National Institute of Allergy and Infectious Diseases NIAID Bethesda, MD USA	**POLICY**	Version No: 5.0 Date: September 4, 2014 Page 1 of 11
	Release Date: October 14, 2014 Effective Date: December 11, 2014	

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

APPROVAL

	Approving Entity	**Date**
Approval Mechanism:	***NIAID Division Directors***	***September 11, 2014***

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. 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)[2]. Although some program variances may be appropriate/necessary, a proposal for some harmonization of key issues across Divisions was put forth at the 2005 NIAID Winter Program Retreat. A working group representing all Divisions collected and analyzed data on Data and Safety Monitoring Board practices. This policy specifies those operational requirements for DSMBs that are mandatory across the Institute.

3.0 DEFINITIONS

The NIH policy states that monitoring 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. This policy addresses only structures that are classified as "data and safety monitoring boards"; refer to Divisions for information on other forms of monitoring.

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.

3.2 DSMB Convening Authority

"DSMB convening authority" is the single entity with authority and responsibility to respond to the recommendations of the Data and Safety Monitoring Board regarding a particular trial. The convening authority may be a different organization than the one

that establishes and operates the DSMB (e.g. when a DSMB established by NIAID monitors a trial for another IC or agency and NIAID is not involved in conducting the trial).

4.0 TRIALS REQUIRING A DSMB

Federal regulations only require a DSMB for research studies in emergency settings in which the informed consent requirement is excepted [21 CFR 50.24(a)(7)(iv)][3]. NIAID operationalizes the NIH DSMB policy and guidance by requiring 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. Additional factors that must be considered for designating other trials for DSMB oversight are long duration, complex design, high-risk interventions (e.g. genetic modification), vulnerable populations, and significant public health impact or high public interest and concern. NIAID Divisions, the NIAID Clinical Director or an IRB may identify particular trials that require a DSMB. Refer to NIAID Divisions for further policies and/or guidance. The FDA "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees"[4] may also be relevant in determining the need for DSMB oversight.

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 including cases when another entity is the convening authority (e.g. when an NIAID-supported trial is monitored by a pharmaceutical company's DSMB).

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 Deputy Director for Clinical Research and Special Projects must

approve any exceptions to this policy, including cases where NIAID is not the DSMB convening authority.

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. 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" [5]. When NIAID is responsible for the establishment and operation of the DSMB, the NIAID Division Director will appoint members directly or delegate that responsibility to designated staff 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 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 participate in 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 serve as DSMB members; they 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) 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, 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.

All such individuals will complete standardized NIAID training relative to their roles and responsibilities in closed DSMB sessions.

6.5 DSMB Recommendations – Routing/Response

DSMB summary recommendations are reported to the DSMB convening authority. Appropriate care must be exercised to prevent premature unblinding of the study team if the DSMB recommends a major change (e.g. including partial or full termination of the study).

The DSMB's convening authority's responsible official may consult with the trial leadership and/or relevant staff before making the final decision regarding the recommendations. A decision to reject a recommendation should be communicated to the DSMB with appropriate rationale.

When an NIAID-established DSMB is asked to monitor a trial for another convening authority, NIAID has special responsibility for ensuring clarity in the relationship and expectations of those parties.

Site investigators receive final DSMB meeting summaries and submit to their Institutional Review Boards (IRBs)/Ethics Committees (ECs) [6].

6.6 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 3.0 (May 4, 2009)

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]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

[3]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

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

[5]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
http://www.niaid.nih.gov/labsandresources/resources/toolkit/guidance/Pages/guidance.aspx

[6]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

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.

(Prior approved version was Version 1.2)