

APPENDIX L GUIDANCE FOR DATA AND SAFETY MONITORING PLANS AND REPORTS

Federal regulations governing research with human subjects require the following:

1. The research plan, when appropriate, shall make adequate provisions for monitoring of the collected data to ensure the safety of research subjects (45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6))
2. There shall be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the research data (45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7)).

To address those regulatory requirements, the University of Pittsburgh (UP) Institutional Review Board (IRB) has developed a policy requiring that each research application, with the exception of studies designated as "exempt," include a formal "data and safety monitoring plan" that addresses how the investigators will assure the safety of research participants and the confidentiality of their research data.

What is a Data and Safety Monitoring Plan (DSMP)?

A DSMP is a specific plan, developed by the local principal investigator (PI) that outlines how study progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data. The method and extent of monitoring may vary across different types of studies, depending on multiple factors, including the experimental design and complexity of the study (e.g., Phase I vs. Phase III trial vs. a descriptive psychosocial interview study), and the degree of risk to subjects. The following factors should also be taken into account when determining the level of monitoring: 1) the policies of the study sponsor; 2) the number of sites involved (single vs. multicenter) 3) the phase of the study; 4) the public profile of the study; 5) any conflicts of interest; 6) the level of risk to subjects and 7) the study locations.

What should be included, at a minimum, in a DSMP?

A DSMP should be developed to address the following:

1. **Who (the individual or entity) is responsible for the oversight of the data and safety monitoring plan?**
2. **What will be monitored?** In developing an appropriate DSMP, consideration should be given to incorporating the following elements:
 - An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data
 - A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is any change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated. If appropriate and if specified in

the IRB protocol, interim analyses of the efficacy of the intervention should be performed in accordance with previously defined stopping rules.

- An assessment of external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study
- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data
- For studies in which the University of Pittsburgh serves as the overall coordinating center, the DSMP must include a description of how the results of monitoring will be communicated to the other sites.

For all research protocols, there must be a stated commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events).

3. **When will the monitoring occur?** The appropriate frequency of data and safety monitoring will be dependent on the nature of the research study but at a minimum formal monitoring must be performed annually.

4. **What will be reported to the IRB?** The DSMP should include information about what will be reported to the IRB at the time of continuing review (or more often as required). At a minimum, the IRB expects the following information to be submitted (i.e., in writing by the person or entity responsible for data and safety monitoring) as part of the process of obtaining continuing IRB approval of a research protocol:

- A list of the research personnel who participated in the data and safety monitoring
- The frequency of monitoring that took place during the renewal interval and/or the date(s) that data and safety monitoring was conducted
- A summary (i.e., for the study as a whole) of cumulative data related to unanticipated problems (including adverse events) including a determination of causality and whether the risk to benefit assessment has changed
- If appropriate, a summary of pertinent scientific literature reports, therapeutic developments, or results of related studies that may have an impact on the safety of study participants or the ethics of the research study
- A summary of the outcome of reviews conducted to ensure subject privacy and research data confidentiality

- Final conclusions regarding changes to the anticipated benefit-to-risk assessment of study participation and final recommendations related to continuing, changing, or terminating the study
- If a recommendation is made to change the research study, an adequate rationale for this decision should be provided.

What is a Data and Safety Monitoring Board or Committee?

A Data and Safety Monitoring Board or Committee (DSMB/C) is a group of individuals with expertise in the area of the proposed research that is responsible for: 1) reviewing on a regular basis, data accumulated from an ongoing trial; 2) advising the principal investigator or study sponsor of necessary changes to elements of the study that affect subject safety; 3) determining whether there has been any change to the risk-to-benefit assessment; and 4) determining whether the study should continue as written.

What type of members should a DSMB/C include?

The DSMB/C should be composed of multidisciplinary representation, including experts from relevant medical and scientific specialities and biostatisticians. This may include other experts such as bioethicists, epidemiologists, and basic scientists. Individuals on a DSMB/C should be free of apparent significant conflict of interest, whether they are financial, intellectual, professional, or regulatory in nature. The appropriate size of the DSMB/C depends on the type of study and types of expertise needed.

When is a DSMB/C needed?

The IRB reserves the right to request a DSMB/C for any study. However, the following are factors that the IRB will consider when making this determination:

1. There is a significant likelihood of a serious adverse event to the involved subject
2. The study is conducted at multiple sites and the level of risk is greater than minimal
3. The study generates data that is blinded or randomized
4. The study involves a large number of subjects (Phase III)
5. The study involves a gene transfer methodology

There are circumstances when the IRB might determine that a group independent of the study team as well as the sponsor must perform monitoring activities.

What should be included in the Data and Safety Monitoring Report?

At the time of continuing review (or more frequently, as necessary), the Principal Investigator is required to submit all required data and safety monitoring reports. The IRB is unable to adequately review an application for continuing review without the local report as well as a report from a central reviewing body, if applicable. The reports should be dated, and signed; and should include the IRB number, Principal Investigator's name, and title of the study.

The report should not be a reiteration of the "plan" but rather should include information related to the monitoring that has occurred over the last renewal period. Even studies that are in 'data analysis only' should include a DSMP report which addresses how the privacy of the study participant and confidentiality of study data has been maintained during the past renewal period. The report should include:

- A list of the research personnel who participated in the data and safety monitoring
- The frequency of monitoring that took place during the renewal interval and/or the date(s) that data and safety monitoring was conducted
- A summary (i.e., for the study as a whole) of cumulative data related to unanticipated problems (including adverse events) including a determination of causality and whether the risk to benefit assessment has changed
- If appropriate, a summary of pertinent scientific literature reports, therapeutic developments, or results of related studies that may have an impact on the safety of study participants or the ethics of the research study
- A summary of the outcome of reviews conducted to ensure subject privacy and research data confidentiality
- Final conclusions regarding changes to the anticipated benefit-to-risk assessment of study participation and final recommendations related to continuing, changing, or terminating the study
- If a recommendation is made to change the research study, an adequate rationale for this decision should be provided.

Additional Information Related to Funding Agency Requirements

Various funding sources have additional requirements related to data and safety monitoring. Before preparing a plan, please refer to the following web sites for further information:

http://www.nci.nih.gov/clinical_trials/doc.aspx?viewid=a7fbcf28-458e-4f1b-a8e4-5d9c4a9171d5 (NCI)

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html> (NIH)

<http://www.nimh.nih.gov/researchfunding/safetymonitoring.cfm> (NIMH)

<http://www.nhlbi.nih.gov/funding/policies/dsm-12.htm> (NHLBI)

<http://www.niaid.nih.gov/ncn/clinical/decisiontrees/datasafety.htm> (NIAID)

In addition, the Office of Clinical Research (OCR) has established an Institutional Data and Safety Monitoring Board (IDSMB) in order to assist in the monitoring of studies that require a DSMB/C. For further information about this service visit the OCR web site at

www.clinicalresearch.pitt.edu/irs/services/DSMB/index.cfm.