MCW Office of Research
Standard Operating Procedure

DATA AND SAFETY MONITORING PLANS

Unit: Human Research Protections Program (HRPP), Office of Research

Applies to: Faculty and Staff involved in human research

PURPOSE:
Federal regulations [45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6)] stipulate that the IRB must determine that: "When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects." Medical College of Wisconsin (MCW) Institutional Review Board (IRB) requires investigators who are planning a research project to describe their strategy for monitoring the data to ensure the safety of research subjects when applicable. The Data and Safety Monitoring Plan (DSMP) is intended to ensure the safety of subjects in the research activity and the validity and integrity of data.

The specific strategy to be used must be described in detail, and it must be appropriate for both the degree of risk involved in participation and the size and complexity of the study. Either the investigator is responsible for the existence of such a plan, as for an investigator-initiated protocol, or the investigator may use the plan described by the sponsor for an industry-sponsored or cooperative group protocol. In specific settings, described below, a Data and Safety Monitoring Board (DSMB) may take responsibility for the monitoring activities.

DEFINITIONS:
Clinical Trial: a research project 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.

Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.1 02(i) and 21 CFR 50.3(k)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

Unanticipated problems involving risk to participants or others (UPIRSO):
Any incident, experience, or outcome that meets **all** of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, Instructions for Use/Device Manual and/or Investigator's Brochure; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the

incident, experience, or outcome may have been caused by the procedures involved in the research) or test article; and
- Suggests that the research places subjects or others at a greater risk of harm (including *physical, psych*ological, *economic, or social harm*) than was previously known or recognized.

PROCEDURE:

1. Investigators who conduct human subject research projects must provide a plan on how subject data will be monitored for safety when applicable.
2. The level and type of safety plan will depend upon the nature of the project, size and complexity of the study, and associated level of risk. The eBridge SmartForm must include the following information to assist the IRB in determining the level of safety monitoring required:
    - The nature of any risks posed by the research project
    - The degree of uncertainty regarding the risks involved
    - The vulnerability of the subject population
    - The experience of the investigators in conducting research
    - The projected rate of enrollment
    - Whether the research project involves novel interventions
3. The following information about the Data Safety Monitoring Plan (DSMP) must be described in the eBridge SmartForm to permit the IRB to assess the level of safety monitoring required:
    a. Qualifications and expertise of those who will carry out the DSMP
    b. Subject safety
        - Expected frequency, severity, and reversibility of the major risks identified and possible late effects of participation (e.g., secondary cancers).
        - Steps that will be taken to minimize risks.
        - Identification of data points which will be reviewed and an explanation of how stopping rules will be invoked, both for the study and for the individual subject
        - Point at which the study will be terminated and how subject safety will be assured during the period when the study will be closed.
        - Safeguards that will be used to protect confidentiality
    c. Data
        - Timeframe for how often data will be examined
        - Timeframe for evaluation of adverse events, including non-serious and expected events. For example, if one arm of a research project results in a substantial increase in a non-serious and expected event (such as insomnia or chronic cough), this information must be evaluated in terms of the continuing conduct of the trial.
        - Plan for prompt evaluation of UPIRSOs and ensuring necessary medical or professional intervention as needed.
        - Plan for evaluation of data accuracy and completeness to ensure that all members of the project team understand and follow the project protocol and that data is accurate.
    d. Efficacy
        - Evaluation of efficacy, if appropriate to the research project. For example, in a placebo-controlled trial, a substantial reduction in death rate among the experimental arm has implications for the safety of subjects receiving the placebo.
    e. Feedback mechanisms
        - Evaluation and response to subject complaints.
        - How, when and at what point events will be reported to the IRB, FDA, and/or HHS, particularly as they relate to timely communication of UPIRSOs.

- Scope of the information to be provided to the IRB at interval of not less than one year.

4. Monitoring Mechanisms
   a. DSMPs may include safety monitoring of the data depending upon the type of research and the level of risk. The type of monitoring may range from monitoring and review by the Principal Investigator or by a group of Investigators to the establishment of an independent Data and Safety Monitoring Board (DSMB). Safety monitoring may be accomplished as follows:
      - The Investigator performs the safety monitoring (i.e. a single site open label trial.)
      - An uninvolved expert in the research performs the safety monitoring (i.e. a single site blinded trial.)
      - The sponsor's medical monitor performs safety monitoring
      - The sponsor's safety monitoring committee performs safety monitoring
      - An independent Data and Safety Monitoring Board (DSMB) performs safety monitoring

