IRB Approval of Data and Safety Monitoring Plans

Overview:
All clinical trials must include plan to monitor the collected data and ensure subject safety. If a data and safety monitoring plan is not included within the protocol document, the plan must be requested and submitted to the IRB in a separate document that can be reviewed and posted as a protocol addendum.

Under 45 CFR 46.111 and 21 CFR 56.111, the IRB must ensure that "the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects" as one of the conditions of IRB approval. Therefore, the IRB must evaluate whether the sponsor's plan to monitor data and safety is adequate given the phase, design, nature and risk of the research.

Requirements:
When a DF/HCC investigator is the sponsor of the trial, the data and safety monitoring plan must, at minimum, include the following:

- All Pilot, Phase I, I/II and II (non-randomized) protocols must be reviewed by the DF/HCC Data Safety Monitoring Committee (DSMC) as per COM-100.
- All Phase III or randomized Phase II protocols must be reviewed by the DF/HCC Data Safety Monitoring Board (DSMB) as per COM-100.
- All interventional, multi-center protocols must incorporate the DF/HCC DSMP template language.

For all other clinical trials, including externally-sponsored trials, the sponsor must develop an appropriate data and safety monitoring plan. The plan may incorporate many different methods of monitoring, but at a minimum should include the following information:

(i) Types of data or events captured, for example:
- What safety information will be collected (including serious adverse events)
- How safety information will be collected (e.g., via case report forms, at study visits, by telephone calls with participants)
- When data will be collected (e.g., frequency; when collection starts)

(ii) Roles and responsibilities for gathering, evaluating and monitoring the data
- Roles of investigators, research staff, sponsor, and monitoring committee/entity
- Who will verify data accuracy, by what method
- Who will verify compliance with the protocol

(iii) Information about the monitoring entity
- Description (e.g., individual Medical Monitor, independent Data Monitoring Committee)
- Appropriate independence of judgment from the investigators conducting the trial

(iv) Timeframes for reporting adverse events and unanticipated problems to the monitoring entity

(v) Frequency of monitoring entity's assessment of data or events.

(vi) Specific triggers or stopping rules:
- Conditions that would trigger an immediate suspension of the research.
- If not using a data monitoring committee, the plan should describe statistical tests for analyzing the safety data to determine whether harm is occurring.

(vii) Procedures for communicating the outcome of the reviews by the Monitoring Entity to the IRB, the study sponsor, and other appropriate entities.

(viii) For multi-center clinical trials involving high risk to subjects, frequent monitoring by an independent board or committee is generally expected.

Examples:
The examples below are provided for reference only. DF/HCC does not require the specific language below.

Sponsor will have access to the safety data on a regular basis. Sponsor will host investigator teleconferences on a regular basis during the study. Further, during the dose escalation part of the study, Sponsor and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. Safety data include laboratory results, ECGs, scans, and adverse events regardless of causality. At the dose escalation teleconference the clinical course for each subject in the current dose cohort will be described in detail. Updated safety data on other ongoing subjects, including data in later cycles, will be discussed as well.

Decisions will be sought to be made by consensus among the medical monitor, PV physician, and PIs. Meeting minutes of the dose determination meeting and dose determination notification are provided to each PI with a request to reply via email their acknowledgement and agreement with the next planned dose.

This protocol will require oversight from an independent Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual continuing review date. Subsequently, the protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator at each site.

The Sponsor pharmacovigilance physician and medical monitor actively monitor all safety data on a regular basis. The safety monitoring is inclusive of laboratory results and ECGs if applicable (e.g. hematology, chemistry, special chemistry). Moreover, the Sponsor conducts weekly investigator meetings to discuss patients receiving study drug that includes a discussion of all adverse events experienced by subjects exposed to study drug irrespective of attribution or severity. Bimonthly listings are reviewed by the medical monitor and an independent review of the bimonthly data is completed by the product safety physician to ensure the absence of significant safety issues that would warrant a protocol and/or ICF change.