Data and Safety Monitoring (DSM) Policies for Extramural Clinical Trials and Clinical Research

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Contents

This document outlines the NICHD policy for DSM of all human subjects research activities it funds.

The National Institutes of Health (NIH) requires the monitoring activities of all NIH-sponsored or -conducted clinical research studies to be commensurate with their risks, nature, size, and complexity. NICHD implements the NIH Policy for Data and Safety Monitoring by requiring an appropriate monitoring system for all NICHD-supported human subjects research and timely notification of recommendations emanating from monitoring activities.

Release of funds for human subjects clinical research activities is contingent upon compliance with this policy, as noted in the NIH Grants Policy Statement and the terms and conditions of a given award/contract.

Background

Clinical trials are a specific type of clinical human research. NIH policy requires that every trial includes provisions for data and safety monitoring. For multisite clinical trials that involve potential risk to participants, establishment of a DSM Board (DSMB) is required.

Applicants proposing a clinical trial must include a DSM Plan (see DSM Plan, G.500 - PHS Human Subjects and Clinical Trials Information page 231; Section 3.3 of the PHS Human Subjects Section) in their applications.

For human subjects clinical research that does not involve a clinical trial, protection of human subjects must be described (see Section 3.1 of the PHS Human Subjects Section), and the applicant or offeror has the option to include a DSM Plan and to identify a DSMB. NICHD has the authority to require a DSM Plan for any proposed study.

How NIH Defines Clinical Research and Clinical Trials[1]

For purposes of this policy, NIH defines **clinical research** as research with human subjects that is:

- Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator or colleague directly interacts with human subjects.
- Excluded from this definition are in vitro studies using human tissues that cannot be linked to a living person.
  It includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.
- Epidemiological and behavioral studies.
- Outcomes research and health services research.

Studies falling under 45 CFR 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition.

NIH defines[2] a **clinical trial** as 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.

NIH Policy for DSM

As mandated by the NIH Policy for DSM, **all** types of clinical trials as defined by NIH require oversight and monitoring. See NIH's Definition of a Clinical Trial.

All multisite clinical trials involving interventions that entail potential risk to the participants must establish a DSMB.

A description of data and safety monitoring plans is required in competing grant applications. NIH provides additional guidance for phase I and II data and safety monitoring.

[1] https://grants.nih.gov/grants/glossary.htm#ClinicalResearch
[2] https://grants.nih.gov/grants/glossary.htm#ClinicalTrial

The NICHD DSM policy requires all investigators it supports to comply with the NIH Policy for DSM as well as NICHD-specific procedures, as outlined at https://grants.nih.gov/grants/guide/notice-files/not98-084.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.

NICHD DSM Policy

NICHD expects all clinical research to be conducted with a high standard of quality that assures the research question is answered in a reliable, valid, and unbiased manner, and that the rights and welfare of human subjects are protected.

To achieve this objective, the institute implemented NICHD Policies on Clinical Research and Related Issues, a set of policies pertaining to clinical trial management and oversight that are consistent with NIH Clinical Trial Requirements for Grants and Contracts.

DSM Plan (DSMP)

NICHD's DSM policy further requires applicants and funded investigators to provide a DSMP as part of a competing application or, in cases of prior-approval review, to conduct delayed onset research consistent with NIH policies on prior-approval. See Prior NIH Approval of Human Subjects Research in Active Awards Initially Submitted without Definitive Plans for Human Subjects Involvement.

According to NIH guidance (PDF 7.25 MB) and NICHD guidance, DSMPs must describe procedures for the following:

- Overall framework for data and safety monitoring and what information will be monitored
- Frequency of monitoring, including any plans for interim analysis and stopping rules, if applicable
- Ensuring compliance with the monitoring plan and requirements for reporting across study sites
- Frequency and means by which monitoring reports are generated and shared with the awarding Institute/Center (IC)
- Management and reporting of Adverse Events, including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events, and Unanticipated Problems (UPs) to the Institutional Review Board (IRB), the person or group responsible for monitoring, the awarding IC, the NIH Office of Biotechnology Activities, and the Food and Drug Administration (See the NICHD AE, UP, and SAE Reporting Policy [PDF 436 KB])

