



ASSESSING THE DATA AND SAFETY MONITORING PLAN

10/31/2007

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."

Consequently the DUHS IRB requires investigators who are planning a research study that places human subjects at more than minimal risk to describe their strategy for monitoring the data to ensure the safety of research subjects. The data and safety monitoring plan is intended to ensure the safety of participants 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 final monitoring activities.

A Data and Safety Monitoring Plan (DSMP) is unique to a particular study. Appropriate DSMPs may fall anywhere along a continuum from monitoring by the principal investigator or 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. (This would be appropriate for a single site open label trial.)
- An uninvolved expert in the research topic performs the safety monitoring. (This would be appropriate for 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.

Regardless of the type of DSMP, the individuals participating in the monitoring plan must be objective.

Safety monitoring must consider periodic evaluation of all adverse events, including non-serious and expected events. For example, if one arm of a study 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. Safety monitoring must also include the prompt evaluation of serious adverse events and other serious unanticipated problems involving risk to subjects or others. When appropriate, safety monitoring must also consider evaluating efficacy. 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.

If a DSMB is to be used, there are two main questions that the DSMB members should answer during their review:

- are there any unexpected or severely toxic effects, and
- has there been a beneficial outcome of the trial thus far?

Their priority is to ensure subject safety by reviewing data that are not available to the investigators or the IRB involved with the research study. In cases where the DSMB members conclude that there is a difference in the safety profile of different arms of the study, the DSMB may receive unblinded data. This allows them to make a more informed judgment as to whether the research study should continue as planned.

The DSMB periodically produces a summary report that provides information concerning the cumulative toxicities observed in trial participants 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.

Research settings where a DSMB may be required:

- A large study population.
- Multiple study sites, since it may be more difficult to recognize a pattern of increased or unusual problems when investigators treat small fractions of the population separately.
- Highly toxic therapies or dangerous procedures.
- High expected rates of morbidity or mortality in the study population.
- High chance of early termination of the study.

Ordinarily at least three of the factors listed are present before the DUHS IRB will require that a DSMB be established.

The DUHS IRB will assess the adequacy of the proposed Data and Safety Monitoring Plan during its review of a protocol, and may require that a DSMB be established for the study, as a condition necessary for the IRB's final approval.