Developing
Data and Safety Monitoring Plans
for research involving human subjects

A Data and Safety Monitoring Plan (DSMP) promotes the integrity of a study and/or enhances the safety and protection of the research subjects. It is unique to any one study but may share common monitoring activities with studies of similar risk, design and purpose. The DSMP is to be commensurate with the study’s potential risks, size and complexity. Subject safety, and data integrity and validity are its foremost considerations.

For studies that present a low risk to subjects, safety monitoring may be conducted annually by the principal investigator (PI) or a PI designee. For studies that present a higher degree of risk, safety monitoring may occur more frequently as well as may be conducted by an independent monitor or a Data and Safety Monitoring Board (DSMB). NIH funded phase III clinical trials are required to have a DSMB. However, a DSMB may be utilized for any phase I, II or III clinical trial that is either multi-center, blinded/masked to the researcher, conducted in an emergency setting, uses a high risk intervention (gene therapy, cancer treatments, AIDS treatment), and/or includes a vulnerable study population (pediatric, pregnant, or psychiatric patients, prisoners). DSMBs are usually appointed for Phase II and III studies, and can be required by the sponsor, federal agency and/or Institutional Review Board.

The Ohio State University human research protection program policies on data and safety monitoring and event reporting are posted at http://orrp.osu.edu/files/2012/02/Data-and-Safety-Monitoring.pdf. There also are questions asked of the investigator concerning data and safety monitoring in the University’s applications for the Initial Review of Human Subjects Research and for the Continuing Review of Human Subjects Research [see http://orrp.osu.edu/irb/forms/].

**Background**

Since 1979, the NIH Office of Extramural Research has recommended that “every clinical trial should have a provision for data and safety monitoring.”(NIH Guide, Volume 8, Number 8, June 5, 1979). A more recent issuance [see http://grants.nih.gov/grants/guide/notice-files/not98-084.html ] stipulates that “all trials, even those that pose little likelihood of harm” should have a data and safety monitoring plan that is commensurate with the level of risk of the investigation. Please go to http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
for additional guidelines for NIH supported projects. Individual NIH institutes and Centers (IC) may have their own specific requirements (e.g., NIAMS, NINDS, etc.) [see http://www.nih.gov, and ‘click on’ the appropriate IC].

The study PI should be familiar with the specific DSMP requirements of the sponsor/funding agency in preparing the final monitoring plan for the protocol.

**Data and Safety Monitoring Plans**

The specifics of a DSMP depend upon the nature, size, complexity, and risk level of the research study. The goal is not to merely ensure regulatory compliance but to provide a framework by which to reduce harm or injury to individuals who are taking part in research, in order to further promote a level of conscientious conduct.

The minimum required content for a DSMP includes the following:

- Assessment of level of risk
- A plan for safety review (by whom and how often)
  - Anticipated adverse events
  - Adverse event (AE) grading and attribution
  - A plan for unanticipated and/or serious AE reporting
  - A plan for [annual] reporting of AEs
- Ensure compliance with the principles and process of informed consent
- Assessment of protocol compliance, including violations and/or deviations
- A plan for compliance with privacy related regulations (e.g., HIPAA)

Additional considerations may include:

- Safety review questions: What are the reasons for drop-outs? Are AEs too frequent or severe for the protocol to continue? Should the protocol be modified?
- Enrollment numbers: Do all of the enrolled subjects meet the inclusion and exclusion criteria as stipulated in the protocol?
- Plan for the ongoing review of results (i.e., specific information to be provided at the time of each periodic review, the basis for selecting that data set, the frequency of review, and the rationale for the recommended review frequency)
- Review of study personnel [qualifications and/or changes]
- Review of IND/IDE information, as applicable
- Assessment of completeness and quality of collected data

The plan may also include the development of prospective stopping rules, developed a priori, based upon futility of recruitment or benefit, unacceptable risk, or clinical superiority.
Once the DSMP is in place, it is important that it be implemented, i.e., safety data are reviewed according to the plan, and that any implications of the results are considered by the investigator(s), monitor(s) and/or DSMB, and acted upon appropriately. For example, if the data do not diverge from the pre-study projected safety profile, event rates and/or study progress, then this can be stated in the requisite report(s) and a recommendation can be made to proceed without modifications to the study. Any divergences from pre-study expectations are to be identified and their potential significance relayed to the sponsor, IRB and/or DSMB.