For Department of Defense supported projects that are greater than minimal risk, the project may identify 1 or more research monitors depending upon the type of research. The eBridge study submission should include the following:

- Identification of the monitor(s). Please note that a monitor may be an ombudsman or a member of the data safety monitoring board. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.
- The duties of the research monitor are determined on the basis of specific risks or concerns about the research, such as:
  - Perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
  - Discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
  - Report observations and findings to the IRB or designated official

5. Data Safety Monitoring Boards (DSMB) or Committees (DSMC)
   a. A DSM Board or Committee is an independent, impartial group set up specifically to monitor a clinical trial (or other study) throughout its duration to determine where continuation of the study is appropriate scientifically and ethically.
   b. If a DSMB/C will be used as a part of the DSMP, the following must be provided in the eBridge Study SmartForm:
      - DSMB/C membership
      - Member expertise
      - DSMB/C contact and their contact information
      - Whether the members are independent of the sponsors/researchers
      - Expected frequency of their meetings
      - Written assurance that the DSMB/C will provide the MCW/FH IRB with a written overall study safety report at intervals of not less than one year
   c. DSMB/C Composition
      - A DSMB/C should have multidisciplinary representation, including physicians from relevant medical specialties and biostatisticians. This may include other experts such as bioethicists, epidemiologists, and basic scientists.
      - Members should be free of apparent significant conflicts of interest, whether they are financial intellectual, professional, or regulatory in nature.

d. DSMB/C Responsibilities
The primary responsibility of the DSMB/C is to safeguard the interests of study subjects. Therefore, the DSMB/C should:

- Approve the safety measures in the protocol to 1) preserve the study integrity and credibility; and 2) to facilitate the availability of timely as well as reliable findings to the broader clinical community.
- Provide written documentation confirming that they have read the protocol and agree with the study design and the DSMP.
- Continually review quality of study conduct including data management and quality control.
- Review the progress of the study, including the following:
  - Each enrolled subject's research chart should be reviewed monthly for side effects and tolerability of the investigational drug.
  - Study accrual, compliance with eligibility, participant adherence to study requirements, and accuracy and completeness of data should be reviewed.
- Recommend early termination based on efficacy results or unfavorable benefit-to-risk or inability to answer study questions.
- Recommend continuation of ongoing studies.
- Modify sample sizes based on ongoing assessment of event rates
- Review final results.
- Ensure subject safety by reviewing data that are not available to the Investigators or the IRB involved with the research project. In cases where the DSMB members conclude that there is a difference in the safety profile of different arms of the research project, the DSMB may receive unblinded data. This allows them to make a more informed judgment as to whether the research project should continue as planned.
- At defined intervals, produce a summary report that provides information concerning the cumulative toxicities observed in subjects and whether it recommends continuation of the study as written. This report, or a summary of its conclusions, must be shared with the IRB of record for the study. All DSMP or DSMB reports are to be submitted to the IRB in accordance with *IRB SOP: Requirements for Reporting to the IRB*.

6. IRB Review of the Data Safety Monitoring Plan (DSMP)

The MCW IRB will assess the adequacy of the proposed DSMP during its review of information provided in the eBridge Study SmartForm and may require that a DSMB be established for the project, as a condition necessary for the IRB's final approval.

a. The IRB Committee or designated reviewer will review the initial submission to assure the adequacy of the DSMP in relationship to the size, complexity, and level of risk of the proposed research.
b. The IRB Committee or designated reviewer will review the qualifications and experience of the designated data and safety reviewer or the composition of the DSMB/C including the qualifications and experience of the individual members. The IRB may make recommendations regarding expertise, frequency of meetings, etc., to the Investigator for the enhancement of human subject protections.
c. The IRB Committee or designated reviewer may request additional information or clarification regarding the DSMP or DSMB/C.
d. Research projects where a DSMB/C may be required:
   - A large subject population

- Multiple sites, since it may be more difficult to recognize a pattern of increased or unusual problems when Investigators enroll small fractions of the population separately
- Highly toxic therapies or dangerous procedures
- High expected rates of morbidity or mortality in the subject population
- High chance of early termination of the project
- Study intent is to provide definitive information about the effectiveness and/or safety of medical intervention
- Prior data suggesting that the intervention under study has the potential to induce a potentially unacceptable toxicity
- Study aim is to evaluate mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications
- Studies where it would be ethically important to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed

REFERENCES:
45 CFR 46.111(a)(6)
21 CFR 56.111(a)(6)

SUPPORTING DOCUMENTS:
IRB SOP: Requirements for Reporting to the IRB

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