Data and Safety Monitoring for PI-Initiated Research

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Please note: Guidance and regulations are subject to change

When developing a prospective, human subjects research study, Principal Investigators (PIs) should consider methods for monitoring study data and the safety of participants (as applicable). All clinical trials supported by NIH must have some form of monitoring based on an established Data and Safety Monitoring plan (DSMP). The level and type of monitoring should be commensurate with the size and complexity of the study, the level of risk to study participants, and phase of the study.

Elements of Data and Safety Monitoring Plans:

These elements should generally be described in the DSMP

- The **individual(s) or group** that will be responsible for study monitoring and advising the study team, describing the roles and responsibilities of those individuals. Because the DSMP will depend on potential risks, complexity, and the nature of the study, a number of options for monitoring are possible. These include, but are not limited to:
  - **Investigator-Physician**: While the PI must ensure that the study is conducted according to the approved protocol, in some cases (e.g., low risk studies, not blinded), it may be acceptable for an Investigator-Physician working on the study (PI or Co-Investigator) to also be responsible for carrying out the DSMP.
  - **Independent safety monitor/designated medical monitor**: a physician or other clinical expert who is independent of the study.
  - **Independent Monitoring Committee or Safety Monitoring Committee (SMC):** a small group of independent experts.
  - **Data and Safety Monitoring Board (DSMB)**: a formal independent board of experts including investigators and biostatisticians. NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally, for all Phase III clinical trials, although Phase I and Phase II clinical trials may also need DSMBs.
    - Describe the general composition of the DSMB without naming specific individuals.
    - Describe the DSMBs independence from the study.
    - Describe activities of the DSMB in providing oversight (frequency of reviews, reports provided, data to be reviewed, stopping rules).
  - **Data Monitor**: Another aspect of study monitoring is the review of data to ensure the reported data are accurate, complete, and verifiable. This aspect of study monitoring is required when a study is run under an IND or IDE and strongly recommended when the study is multi-center. If applicable, describe that a study monitor will periodically conduct a review of specific proportion of the participant data and source documents at the study site.
- The overall framework for safety and/or data monitoring and what information will be monitored.
- The frequency of monitoring activities, including plans for safety, interim and/or futility analysis, as appropriate.
- If applicable, the frequency that the study monitor will review study data and source documents.
- If applicable, the type and number of events that would halt accrual and prompt review of eligibility, monitoring, assessments, intervention, and how the resumption of accrual would occur (i.e., study-wide stopping rules).
- The process by which Adverse Events (AEs), including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events and Unanticipated Problems (UPs), will be

identified, reviewed and reported, as required, to the IRB, the NIH (i.e. program officer, and the Food and Drug Administration (if applicable). For more information see
    - OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html
    - Describe the person or group responsible for submitting necessary reports to NIH
- For multi-site studies, procedures to ensure compliance with the monitoring plan and reporting requirements across study sites.
- An assessment of external factors or relevant information (e.g., developments in the literature, results of related studies) that may have an impact on the safety of participants or on the ethics for the research study.

Examples of Monitoring Plans Based on Level of Risk:

Safety monitoring for a protocol must be appropriate for the level of risk identified. The combination of factors used in assessing the level of risk drives the intensity of monitoring required for a protocol. The requirements outlined below represent the minimum amount necessary to assure subject safety.

Low Intensity Monitoring –The PI or co-investigator will monitor the study with prompt reporting of adverse events and other study related information to the IRB, sponsor, and other agencies as appropriate. Team meetings by the PI and his/her staff will be conducted on a routine basis to discuss protocol issues and review adverse events. **Examples of studies requiring low intensity monitoring include:**

- Studies of normal volunteers using well-described research procedures and/or single dose of experimental agent;
- Post-marketing study, phase IV drug study or device (as defined by FDA) with minor safety concerns (may include UNC investigator-initiated IND study if minor safety concerns);
- Interventions or invasive procedures present low risks, reasonably commensurate with those expected in medical or dental practice**.**

Moderate Intensity Monitoring – The PI or co-investigator monitors the study on a day-to-day basis and includes all monitoring activities described above in low intensity monitoring. In addition, most protocols will require well-described criteria for dose escalation, criteria defining maximum tolerated dose (MTD), and/or criteria for stopping the trial or involvement of a subject. Surveillance and protections are in place to adequately identify adverse events promptly. An independent medical monitor or safety monitoring committee may also be utilized to review adverse events as they occur and make recommendations to the protocol team. If the study is run under an IND or IDE, include a study monitor to review collected data to ensure the reported trial data are accurate, complete, and verifiable. **Examples of studies requiring moderate intensity monitoring include:**

- Subjects treated with placebo for a recognized disease;
- Substantial risk of a serious adverse event originating from the underlying condition of the subject;
- Research involves subjects with serious viral, autoimmune, and malignant illness in a treatment study of moderate risk;
- Phase I or II, clinical trial with available safety data in humans (may include UNC investigator-initiated IND study of moderate risk);
- Minimal risk studies involving vulnerable populations (e.g. subjects with impaired capacity to give informed consent).

High Intensity Monitoring – The PI or co-investigator monitors the study on a day-to-day basis and includes all monitoring activities described above in low intensity monitoring. Most high-risk protocols will also require a Data Monitoring Committee to monitor the safety and efficacy of the study. An independent Data Safety Monitoring Board (DSMB) is required by NIH Guidelines for all Phase III clinical trials. Based on the level of risk, the complexity of the protocol, and the patient population, the IRB may determine that a clinical trial or protocol requires an independent DSMB or DSMC. This may include a single institution, investigator initiated, clinical trial or protocol deemed of significant risk. If no other DSMB is in place for a single institution clinical trial, the PI may use the TraCS DSMB an independent board to fulfill this function. If the study is run under an IND or IDE, include a study monitor to review collected data to ensure the reported trial data are accurate, complete, and verifiable. **Examples of studies requiring high intensity monitoring include:**

- Clinical trials of interventions to prevent or treat a disease that leads to death or irreversible morbidity;
- Studies involving interventions or invasive procedures with substantial risk or potential severe toxicity;
- An investigator-initiated IND trial of higher risk;
- Implantation of a device with an IDE;
- Study using a new chemical or drug for which there is limited or no available safety data in humans;
- A gene transfer study or research involving recombinant DNA molecules;
- Industry sponsored, multi-center, randomized, clinical trials (phase IIb, III, and IV).

For more information:

- DSMB Training Manual: https://www.tuftsctsi.org/research-services/regulatory/data-and-safety-monitoring-board-training-manual-for-investigator-initiated-studies/
- NIH Grants Policy Statement, Section 4.1.15.6: Data and Safety Monitoring
- https://grants.nih.gov/policy/humansubjects/policies-and-regulations/data-safety.htm
- https://www.nia.nih.gov/research/grants-funding/nia-guidance-clinical-trials
- https://www.niaid.nih.gov/grants-contracts/decision-tree-data-safety-monitoring-plan
- NC TraCS DSMB: https://tracs.unc.edu/index.php/services/regulatory/data-and-safety-monitoring-board
- Contact NC TraCS Regulatory Service to Request help with Monitoring Plan Development