grants/guide/notice-files/not98-084.html

[2]FDA - CFR 50.24(a)(7)(iv) Exception from informed consent requirements for emergency research
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24

[3]Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials (June 5, 2000)
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

[4]Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

[5] Use of Data Monitoring Committees in Clinical Trials (February 2024).
https://www.fda.gov/media/176107/download

[6]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
DSMB COI Appendix 1
DSMB COI Appendix 2
https://www.niaid.nih.gov/sites/default/files/dsmbcoipolicypostexcom.pdf

[7]Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials (June 11, 1999)
http://grants1.nih.gov/grants/guide/notice-files/not99-107.html

8.3 Other Resources:

DeMets, DL, Furberg, CD, Friedman, LM (editors) (2006) *Data Monitoring in Clinical Trials: A Case Studies Approach*. Springer, New York, NY.

Ellenberg, SS, Fleming, TR, DeMets, DL (2003) *Data Monitoring Committees in Clinical Trials.* John Wiley & Sons Ltd, West Sussex, England.

Herson, Jay (2009) *Data and Safety Monitoring Committees in Clinical Trial*s, Taylor and Francis Group, Boca Raton, FL.

European Medicines Agency – Committee for Medicinal Products for Human Use (CHMP) – Guideline on Data Monitoring Committees
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf

9.0 INQUIRIES/CONTACT INFORMATION

For questions or comments please contact NCRSexec.sec.@niaid.nih.gov

10.0 AVAILABILITY

This policy is available electronically on the NIAID website. Archived versions are available by contacting the NCRS Executive Secretary at NCRSexecsec@niaid.nih.gov.

11.0 ATTACHMENTS

Attachment A – Implementation of Reimbursement of the Cost of Premiums for NIAID DSMB (SMC/ISM) Members Who Obtain Individual Liability Insurance Policies.

12.0 REVIEW SCHEDULE/CHANGE SUMMARY

12.1 This policy will be reviewed at least every two years. Interim revisions will be made as needed to comply with NIH or other federal regulatory changes and/or at the request of the DCR Director.

12.2 The change summary table below will be updated when the document is reviewed or revised.

Version #	Date	Replaces	Date of Review /Revision	Rationale for Revision/Retirement
2.0	11/20/07	1.0	11/20/07	Clarification enhancements; Addition of procedures for access to closed safety data and new special exceptions for data access
3.0	5/04/09	2.0	5/04/09	Overall simplification of content; Title change; deletion of specific case example; new definitions section; additional charter requirements; minimum # of members established; review interval changed to every 2 years
4.0	9/30/13	3.0	9/30/13	More explicit background & authority; acknowledgment of other monitoring options; clarifications regarding convening authority; revised designation of studies needing DSMB oversight; addition of voting rights as a mandatory charter element; referral to separate policy on conflict of interest; clarification of executive secretary's role; addition of mandatory DSMB access to unblinded data; revisions to communications with convening authority; new provisions for record retention; new provision of reimbursement for liability insurance; addition of links and new references
5.0	9/4/14	4.0	9/4/14	Additions to charter; details on DSMB review procedures including general session descriptions; additional details re DSMB access to unblinded data; more detailed description on roles and responsibilities of NIAID staff or contractors attending closed sessions
6.0	6/27/24	5.0	6/27/24	Revised policy threshold requiring a DSMB to be focused on trials at highest risk (IND trials, large trials, and phase 3 trials). Revised and clarified the sections that described the party that convenes the DSMB and how recommendations are reported. Clarified wording for NIAID employees in membership and attendance in meetings.

13.0 ATTACHMENT A

Implementation of Reimbursement of the Cost of Premiums for NIAID DSMB (SMC/ISM) Members Who Obtain Individual Liability Insurance Policies
(Version 2.0 May 17, 2013)

BACKGROUND:
In the mid-2000s, NIH explored possible actions to address concerns about potential liability issues for individuals who serve on Data and Safety Monitoring Boards (DSMBs) appointed by NIH. A trans-NIH working group was formed to assess options for addressing this topic. No trans-NIH approach was implemented. Subsequently, some NIH Institutes have addressed this issue by arranging for group insurance coverage; other Institutes do not provide such coverage. NIAID leadership reviewed potential options to address the issue of liability insurance. NIAID leadership took into consideration the lack of published law cases naming data safety monitoring boards as defendants*, the advisory nature of the DSMB, and other factors, including cost, in deciding on the option to offer reimbursement for individual policies to members who voluntarily obtain this coverage on their own and are eligible for reimbursement.

Who may receive reimbursement for the cost of a premium?** Voting members of DSMBs or Safety Monitoring Committees (SMCs) or Independent Safety Monitors (ISMs) who participate in making recommendations to NIAID and who request reimbursement may be eligible to receive reimbursement. Ad-hoc members and Executive Secretaries may also be eligible to receive reimbursement.

For what timeframe will reimbursement be available? Members may receive reimbursement for premium costs for a policy covering their activities during their period of appointment.

What is the limit of reimbursement for premiums? Members may be reimbursed for reasonable costs for a policy that covers their activities during their period of appointment on the DSMB/SMC or as an ISM. Members who have existing individual or institutional liability policies may choose to clarify whether those policies cover their DSMB (SMC/ISM) activities. Members who have existing liability insurance for other professional activities who add (or have) coverage for their DSMB/SMC/ISM participation, may be eligible to receive reimbursement of their premium cost on a prorated basis.

How will reimbursement be implemented? Each Division will administer the reimbursement process according to available methods. Each Division will identify an individual to facilitate this process and to track activities associated with the reimbursement process. At a minimum, Divisions will track the name and total number of members who request reimbursement, the amount of the reimbursement, whether the reimbursement was for a policy that was obtained solely to cover DSMB activities or was a prorated reimbursement of an existing policy, and the name of the company providing coverage.

How will the availability of reimbursement be communicated? Reimbursement availability is noted in the NIAID DSMB operations policy.

To whom can members address questions? DSMB and SMC members and ISMs may contact Division staff for questions or concerns. Each Division will identify and communicate a contact name and phone number to provide support to members. A list of names of insurance contacts, that may supplement DSMB/SMC/ISM member's investigation of options to provide insurance, will be kept and provided upon request. **In providing these names, no endorsement of the contact, their company or their products, or legal advice, is implied or intended. The list should not be considered a comprehensive list of contacts.** Additions to the list of potential contacts by DSMB and SMC members and ISMs are welcomed.

How will the system be evaluated? In the fourth quarter of each calendar year, the NIAID Clinical Research Subcommittee of the Executive Committee (NCRS) will review the activities associated with the reimbursement process (number of requests, member satisfaction, and administrative/cost issues).

*As documented in the 2012 book by Patricia Tereskerz, Clinical Research and the Law (Wiley-Blackwell publisher)

**NOTE: Federal employees are not eligible for this reimbursement and should communicate with their supervisors and see the Federal Tort Claims Act for related information. Federal employees are encouraged to ensure their official appointment letter in their personnel folder states that their work as a DSMB, SMC, or ISM, is part of their official duties. It is considered that special volunteers (as defined in the NIH Policy manual) may be eligible for coverage under the Federal Tort Claims Act (28 U.S.C. 2671 et seq.) and under section 224 of the PHS Act, from personal liability for damages or injuries that arise from actions occurring within the scope of their Federal assignment and while under the direct supervision of a Federal employee. However, the ultimate decision on issues of liability and coverage depends on the circumstances of each situation. Thus, the U.S. Department of Justice may decline to represent a volunteer in a given situation. Special volunteers may purchase liability insurance but are not eligible for reimbursement.