CARILION CLINIC INSTITUTIONAL REVIEW BOARD
Standard Operating Guidelines

Title: 3.9: Reviews Requiring Special Consideration: DATA SAFETY MONITORING PLAN (DSMP), DATA SAFETY MONITORING BOARD (DSMB)	
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Objective:

Guidance is provided for designing a Data Safety Monitoring Plan (DSMP). Guidance is also provided for when a Data Safety Monitoring Board (DSMB) is necessary and to define the composition, structure and responsibilities of the DSMB.

General Description:

Data safety monitoring is necessary for all greater than minimal risk studies. Some research studies require the involvement of a DSMB for this process. A DSMB is a group of individuals with pertinent expertise that reviews, on a regular basis, accumulating data from one or more ongoing clinical studies. The DSMB advises the sponsor and/or the principal investigator regarding the continuing safety of trial subjects, as well as the continuing validity and scientific merit of the trial.

Procedure:

Assignment of Responsibility for Data Safety Monitoring

A range of options may be appropriate, depending on the risk level of the study and design, including but not limited to the following:

- The principal investigator will have sole responsibility for monitoring; or
- A group of designated Carilion faculty/staff will have responsibility for monitoring; or
- An independent individual or group of non- Carilion individuals will have responsibility for monitoring; or
- A combination of Carilion faculty/staff and non- Carilion individuals will share responsibility; or;
- A designated medical monitor, or group of monitors, for commercially funded or for not-for-profit sponsored studies will have responsibility for monitoring; or
- A formal Internal or Independent DSMB (also referred to as a Data Monitoring Committee) will have responsibility for monitoring.

Data Safety Monitoring Plan (DSMP)

A DSMP prospectively identifies and documents monitoring activities intended to protect the safety 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 and/or the appropriate termination of a study. A DSMP should be tailored for the study in regard to the risk level and study design.

The criteria for approval of research states that when the research involves more than minimal risk, the research plan makes adequate provision to monitor the data collected to ensure the safety of subjects and that adequate provisions to protect the privacy of subjects and the confidentiality of the data are maintained (45 CFR 46.111).
If the research is considered minimal risk, a DSMP is not required by the IRB unless it is determined to be necessary for the oversight of the study. A plan may still be useful for data integrity.

A Data Safety Monitoring Plan must be included in the IRB submission when the study is greater than minimal risk. The following items should be described as applicable to the study:

- A description of the systems for storing and backing up the data;
- A listing of who will monitor and review the data, and a description of the monitor's qualifications;
- The frequency of review (e.g. specific points in time, or after a specific number of participants have enrolled);
- A description of the data to be monitored;
- Procedures for analysis and interpretation of the data;
- Stopping rules or actions to be taken upon specific events or endpoints;
- Assessment of Study accrual rate;
- Assessment of Participant adherence with assigned therapy, intervention, or study procedures;
- Compliance with eligibility criteria;
- Procedures for communication from the data monitor to the IRB and other sites;
- Protection of the rights and welfare of subjects during the recruitment, consenting process and study participation;
- Protection of subject privacy and confidentiality;
- Description of how AEs (adverse events) are graded;
- A description of the mechanisms for detecting, reviewing and reporting unanticipated problems involving risks to subjects or others by the investigative team at a frequency and intensity sufficient to ensure the safety of participants;
- If there are external reporting responsibilities, the plan should describe the processes and oversight the investigator has in place to report unanticipated problems and SAEs to the following as applicable: the FDA and the study sponsor;
- Assurance that research responsibilities delegated by the principal investigator to investigative team members are carried out in accordance with the protocol,

federal regulations, federal, state and local laws and institutional policies and procedures.

Determining the Need for a DSMB

All clinical studies require safety monitoring, but not all studies require a DSMB. DSMBs are generally established for large, randomized, multi-site studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome. DSMBs are recommended for any controlled trial of any size that will compare rates of mortality or major morbidity. There are several factors to consider when determining whether to establish a DSMB for a particular trial, including factors related to safety, practicality and scientific validity.

A DSMB should be established in situations where safety concerns may be unusually high, in order that regular interim analyses of the accumulating data are performed. DSMBs are recommended when:

- There is a reasonable likelihood that the study may be terminated early for reasons of safety, futility or efficacy
- There is a large study population or the study is of long duration
- There are multiple study sites
- Prior information suggests the possibility of serious toxicity or safety concerns with study treatment
- The study is being performed in a vulnerable population (i.e. children, the elderly, pregnant women, the terminally ill or those of diminished mental capacity)
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint
- Planned emergency research
- The IRB determines that a DSMB is necessary to provide for the safety of subjects

It must also be practical to engage a DSMB with regard to timing. If a study is likely to be completed quickly, a DSMB may not have an opportunity to have a meaningful impact. However, pauses could be built in to short-term studies with important safety concerns so that interim data could be reviewed before any additional subjects would be enrolled.