- Individual or group that will be responsible for trial monitoring and advising the appointing entity
- How the confidentiality of participant data will be protected
- Ensuring the overall assent and consent process for all participants including special needs populations, such as, but not limited to, children, individuals with developmental disabilities, individuals with intellectual disabilities, and vulnerable populations
- Management of incidental findings, such as aberrant findings on imaging scans or other assessments conducted as part of the research protocol
- How protocol violations will be handled by the principal investigator (PI) (The term protocol deviation is also used to refer to any other unplanned instance of protocol noncompliance https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-c/index.html)

DSMP Review Process

The DSMP in the competing application will be considered during peer review and by the NICHD program officer (PO) after review. If concerns are identified, the applicant will modify the plan in conjunction with program staff. Following approval, the applicant will enter the approved revised plan into the Human Subjects System.

If further modifications to the DSM plan are made before the trial begins, the revised monitoring plan must be submitted to NICHD and the IRB for approval before initiating the trial. The grantee or awardee must promptly request approval from NICHD staff prior to making any changes in the DSMP during the award/contract.

For all clinical trials and clinical research for which NICHD may require a DSMP, approval of the DSMP must be obtained from the IRB before the trial/study begins. NICHD will indicate in the Notice of Award that the recipient may not recruit participants until: (1) the DSMP has been approved by NICHD, and (2) the NICHD-funded investigator's IRB has approved the DSMP.

NICHD POs may determine that a clinical trial or clinical research study needs a different level of monitoring than determined by the applicant/offeror or awardee.

NICHD DSMB Policy

All NIH-sponsored multisite clinical trials that pose potential risk and some single site clinical trials require DSMB oversight. A DSMB is an independent group of experts charged with reviewing study data for integrity, participant safety, study conduct and progress, and providing directives regarding study continuation, modification, and

termination. Applicants will be expected to establish an independent, external DSMB (i.e., appointed by the institution) that is approved by the IRB if one is required either by NIH policy or NICHD.

DSMB members are expected to be independent from any professional or financial Conflict of Interest (COI) with the research project and investigators. Please see the sample COI assessment tool for DSMB members (PDF 164 KB) provided by NICHD.

Independence ensures that competing interests do not unduly influence the DSMB and supports objectivity that enhances the safety of participants and the integrity of trial data. Prior to the start of a trial, grantees or contractors will provide a roster of DSMB members that designates the chair and executive secretary of the DSMB to the PO and/or contracting officer representative (COR). This roster will include a written statement indicating that proposed members have no direct involvement with the study or COI with the investigators or institutions conducting the study.

In addition, PIs need to submit recommendations from the DSMB to the NICHD PO/COR within two weeks (14 business days) of each of its meetings. For DSMBs appointed by awardee institutions, the board's recommendations should be submitted to the PI and IRB. The PI then must send the recommendations to the NICHD PO/COR via email with the subject line stating the grant/contract number and noting that DSMB recommendations are attached. For cooperative agreements, the recommendations should also be submitted to the steering committee chairperson.

Complete board meeting minutes that summarize the topics discussed and list all recommendations must be signed by the board chair and submitted to the NICHD PO/COR at least one week (7 business days) before the next meeting.

NICHD expects that reporting requirements and timeframes for SAEs and UPs will be outlined in the DSMB policy/charter for that study or project. Those requirements should reflect consistency with NICHD AE, UP, and SAE Reporting Policy (PDF 436 KB).

The DSMB can be blinded or unblinded to the intervention assignment; those that are blinded to the intervention must have the documented option to be unblinded if needed. The DMSB monitoring responsibilities enhance, but do not replace, PI responsibilities and IRB oversight.

A DSMB Training Manual, which was developed with funding from NIH's National Center for Advancing Translational Research for members of a DSMB, is an excellent

resource[3] for board members. Both well-researched and vetted by academic medical centers, the manual is appropriate for novice and advanced users who need to set up a DSMB. It covers NIH IC considerations, including the practice of appointing members of a DSMB for NIH-funded networks that implement multisite clinical trials at academic centers.

[3] Clinical and Translational Scientist Award Collaborative Workgroup, Tufts University. 2018. *DSMB Training Manual.* Tufts Digital Library, Medford, MA. Retrieved 10/26/20 from https://tuftsctsi.wpengine.com/research-services/regulatory/data-and-safety-monitoring-board-training-manual-for-investigator-initiated-studies/