

CPRC Data & Safety Monitoring Policy

1. Every trial needs to list a provision for data and safety monitoring within the protocol. All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee that is external to the trial organizers, sponsors, and investigators.
2. The CPRC has responsibility of informing trial investigators concerning the data and safety monitoring policy and procedures. Considerations such as who shall perform the monitoring activities, the composition of the monitoring group (if a group is to be used), the frequency and character of monitoring meetings (e.g., open or closed, public or private), and the frequency and content of meeting reports should be a part of the monitoring plans.
3. Conflict of Interest Suggestions
 - a. NIH: "Ideally, participants in monitoring outcomes of a trial are in no way associated with the trial."
 - b. FDA:
 - i. "We therefore recommend that DMC members for a given trial not include investigators in that trial."
 - ii. "Individuals known to have strong views on the relative merits of the interventions under study may have an "intellectual" conflict of interest and might not be able to review the data in a fully objective manner; such individuals may therefore not be optimal DMC members. We recommend that sponsors avoid appointing to a DMC any individuals who have relationships with trial investigators or sponsor employees that could be considered reasonably likely to affect their objectivity."
4. We recommend that sponsors consider using a DMC for clinical trials when:
 - a. The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
 - b. There are a priori reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
 - c. There is prior information suggesting the possibility of serious toxicity with the study treatment;
 - d. The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity
5. Phase Guidelines
 - a. **Phase I:** The CPRC may require the study investigator to perform continuous monitoring of participant safety with frequent reporting to staff with oversight responsibility.
 - b. **Phase II:** The CPRC may require monitoring similar to that of a phase I trial or supplement that level of monitoring with individuals with expertise relevant to the study who might assist in interpreting the data to ensure patient safety.
 - c. **Phase III:** The CPRC will require a DSMB to perform monitoring functions. This DSMB would be composed of experts relevant to the study and would regularly assess the trial and offer recommendations concerning its continuation.
 - i. Data and Safety Monitoring Boards (DSMBs) are required for Phase III multi-site interventional trials. It is highly suggested that investigators and/or sponsors adhere to the conflict of interest policies suggested by the NIH and FDA as outlined below. While failure to do so may not result in rejection of the study application by the CPRC, the committee may request further

information regarding the DSMB membership and practices to assure study participant safety; ultimate approval of the study by the CPRC will be contingent upon the investigator and sponsors' responses.

MONITORING ENTITY DEFINITIONS

<p>Data & Safety Monitoring Committee (DSMC)</p>	<p>An institutional committee <u>setup to have oversight over all trials within that institution.</u></p> <p>The DSMC advises these bodies on continuation or stopping based upon safety and efficacy considerations. The primary objective is to assure safety for the patients in the trial. The DSMC is composed of three to five members and should include one or two clinicians knowledgeable in the field of the trial, one or two statisticians and in some situations a pharmacologist and an ethicist. It is important that the members have experience from other trials and have high integrity. Rules for the statistical analyses have to be set up in the beginning of the trial. However, the DSMC cannot rely only upon statistical rules. Information from other sources may cause stopping before the scheduled end of the trial. The DSMC has to check that the overall quality of the data is good and that everything is current with classification of endpoints. Legal requirements to report serious adverse events to legal authorities may be taken over by the DSMC, which ideally is the only body that has access to unblinded data.</p>
<p>Data Safety Monitoring Board (DSMB)</p>	<p>An independent group of experts that advises the sponsor and is <u>setup for an individual trial.</u></p> <p>The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the sponsor concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.</p> <p>The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review.</p> <p>During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.</p>

<p>Independent Safety Monitor (ISM)</p>	<p>A physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.</p> <p>An ISM could be the sole monitor for the study or may perform this role as a member of a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC). An ISM is appropriate as the sole independent safety monitor for small, early phase studies considered to be low risk, such as some pharmacokinetics or immunogenicity studies, or other studies of short duration. DSMBs and SMCs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events (SAEs) rather than all adverse events (AEs).</p> <p>No ISM should have direct involvement in the conduct of the study. Furthermore, no ISM should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making.</p>
<p>Medical Monitor (MM)</p>	<p>Medical Monitor (MM) oversight process is appropriate for studies that are deemed as needing additional oversight, but not requiring the intensity of the other monitoring models listed previously. These are studies that may include procedures that are considered greater than minimal risk (punch biopsy, additional x-rays, etc.), may be high profile for the sponsor, or involve a substantial investment on the part of the sponsor. Generally the PI will submit a report to the Medical Monitor every 6 months. This report will include data regarding enrollment and retention, unanticipated problems and protocol deviations, disposition of biospecimens, outcome measures and other relevant parameters.</p>