Health Sciences-IRB Memo

RE: Guidelines for Data & Safety Monitoring in Protocols Submitted to the HSIRB

Date: Nov. 26, 2003  (Updated July 14, 2004)

The HSIRB is concerned with a study’s plan for monitoring the safety of the participants/subjects, the validity and integrity of the data and the efficacy of the intervention under investigation. An appropriate data and safety plan is needed for human subjects’ studies. Various approaches can be taken depending upon risk to subjects, the design of the study and the complexity of the data.

After reviewing numerous Federal guidelines and other Universities’ and medical centers’ guidelines about approaches to data and safety monitoring, we concluded that all research studies with human subjects require some form of monitoring, with the method and degree being commensurate with the degree of risk to subjects and the complexity and size of the study. Therefore, a protocol being submitted to the UB HS IRB for review should have a section, “Data and Safety Monitoring Plan”, which assures the study has proactively defined a system for oversight and monitoring by detailing the approach that will be used and the criteria for determining data integrity and validity, and subject safety.

“Monitoring” exists on a continuum, from reviewing data and events on an ongoing basis by the PI and/or project manager, to a Safety staff member (internal), to a data safety committee (internal) to a data safety monitoring board (external). The nature of the plan is also related to the Phase of the study.** Definitions follow on page 3.

The following are guidelines which the UB HS IRB is establishing for investigators who are submitting studies for IRB approval:

- Written policies and procedures must be included in the proposal for the protocol, in a section called “Data and Safety Monitoring Plan.”
- Regardless of the method, monitoring must be prospective and on-going.
- A plan for reporting Adverse Events to the IRB and the respective oversight agency (NIH, FDA, sponsor, DSMB) must be detailed.

In Pharmaceutical Clinical Trials, we are looking for your plan:

Phase I and II studies – are allowed flexibility in monitoring approach.
  o A PI may monitor subject safety & or data integrity.
  o A Project coordinator may monitor subject safety & or data integrity.
A data monitoring committee or board may be indicated (if the study is multi-site, blinded and includes a large sample and the intervention is more than minimal risk/vulnerable populations).

Important: if multi-site, at minimum there needs to be a central reporting entity that is responsible for collecting SAEs from all sites, compiling them, and preparing a timely summary report to sites and their IRBs.

**Phase III studies** - *All Phase III studies require a formal data and safety monitoring plan.*

- This may be a data and safety monitoring committee (Internal to the institution) or a may mean a data safety monitoring board (external/independent).
- A Data Safety Monitoring Board (DSMB) is needed when the study involves:
  - A large study population
  - Multi-sites
  - Highly toxic/dangerous interventions; high risk
  - High expected morbidity or mortality in the population.
  - Vulnerable subjects
  - Long duration.

**In Other Intervention or locally initiated Studies, we are looking for a detailed description of the actions and follow up that will be part of the procedure to monitor for safety.** For example, if a single intervention or research event takes place at a health care facility, how long will the person stay and be observed at the site? When and who will make a follow up contact (that is reasonable in relation to the intervention or activity) to determine there was not an adverse reaction after leaving the facility? A general guide is:

  **Minimal risk**, small number of subjects, single site – monitoring can be performed by PI or designee on the research staff.

  **Moderate risk**, larger number of subjects, and/or multiple sites – a specific person who is external to the research project should review data and safety reports. Monitoring subject reactions can be part of the research personnel responsibilities.

  **High Risk**, large number of subjects and/or multiple sites - an oversight board should be set up to monitor data and safety of research subjects (usually referred to as a Data and Safety Monitoring Board.) Monitoring subject reactions should still be part of the research personnel responsibilities.

**What is monitored by the designated person/board?**

1. Safety of subjects.
   - Most obvious indicator- SAEs.
   - Need to look at rates by arm of trial, and rates across all sites.
   - Compare to usual incidence of event in like population not on study.

2. Effectiveness.
   - If benefit becomes apparent.
   - If NO benefit becomes apparent.

3. Conduct.
   - Recruitment rates adequate.
   - Eligibility criteria held.
   - Protocol followed.
   - Data complete and timely.
   - Drop out rates accounted for and comparable among arms.
Accrual rates adequate to proposed plan.

**What Study Safety Plan Includes?**
- Format of the monitoring plan.
- What the follow-up entails
- Persons responsible.

**Review Process, to include:**

- **Safety:**
  - Conditions of Serious Adverse Events (SAEs) and who/how/when reported.
  - Plan of how and when to un-blind subjects if applicable.
  - Stopping criteria (“rules”):
    - Evidence of harm (SAE rates and threshold)
    - No likelihood of benefit
    - Overwhelming evidence of benefit.

- **Data management and integrity:**
  - Verification plan
  - Valid analysis (unbiased)
  - Data review plan and intervals
  - When / how any interim data will be released.

For multi-site studies, indicate how and when comparison of safety data and outcome indicators will be made across sites. Indicate who will review this.

**What is the ongoing responsibility for data and safety monitoring?**
- *Monitor your data and subject safety as specified in your approved protocol.*
- *If your study has a Data and Safety Monitoring Board, any report from the DSMB which the investigator receives should be forwarded to the IRB; at the time of your protocol renewal application, the DSMB findings should be attached, or a statement that there are no findings reported by the DSMB to date.*
- *Report SAEs to the IRB, the oversight agency (FDA, NIH) and the sponsor, if there is one, according to the approved format, in a timely fashion.*

**Definitions:**
- **Safety Monitoring**- any process during a clinical trial that involves the review of accumulated outcome data for groups of patients to determine if any of the treatment procedures should be altered or stopped. Focus is safety of patients and validity of data. (National Arthritis, Musculoskeletal and Skin Diseases Division of NIH, 6/2/20030).

- **PI / Study Coordinator Monitors** – Internal study personnel monitor the data for safety and effectiveness with a prospective plan for criteria, when a study is short in duration, has a small number of subjects, is low risk and is at a single site.

- **Data Monitoring Committee (DSC)**- a group within the organization with clinical expertise regarding the topic of the study, + biostatistician, possibly an ethicist, which performs independent reviews to measure and report on continuing safety of current research on subjects. (Dunn and Chadwick, Protecting Study Volunteers in Research)

- **Data Safety Monitoring Board (DSMB)** – an independent group, external to the organization, which performs independent reviews of aggregated data across all sites and recent literature
relevant to the study topic to measure and report on continuing safety of the current study on subjects.

**Phases Defined:** (**UCLA defines study stage and size; NIH defines by function**)

**Phase 1** – trial- introduction of an investigational new drug into humans, closely monitored, small N, and healthy volunteers. N= 20 to 80 subjects. NIH- study of physiology, toxicity, dose finding.

**Phase 2** – trials of controlled clinical studies to evaluate effectiveness of a drug for a particular condition in patients with the disease / condition of interest. Well controlled, closely monitored, usually N= several hundred subjects. NIH- Efficacy studies.

**Phase 3** – administration of new drug to large number of patients in different clinical settings to determine safety, effectiveness and appropriate dosage, after preliminary evidence of effectiveness. Large N of subjects – several hundred to several thousand Ss. NIH- Effectiveness, efficaciy, comparison studies.

**Phase 4** – Post marketing studies to determine risks, benefits, optimal use, other populations, other disease stages. (UCLA & NIH)