Policy Number: 503

SOP Title: Data and Safety Monitoring

Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB Chairs, IRB Administrators, Protocol Navigators

Revision Approval: Deputy Director for Intramural Research

Implementation date: 10/26/2020
POLICY

A. PURPOSE

1. This policy establishes the requirements for inclusion of a Data and Safety Monitoring Plan (DSMP) in non-exempt human subjects research protocols conducted by the NIH Intramural Research Program (IRP) and the requirements for IRB review of such DSMPs.

B. SCOPE

1. This policy applies to NIH investigators conducting non-exempt human subjects research.

2. This policy applies to NIH Institutes and Centers (ICs) that support and manage non-exempt human subjects research conducted by NIH investigators.

3. This policy applies to the NIH Institutional Review Board when it is the reviewing IRB.

4. This policy applies to non-NIH investigators when submitting to the NIH IRB as the Reviewing IRB.

C. POLICY

1. All non-exempt human subjects research protocols must include: a data safety monitoring plan (DSMP) that is commensurate with the level of risk of the research to monitor the data collected to ensure the safety of subjects, consistent with regulatory criteria for approval by an IRB at 45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6), and consistent with NIH policy (e.g., the Policy for Scientific Review of Clinical Protocols Utilizing the NIH Intramural Program Submission Requirements and Review Criteria).

2. The DSMP must be described in the protocol submitted to the IRB for review.

    a. For FDA-regulated emergency research for which informed consent is excepted, the requirement at 21 CFR 50.24(a)(7)(iv) specifies the establishment of an independent data monitoring committee to provide oversight over the clinical research.

3. Institutes and Centers (ICs) are required to ensure a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of research subjects and the validity and integrity of the data.
D. DEFINITIONS

1. 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 the interventions on biomedical or behavioral health-related outcomes. (45 CFR 46.102(b))

2. Data and Safety Monitoring – a formalized process for reviewing accumulated outcome data from an ongoing research study to ensure the continuing safety and welfare of current research subjects and those yet to be enrolled, as well as the continuing validity and scientific merit of the study.

3. Data and Safety Monitoring Board (DSMB) – For purposes of this policy, the terms DSMB, independent Data and Safety Monitoring Committee (DSMC), Data Monitoring Committee (DMC), will be considered synonymous and will be referred to herein as “DSMB”. A DSMB is a formal committee made up of independent experts, which reviews accumulating data and critical efficacy endpoints from one or more ongoing clinical trials, including multisite research.

4. Data and Safety Monitoring Entity – The identified individual or group (e.g., the investigator, a coordinating or statistical center, a medical monitor, an IC monitor, independent Data and Safety Monitoring Board (DSMB), Data and Safety Monitoring Committee (DSMC), Data Monitoring Committee (DMC), or other entity) assigned to conduct interim monitoring of data from research activities.

5. Data and Safety Monitoring Plan (DSMP) – A written description that prospectively identifies and documents monitoring activities, or that are none are needed, to protect the safety and welfare of the subjects, the validity of the data, and the integrity of the research study. The DSMP may also identify when to terminate a subject’s participation (i.e. individual stopping rules) and/or the appropriate termination of a study (i.e. study stopping rules).

6. Medical Monitor (also known as Safety Monitor) – a health care professional capable of overseeing the progress of the research protocol, especially individual subject management and safety. Depending on the level of risk, the IRB may require that the medical monitor be independent of the investigative team. The medical monitor must possess sufficient educational and professional experience to serve as the subject advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more phases of a research project.
7. **Study Monitor (also known as a Clinical Monitor or Clinical Research Associate)** – A qualified and objective individual who reviews the research records and processes to look at the timeliness of accrual and ensure that the trial is being conducted as planned.

8. A study monitor is someone with no direct involvement in the design and conduct of a study. Study monitors inspect regulatory binders (including informed consents and eligibility criteria) and study data (including source documents and case report forms (CRFs)).

9. **Sponsor** – A person (or other entity) “who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A[n] [entity] other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct a clinical investigation that it has initiated is considered to be a sponsor, and the employees are considered to be investigators.” *(21 CFR 50.3(e))*

10. **Stopping rules** – Predetermined guidelines as to when enrollment or study interventions in one or more study arms should be altered or stopped.