A DSMB can help assure scientific validity of a study. Sometimes changes are made to a study based on information obtained from outside sources, such as a new understanding of a disease or an updated standard treatment. As long as the DSMB is the only group to be unblinded to study results, these changes can be made without raising concerns that such changes might have been at least partly motivated by knowledge of the interim data. Therefore, trial integrity remains intact.

The need for a DSMB may extend beyond the time when subjects are being treated, since trends in survival or other serious outcomes may not become evident until the follow-up period. Thus, the DSMB's responsibility to monitor the study generally

continues until the planned completion of follow-up, regardless of the duration of treatment.

Board Composition

The selection of DSMB members is extremely important. Factors to consider when establishing a DSMB include relevant expertise, experience in clinical trials and in serving on other DSMBs, and absence of serious conflicts of interest. In addition to clinicians with expertise in relevant clinical specialties, it is recommended to have one biostatistician knowledgeable about statistical methods for clinical trials and sequential analyses of trial data. A medical ethicist knowledgeable about the design, conduct and interpretation of clinical trials may be necessary if the study has unusually high risks or broad public health implications. Toxicologists, epidemiologists and clinical pharmacologists may also be necessary if such expertise is important for informed interpretation of interim results.

A DSMB should consist of a minimum of three members. Conflicts of interest deserve special consideration when choosing individuals to serve on a DSMB. DSMB members for a given trial should not include investigators in that trial, as their knowledge of interim results could influence their conduct of the trial. Members who have strong views on the relative merits of a particular intervention under study may have an "intellectual" conflict of interest and should not serve on the DSMB. Individuals who have relationships with trial investigators or sponsor employees should not be on the DSMB. Prior experience, while important for all DSMB members, is most important for the Chair. The Chair will provide leadership at meetings and in-between meetings. A DSMB should be independent of the sponsor.

For Planned Emergency Research: The Independent Data Monitoring Committee (DMC) is a requirement of 21 CFR 50.24(a)(7) (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation. Independence is described as "greatest when members have no involvement in the design and conduct of the trial except through their role on the DMC, and have no financial or other important connections to the sponsor (other than their compensation for serving on the DMC) or other trial organizers that could influence (or be perceived to influence) their objectivity in evaluating trial data."

DSMB Procedures and Responsibilities

DSMBs should have well-defined procedures in place and documented in a written plan, including:

- A schedule and format for meetings
- Format and types of reports and data it will review
- Format for presentation of data
- The timing of the committee's recommendations and reports
- The statistical approach that will be used to analyze data
- Specification of who will have access to interim data
- Specification of who may attend all or part of DSMB meetings

- Definition of a quorum of DSMB members
- Handling of meeting minutes
- Other issues relevant to committee operations
- A commitment to send summary reports of the interim analyses to each IRB that has approved the study in a timely manner
- A description of how and when interim analyses of data will be conducted to determine whether the research should continue as originally designed, should be changed, or should be stopped

One decision a DSMB faces is whether a study should be stopped. This can happen for several reasons, such as:

- Efficacy – with high certainty, the study question has been answered
- Futility – the study question will not be answered when the study is completed (i.e., too many subjects have been lost to follow-up or stopped the intervention)
- Safety – risks to subjects are too high

Face-to-face meetings are preferable, but telephone meetings may be necessary in some situations, such as when new information must be urgently considered. The initial frequency of DSMB meetings will depend on the expected rate of accrual and event occurrence at the time the trial is designed as well as the perceived risk of the experimental and/or control interventions. Meetings will be held at least annually. The study protocol will generally describe the schedule of interim analyses to be considered by the DSMB, or the considerations that will determine the timing of meetings. The study protocol will also typically describe the statistical approach to the interim analysis of trial data. To minimize the potential for bias, these descriptions should be complete before the conduct of any unblinded interim analyses.

Responsibilities of the DSMB include but are not limited to the following:

- Familiarize itself with the research protocol and plan for data and safety monitoring
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- Review reports of related studies to determine whether the monitored study needs to be changed or terminated
- Review major proposed modifications to the study prior to their implementation
- Appropriately document all proceedings of the DSMB

Most investigators and sponsors immediately accept and implement the conclusions of the DSMB, but occasional disagreements may require negotiation. The IRB, however, must be notified immediately of any recommendation by the DSMB to modify or stop a study.

Further guidance with regard to DSMBs can be found at the U.S. Food and Drug Administration website: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees