Data and Safety Monitoring Plans and Boards

Data and Safety Monitoring Requirements

All interventional studies involving greater than minimal risk must include a Data and Safety Monitoring Plan (DSMP). The DSMP should specify whether or not there will be an independent Data and Safety Monitoring Board (DSMB). Not all trials require an independent DSMB.

> **Interventional research studies** are prospective, human research studies that are designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention, or are designed to answer specific questions about human physiology.

> **Greater than minimal risk research studies** are those where the probability and

magnitude of harm or discomfort anticipated in the proposed research are greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Data and Safety Monitoring Plans

The PI is responsible for ensuring that there is an appropriate DSMP in place at the time of IRB submission and for ensuring that the safety-monitoring plan is implemented over the life of the protocol.

What is a DSMP? [1]

A DSMP is a plan established to assure that each research study has a system in place for appropriate oversight and monitoring of the conduct and progress of the study that ensures:

1. Important information that may affect the safety or welfare of participants comes to light and is acted upon as quickly as possible, and
2. The validity and integrity of the data.

What type of DSMP is appropriate?

Development of an appropriate DSMP must include consideration of the following:

Is the DSMP commensurate with the risks involved with the research? Safety monitoring intensity and frequency should be tailored to fit the expected risk level, complexity, size, type of participant population and type of study (i.e., biomedical vs. behavioral research).

Where does the DSMP fall along the continuum from monitoring by the PI or group of investigators to the establishment of an independent DSMB or DMC? The DSMP should indicate specifically whether or not there will be a DSMB or DMC.

Does the DSMP include a specific plan for capturing and reporting post-approval events to the IRB and other entities (e.g. medical monitors, study sponsors, and/or federal agencies, as appropriate)?

What should you include in a DSMP?

Key areas that should be included in the plan are:

- An explanation of the plan to monitor study progress and safety.
- A description of who will perform the monitoring reviews and at what frequency.
- The type of data and events (i.e., efficacy data, adverse events, unanticipated problems involving risk to participants or others) that are to be captured under the monitoring plan.
- Procedures for communicating the outcome of reviews by the monitoring entity to the IRB, the study sponsor and/or other appropriate entities.

As appropriate, also include the following:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study intervention(s)

What if a DSMP or DSMB/DMC is already required by other entities (e.g. CRS, Cancer Center, FDA)?

A DSMP should already be part of the application for studies conducted at a Clinical Research Services (CRS) facility or the Cancer Center. It is acceptable to cut and paste a plan accepted by the CRS or Cancer Center into your IRB Application.

For studies conducted under the jurisdiction of the FDA, you may need to summarize and add supplemental information from the sponsor?s protocol for the DSMP section of the IRB Application.

What about investigator-sponsored IND/IDE research?

When an investigator files an IND [2] or an IDE [3], the investigator is considered to be the study sponsor and as such carries all of the FDA regulatory responsibilities and safety-reporting obligations of both the Investigator and the sponsor, as described in the FDA regulations 21 CFR 312 (drugs) [4] and 21 CFR 601 (biologics) [5] and 21 CFR 812 (devices) [6]. Please refer to these regulations for complete information regarding reporting responsibilities.

Data and Safety Monitoring Boards

What is a DSMB or Data Monitoring Committee (DMC)?

A DSMB or DMC is a formal committee ? independent of the trial organizers and investigator(s) ? that is specifically established to conduct interim monitoring, oversight and analysis of study information and data to assure the continuing safety of research participants, efficacy of the study intervention, appropriateness of the study, continued relevance of the study question, and integrity of the accumulating data throughout the life of a research project.

DSMBs/DMCs are typically made up of individuals who have expertise in the field of investigation, experience in the proper conduct of clinical trials, and/or statistical knowledge, and who do not have any serious conflicts of interest (i.e., financial, intellectual, professional or regulatory).

What is the purpose of an independent DSMB?

The primary purpose of an independent DSMB is to protect the research subjects through independent analysis of emerging data from the trial. This differs from adverse event reporting

in that the DSMB can review aggregate and unblinded data as the data accumulate, identify significant issues and trends during the study, and recommend changes in the study including recommending early termination of the study.

The DSMB reviews data for both safety and efficacy. The protections afforded by this review apply to both current subjects and future subjects if the DSMB identifies the need to modify or even halt the trial.

In addition to the above, an independent DSMB protects the credibility of the trial by virtue of its independence from the study sponsors, and helps to ensure the validity of study results by reviewing data on subject accrual and conducting interim reviews.

When is an independent DSMB needed?

The IRB generally expects DSMBs in the following situations:

- **All Phase III studies** require a DSMB, with the exception of low-risk behavioral and nutritional studies. For this discussion, ?low-risk? refers to trials where subjects are expected to experience only minor side effects, and interim analyses are not crucial for the protection of the subjects.The involvement of a DSMB may still be requested for low-risk studies if the studies are exceptionally large, long term, and/or involve vulnerable subjects.
- **Phase II clinical trials which are multicenter and randomized** require a DSMB, with the exception of low-risk behavioral and nutritional studies.
- **Phase II studies which are ?high risk?** require a DSMB. For this discussion, ?high-risk? refers to trials of interventions associated with substantial side effects to subjects (e.g., side effects that could result in serious morbidity or death, or are irreversible), trials of diseases associated with high mortality or morbidity, and trials of highly experimental therapies (e.g., gene therapy). As a general guideline, DSMBs are needed for clinical trials of diseases with high mortality or morbidity, for clinical trials involving high risks, and for large, multicenter clinical trials.

Note: This guidance is based on and consistent with NIH policies and guidance on requirements for DSMBs [7]. The NIH requires DSMBs for all Phase III clinical trials, and many of the individual Institutes require broader use of DSMBs. This is slightly more stringent than FDA guidance [8], which generally recommends Data Monitoring Committees/DSMBs for controlled trials comparing rates of mortality or major morbidity.

When is an independent DSMB not needed?

The IRB does not generally expect DSMBs in the following situations:

- Single-center open-label Phase I and II clinical trials generally do not need a DSMB since the local investigator will have access to all data.
- A multicenter, high-risk Phase I clinical trial should not require a DSMB if there are very clear rules for stopping the trial. For example, the IRB would not ask for a DSMB for a classic open-label dose escalation trial with clear and objective criteria for halting the

dose escalation when unacceptable side effects are observed. A DSMB is likely to be requested if the DSMP lacks objective criteria for continuing or halting the trial.
- A DSMB may not be feasible for clinical trials that are expected to accrue too quickly to allow for a DSMB to be constituted and complete data and safety monitoring.

Important Note: For some studies involving particularly vulnerable study participants (e.g., children or persons with impaired ability to consent), the IRB may also ask for a DSMB as an additional measure of subject protection.

What to include in the IRB Application?

If your study utilizes a DSMB, include additional details about the membership and function of the DSMB in the "Data and Safety Monitoring Plan" section of the IRB Application. In particular, include the following information in the :

- **Composition**: Describe the expertise represented by the members of the DSMB. DSMBs generally include members with expertise in biostatistics, clinical trials, and the disease and treatment being studied. Other areas of expertise such as bioethics may also be useful.
- **Independence**: You will be asked to confirm that the DSMB members are independent of the study sponsor and will not participate in the study as investigators, nor will they have conflicts of interest regarding the study, the study sponsor, or any study drugs or devices being tested.
- **Data**: Briefly describe the data the DSMB will review, e.g., data for primary or secondary endpoints (safety and efficacy), data for early termination of trial (stopping rules), or adverse events.
- **Frequency of Review**: Describe how often the board will meet, whether based on the calendar or accrual targets. If formal interim analyses are planned, describe when they will occur.
- **Authority**: Describe the actions the DSMB is authorized to take. DSMBs should have authority to recommend changes in the study, including discontinuation, if significant trends in safety or efficacy are identified earlier than expected.

You can submit a copy of the DSMB Charter, but it is not required.

What if the sponsor's plans do not satisfy these guidelines?

We understand that site investigators may not have authority to make changes in multicenter studies. However, there have been numerous cases where the concerns or recommendations of local IRBs and site investigators have led to changes in multicenter studies. You are strongly encouraged to share these guidelines with study sponsors or steering committees before submitting to the IRB.

If plans involving a DSMB diverge from these guidelines, the "Data and Safety Monitoring Plan" section of the IRB Application should include a clear and complete rationale. Contact us [9] for advice.

How do I submit DSMB reports to the IRB?

DSMB reports must be submitted to IRB via iRIS following these instructions [10].

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Links
[1] https://irb.ucsf.edu/#
[2] https://irb.ucsf.edu/investigational-new-drugs-and-biologics
[3] https://irb.ucsf.edu/investigational-devices
[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312
[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=601
[6]
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1
[7] http://grants.nih.gov/grants/policy/hs/data_safety.htm
[8] http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm
[9] https://irb.ucsf.edu/contact-us
[10] http://irb.ucsf.edu/sites/hrpp.ucsf.edu/files/post-approval-reporting-summary-sheet.pdf