**E. RESPONSIBILITIES AND REQUIREMENTS**

1. The PI is responsible for the following:
   a. Providing to the IRB a DSMP for all non-exempt human subject research protocols. The DSMP should be commensurate with the level of risk, nature and complexity of the research, and the population under study. As applicable, the DSMP should:
      I. Identify the data and safety monitoring entity (e.g. PI, medical monitor or DSMB).
      II. The investigator should also provide the following in the DSMP, commensurate with the level of risk and complexity of the study:
         i. The schedule for reporting to the data and safety monitoring entity;
         ii. The frequency of assessments of data or events;
         iii. The stopping rules;
         iv. Plans for interim and/or futility analyses;
         v. Procedures for communication between the PI, research team members, the study sponsor, the data and safety monitoring entity, the IRB, others at
NIH and, as applicable, the coordinating or statistical center, FDA and other study sites.

b. Ensuring that the DSMP as outlined in the IRB-approved protocol is followed;

c. Ensuring that required information is promptly provided to the data and safety monitoring entity;

d. Notifying the data and safety monitoring entity when there are amendments to the protocol that affect the DSMP;

e. Responding to the data and safety monitoring entity recommendations. Responses may include providing corrections to errors in fact, responses to recommendations, or requests for corrective action plans;

f. Providing DSMP reports to the IRB at the time of continuing review or sooner if the report meets the requirements for prompt reporting to the IRB as specific in Policy 801 Reporting Research Events.

g. For FDA-regulated emergency research for which informed consent is excepted, the requirement at 21 CFR 50.24 (a)(7)(iv), the PI must ensure the establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.

h. Investigators are expected to be familiar and comply with additional NIH requirements (e.g. the Policy for Scientific Review of Clinical Protocols Utilizing the NIH Intramural Program Submission Requirements and Review Criteria).

2. The NIH IRB Responsibilities:

a. The IRB is responsible for reviewing the DSMP to determine whether there are adequate provisions to ensure, to the extent possible, the safety of research subjects and the integrity of the data. If necessary, the IRB may require changes to secure approval.

b. The IRB is responsible for reviewing data and safety monitoring reports at the time of continuing review, or sooner if submitted to the IRB (e.g., under Policy 801 Reporting Research Events or protocol reporting requirements) and IRB review is deemed necessary by the IRB Chair, IRBO Director or Director OHSRP in order to determine if the study remains approvable or needs amendment.

I. IRB review of data and safety monitoring reports includes the following:
i. Review of the findings and, if applicable, review of the investigator’s proposed actions in response to monitoring report findings (e.g., amendments of the protocol or consent(s), placing of administrative hold, study closure, etc.);

ii. Determining whether any additional changes are needed based on the report. (For example, deciding if the frequency of continuing review is still adequate, requiring modification to the protocol or consent(s), or deciding whether the protocol will be suspended or terminated, based on reported results.) (Policy 203 Support of IRB Operations)

3. Institute/Center Responsibilities:
   a. Institute/Centers are responsible for the establishment of Data and Safety Monitoring Entity (DSME) for multi-site clinical trials, or when the protocol contains a DSMP that calls for the use of a DSME, or the DSME is requested by the IRB. Generally, the establishment of a DSME is governed by the IC’s written procedures and NIH policies (e.g., the NIH Policy for Data and Safety Monitoring).

   I. The NIH Institute or Center (IC), the FDA, a Sponsor, or an IRB can require that a DSMP identify an independent data and safety monitoring entity (e.g. a medical monitor or a Data and Safety and Monitoring Board).

   b. ICs are responsible for providing adequate resources and staff support to the data and safety monitoring entity and for appointing a medical monitor or members to the DSMB.

   I. Establishment of formal DSMBs must be consistent with written IC procedures and NIH policies, e.g. the NIH Policy for Data and Safety Monitoring. (See References.)

   II. The IC must ensure that conflict of interest requirements are addressed for DSMB members, as applicable.

   c. Supporting PIs to address the data and safety monitoring entity’s recommendations, as applicable.

   d. When NIH is the sponsor, the IC may require post-approval monitoring to review data on a pre-determined basis or randomly.

F. REFERENCES

1. Federal Regulations
2. **NIH Policy**

   - **Policy 203 Support of IRB Operations**
   - Policy 500 Research Involving Drugs, Biologics, and Nutritional Products
   - **Policy 801 Reporting Research Events**

3. **Guidance**


G. **APPENDICES: NA**

H. **REVISION HISTORY: NA**

I. **SUPERSEDES DATE: 10/26/2020**

   - SOP 17 Data and Safety Monitoring