Marshfield Clinic

Data and Safety Monitoring Plans

1. SCOPE

1.1. System Wide

2. DEFINITIONS & EXPLANATIONS OF TERMS

2.1. **Minimal Risk Studies**: Those in which the risk of harm to subjects is no more than would be encountered in daily life or during a routine medical appointment or psychological assessment. 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 a routine physical exam. Procedures which are considered to be of minimal risk include phlebotomy, non-invasive and non-radiographic testing (e.g. ECGs, exercise testing) most surveys and non-therapeutic testing. Note that protocols that require no direct personal contact or subject intervention may pose a minimal risk of breach of confidentiality when examining health records, etc. Consequently, even protocols that are determined to pose minimal risk to participants' health or privacy should acknowledge that risk and should outline a plan for overseeing and monitoring study performance to ensure adequate recruitment, data integrity, and progress toward the specific aims of the research activity.

2.2. **Greater than minimal risk studies**: Those in which procedures are consistent with moderate risk interventions including: exposure to x-rays, invasive monitoring, collection and storage of biological specimens for future research, and use of pharmacologic agents according to their FDA approved indications. For example, some oncology clinical trials require radiographic staging beyond what is considered the standard of care. Studies for which the frequency of adverse effects is expected to be high, or studies which may pose challenges to the enrollment or consent processes may be of even higher intrinsic risk. (e.g. clinical trials, gene therapy studies, research involving interventional procedures, studies with a high likelihood of death or morbidity, or multi-site treatment studies where it may be more difficult to recognize a pattern due to investigators enrolling portions of participants in different places.)

2.3. **Serious Adverse Event**: Undesirable outcome from the use of a medical product or intervention. Such outcomes include: death, life threatening event, hospitalization, disability, congenital anomaly/ birth defect, or event requiring intervention to prevent permanent damage.

3. RESOURCE GUIDE BODY

The purpose of this document is to provide guidance to investigators on crafting an appropriate Data and Safety Monitoring Plan for their research activities

3.1. Background

a. The IRB has a responsibility to participants in human subjects research to ensure that risks are minimized to the extent possible. 45 CFR 46.111 and

21 CFR 56.111 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." This is most often accomplished with Data Safety Monitoring Plans (DSMP). The level of review should be proportional to the level of risk inherent in the research protocol.

b. Risk is a difficult concept to fully grasp, and is harder yet to accurately measure. Essentially, what you are attempting to quantify is the likelihood that a particular event will happen. Typically, such events are dependent upon myriad variables, making the frequency of occurrence difficult to accurately calculate. However, it is possible to estimate the relative frequency with which a given event is likely to occur.

3.2. Types of Data Safety Monitoring Plans

a. Monitoring by Principal Investigator (PI)

- This is the simplest type of risk monitoring and is reserved for minimal risk research. As in all determinations of risk, the level of risk is formulated by subjective interpretation of a combination of factors, including study size (smaller is usually associated with less risk, as are studies conducted at a single site) and study type (interventional vs observational, studies) as well as target population. Thus, a small observational study targeting healthy adults would be considered appropriate for PI monitoring , whereas a large, phase III multisite trial of a new pharmaceutical delivery method would not. The smaller study population often recruited from investigators' own patient list, permits close, essentially continuous monitoring.
- Retrospective data-only studies and observational studies requiring no contact with research subjects, generally present less risk than clinical trials and also would be appropriate for this level of oversight.

b. Monitoring by Small Group or Individual

- This degree of safety monitoring is intended for small to medium-sized studies that are of greater than minimal risk. This small group (2 or 3 individuals) monitors the research activity and data collection, reviewing of potential risks and adverse events. A small review panel is also appropriate in situations involving studies that may be large in size or of brief duration, or those in which the research activity spans a number of sites. The frequency with which the small group will meet should be specified.
- Small group review may occur either independently of the study sponsor, or the small group may consist of employees of the study sponsor. This latter method of safety review is relatively common, but it does carry with it the possibility of the perception of bias by the internally appointed review groups.

c. Data Safety Monitoring Committee (DSMC)

- A full-fledged DSMC is appropriate to the task of overseeing larger studies that may be blinded, or studies which demand a high degree of sophisticated analysis. Such studies generally carry higher levels of inherent risk. DSMCs are also commonly used in studies for which mortality is anticipated to be high, those that are highly invasive, or those seeking to specifically target the enrollment of vulnerable subjects. As in small group monitoring, the DSMC advises the sponsor and or PI regarding the continued safety of study participants by periodic assessment of risk/benefit ratio of the study. As such, DSMCs have the responsibility of determining whether the research should continue with or without modification to the study design and methodology, or whether the study should be stopped by virtue of having reached meaningful pre-determined efficacy or safety endpoints (stopping rules).
- Since DSMC's are independent from the research team, they can review unblinded data without biasing the conduct of the ongoing research. For this reason, when assembling a DSMC care should be taken to exclude any members with potential or acknowledged conflicts of interest that would preclude an unbiased review process. Members should have no professional or financial interest in the outcome of the study, and should be knowledgeable about both about the disease under study and the proposed analytic methodology.
- The size of the DSMC will vary with the study, but usually consists of a chair with 2-4 clinician/scientists and 1 biostatistician.
- The duties of the committee should be clearly specified in the protocol, as should the extent and frequency of monitoring, the mechanism of communication, and the existence of any stopping rules.
- Based upon its periodic review of available data, the DSMC may recommend continuation, modification or termination of the research activity.

3.3. Contents of the Data Safety Monitoring Plan

a. The degree of risk of a research protocol should guide the content of the DSMP. At a minimum, the DSMP should include identification of the type of monitoring that will be expected of study staff at the site(s) where the research will be conducted.

b. Additional aspects of the DSMP will depend on the complexity of and level of risk inherent to the protocol. These will include details pertaining to the Who, What, Where, When and How of the activity:

- Names, affiliations and expertise of participants in the monitoring process;

- Description of what events (e.g. adverse events, unanticipated problems, enrollment outcomes, participant complaints) will be reported and to whom;
- Identification of data points which will be reviewed and an explanation of how stopping rules will be invoked, both for the study and for individual participants.
- Frequency with review of data should occur including the timeframe for the valuation of adverse events, so that the information may be evaluated in terms of continuing conduct of the trial;
- Evaluation of efficacy, if appropriate to the research project.
- Procedures for analysis of the data, as appropriate.
- Feedback mechanisms such as how and at what point events will be reported to the IRB, FDA and or HHS, particularly as they meet the definition of unanticipated problems.

3.4. IRB Review of the Data Safety Monitoring Plan

a. The IRB will assess the adequacy of the proposed DSMP during its review of the study submission.

b. The IRB will consider the size, complexity and level of risk of the proposed research, and will review the qualifications and experienced of the designated data reviewer or the make-up of the DSMC.

c. The IRB may require that a DSMC be established for the project, as a condition of approval.

d. The IRB will generally require a DSMC be in place when research includes:

- Greater than minimal risk research involving a large participant population;
- Toxic therapies or dangerous procedures
- High rates of morbidity or mortality in the subject population
- Study intent to prove effectiveness and or safety of a medical intervention;
- Study aim to evaluate mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications.

4. ADDITIONAL RESOURCES

4.1. References:

- None

5. DOCUMENT HISTORY

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1.0	New Document in Document Control transferred from Policy & Handbook Library - #5266.0
2.0	
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6. DOCUMENT PROPERTIES

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