Other possible recommendations may include changes in the monitoring frequency and in the reported data elements for the periodic reports, amendments to the protocol (e.g., revisions to frequency of procedures, safety assessments, etc.), and/or modifications to the consent document and/or process. While the DSMP can be modified during the course of a study, any modification(s) to the DSMP may need to be submitted to the relevant entities (e.g. IRB, sponsor, DSMB).

The OSU Comprehensive Cancer Center (CCC) has a DSMP that is to be followed for all CCC protocols. Contact the CCC Clinical Trials Office at (614)293-4208 for assistance.

Every protocol that uses services of the Clinical Research Center of The Center for Clinical and Translational Science at OSU, must have a DSMP. Contact ccts-regulatory@osumc.edu, or call (614)293-9274 for further information.

**Data and Safety Monitoring Boards (DSMBs)**

DSMBs, (aka, data monitoring committees, safety monitoring committees) need to be considered for protocols that involve significant risk. Board members should be knowledgeable about the intervention being studied, have no conflict(s) of interest regarding the study, and be able to provide an independent perspective when considering safety, efficacy and conduct of the study. The role of the DSMB is to review study data and clearly express its recommendations to the researchers, e.g., PI and/or sponsor.

Reasons for a DSMB:
- To ensure that participants are not exposed to undue risk
- To ensure that the study will yield usable results
- To balance interests of subjects within the study with those outside the study
- To maintain trial integrity
- To ensure unbiased, timely publication of results
The composition of the DSMB should include:

- Researcher(s)/Clinician knowledgeable of the science of the study [science]
- Biostatistician and/or Epidemiologist [study design/analysis]
- Research subject advocate and/or ethicist [research ethics]

The description of the DSMB should include:

- The DSMB chairman and members
- How frequently the study will be evaluated, e.g. annually, quarterly, etc.
- Adverse event reporting requirements
- A description of interim efficacy analyses, if appropriate
- Study stopping rules, if appropriate
- The distribution of DSMB reports.

The activities of the Board may include:

- Review the research protocol, informed consent documents, and the data and safety monitoring plan including providing revision recommendations;
- Evaluate the progress of intervention trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk(s) versus/and benefit(s), performance of the trial site(s), and any other factors that may affect study outcome;
- Evaluate if clinical equipoise or “principle of uncertainty” has been disturbed;
- Consider relevant factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- Compliance;
- Protect the safety of the study participants;
- Report on the safety and scientific progress of the trial;
- Make recommendations to the PI, sponsor, and, if required, to the FDA concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the intervention(s) and/or procedure(s) involved in the study;
- Assist the sponsor by commenting on any problems with study conduct, enrollment, sample size, and/or data collection;
- If appropriate, review interim analysis of efficacy (and/or safety) in accordance with stopping rules that are clearly defined in advance of data analysis. In most cases, these stopping rules are proposed by the PI and approved by the DSMB with modification(s) as necessary to ensure patient safety.
- Ensure the confidentiality of the study data and the monitoring recommendations.

The meeting frequency of the DSMB, its composition and responsibilities are to be tailored to the design and level of risk of each investigation. Minutes of each DSMB are to be maintained.
Following each DSMB meeting, the DSMB chairman is to provide the study leadership [e.g., PI, Steering Committee, etc.] with a written report concerning the DSMB’s review, its finding and recommendations. The leadership in turn will respond and proceed in resolution with the Board, making any required notifications for protocol revisions and/or safety concerns, including adverse event reporting, to the IRB and/or sponsor.

It is the responsibility of each principal investigator, to establish a DSMB for any protocol that poses elevated risk (e.g. significant risk, double-blind investigational therapeutic intervention) and/or is a multi-center clinical trial. The DSMB should include an individual or individuals with sufficient expertise to make safety decisions for the study, e.g., clinician, statistician, ethicist, research subject advocate, epidemiologist, data manager and/or a scientist from other (related) fields. Members from within the principal investigator’s home institution who are not directly affiliated with the study may be recruited and enrolled to serve. Members of the DSMB should familiarize themselves with the research protocol and the plans for data and safety monitoring, i.e. DSMP; review reports of related studies to determine whether the current study needs to be changed or terminated; review any major proposed modifications to the study prior to their implementation (e.g., termination, data collection procedures, study design, sample size). DSMB members should in no way be directly associated with the study so as to be impartial (e.g. no financial or other conflict of interest) to the study’s outcome.

For some studies (e.g., multi-center industry initiated and/or sponsored studies, multi-center government sponsored studies), the sponsor or contract research organization will create an external DSMB that will assume the responsibility of monitoring and conducting data and safety reviews. For other studies an investigator may recruit [local] colleagues or experts in the area of study, who are independent from the research, to form a DSMB to monitor the safety and efficacy of the study. Generally, these are investigator initiated, single-center, double-blind investigational intervention studies for which monitoring by the PI alone does not confer adequate safety for the participants.

For any DSMB consideration must also be given regarding honorariums as well as compensation for per diem and other travel expenses, if such expenditures are necessary. Meetings may be held face-to-face and/or via teleconference. Regardless, some provision in the study budget may need to be made for these various potential costs.

DSMBs may be liable for their actions. Consideration should be given on how its members can be protected. For NIH-funded projects such discussions could be initiated with the respective IC Project Officer; and for industry-sponsored studies with the Project Manager. While there is a
low probability of litigation, it is a risk that should be addressed. [see reference http://ctj.sagepub.com/cgi/content/abstract/1/6/525]


Whereas most clinical trials involve some method of ‘blinding’ (aka ‘masking’), the DSMB must have access to all study data in order to make judgments concerning the safety of the human subjects. Therefore, explicit operating rules must be written to ensure that no inappropriate information or assessments are provided to the researchers, i.e., investigators and/or study coordinators yet, are provided for the DSMB. Safety monitoring guidelines should also include preparation of reviews, minutes or recommendations not provided to the (blinded/masked) investigator(s), unblinding of data, in order to ensure study participant safety and/or to address a study hypothesis.

During queries, review and reporting, subject data should be presented without specific subject identifiers, i.e., subject confidentiality must be maintained throughout the monitoring process. Where necessary for identification by the DSMB, reference to a specific study participant will be made by non-personal identifier(s), e.g., study ID number. [NOTE: Neither a Medical Record Number, nor Social Security Number are acceptable methods for human subject identification.]

During the course of the study, the study team under the direction of the Principal Investigator, is to provide written reports to the DSMB in preparation for its specified reviews. For certain protocols the report [and meeting] may need to be submitted [conducted] in two parts: an “open” section [session], which presents data only in aggregate and focuses on trial conduct issues, timeliness of data submission, eligibility rates and reasons for ineligibility; and a “closed” section in which outcome data (e.g., safety, and efficacy) are presented.

Conclusion

The DSMP does not replace the investigator’s responsibility for required reporting (e.g., the IRB, sponsors, FDA). Any reporting stipulated by the DSMP may be in addition to these core obligations. The DSMP and/or DSMB are intended to be complementary to other institutional and/or governmental obligations, and to promote the quality and integrity of the research endeavor as experienced by all of its participants.
Please email  ccts-regulatory@osumc.edu  or telephone (614)293-9274 for further information about DSMPs and/or DSMBs.

Bibliography

Cairns JA, Hallstrom, Held P. Should all trials have a data safety and monitoring committee? *Am Heart J* 2001;141:156-163.


Califf RM, Ellenberg SS. Statistical approaches and policies for the operations of data and safety monitoring committees. *Am Heart J* 2001;141:301-303.


