Department: **UAMS Institutional Review Board**
Policy Number: **7.8**
Section: **Procedures for Study Review**
Effective Date: **July 31, 2002**
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Subject: IRB Oversight of Activities for Data Safety Monitoring

Definitions:

1. **Data Safety Monitoring Plan (DSMP):** A DSMP describes how the Investigator plans to oversee the research participant's safety and welfare and how adverse events will be characterized and reported. The intensity and frequency of monitoring should be tailored to fit the expected risk level, complexity, phase and size of the particular study.
2. **Data and Safety Monitoring Board (DSMB)**: A formally appointed independent group consisting of a least three (3) members assigned to conduct interim monitoring of accumulating data from research activities to assure the continuing safety of research participants, relevance of the study question, appropriateness of the study, and integrity of the accumulating data. Membership should include expertise in the relevant field of study, statistics, and research study design. DSMBs are often referred to as Data and Safety Monitoring Committees (DSMC).
3. **IND Monitoring Plan**: Existing requirements for sponsors of clinical investigations involving new drugs for human and animal use (including biological products for human use) and medical devices under 21 CFR Parts 312 and 314, and 812 and 813, respectively, require that a sponsor or sponsor/investigator monitor the progress of a clinical investigation. The monitoring functions may be delegated to a contract research organization as defined under 21 CFR 312.3. Proper monitoring assures adequate protection of the rights of human and safety of all participants involved in clinical investigations and the quality and integrity of the resulting data submitted to the Food and Drug Administration (FDA).
4. **Data and Safety Monitor (DSM):** An individual assigned to conduct interim monitoring of accumulating data from research activities to assure the continuing safety of research participants, relevance of the study question, appropriateness of the study, and integrity of the accumulating data. The individual should have relevant medical, ethical and scientific, and monitoring expertise.

Policy: The UAMS IRB requires that each new research application except those qualifying as "Exempt" will include a plan to assure the safety and welfare of its participants. The IRB will review and approve these plans. The IRB will be the final arbiter of the type of plan needed.

A. The **Principal Investigator** should appoint a DSM or DSMB for his or her study as appropriate for the size, complexity, and level of risk involved in the research.

1. **Data Safety Monitoring Plan**.
   Some studies do not require a DSM or a DSMB. However, a detailed DSMP is required for all research that is not "Exempt" under Federal regulations. The

level of detail in the plan should be based on the degree of risk entailed by the research participants. All DSMPs must contain at a minimum the following:

a. A description of how risks are minimized;
b. A description of how risks are reasonable in relation to anticipated benefits;
c. Identification of a DSM or DSMB;
d. A description of the general data safety monitoring plan;
e. A description of the plan to monitor progress and safety;
    i. This may include a plan for safety review either by an assigned board, committee or monitor at predetermined intervals relevant to the complexity of the research;
    ii. Depending on the complexity of the research, the plan may include assessments of data quality, timeliness, participant recruitment, accrual and retention.
f. A description of the plan to assure compliance with reporting of adverse events and/or unanticipated problems involving risk to participants or others. This may include:
    i. A description of the process for detecting and reporting serious and unexpected adverse events and/or unanticipated problems involving risk to participants or others;
    ii. A description of who will be monitoring and collecting the adverse events (e.g., PI, Research Nurse, etc.);
    iii. Specification of who will be notified of an adverse event (e.g., IRB, NIH, FDA, PI, etc.)
    iv. A reporting plan indicating the timing of reports;
    v. A plan for annual reporting of adverse events if study longer than one year;
g. A description of the plan to assure suspensions of funded trials are reported to the grants program director; and
h. A description of the plan to assure data accuracy and protocol compliance.

2. Research Activities that Should Include a DSM or DSMB.

a. The study is intended to provide definitive information about the effectiveness and/or safety of a medical intervention;
b. Prior data suggests that the intervention under study has the potential to induce a potentially unacceptable toxicity;
c. The study is evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications; or
d. It would be ethically important for the study to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.

3. **DSMB Composition**.

a. The DSMB should have multidisciplinary representation, including physicians from relevant medical specialties and biostatisticians. This may include other experts such as bioethicists, epidemiologists and basic scientists.

b. The DSMB should have membership limited to individuals free of apparent significant conflicts of interest, whether they are financial, intellectual, professional, or regulatory in nature.
c. The appropriate size depends on the type of study and types of expertise needed.

4. **DSM or DSMB Responsibilities**.
    a. The primary responsibility of the DSM or DSMB is to safeguard the interests of study participants. Therefore, the DSM or DSMB will approve the safety measures in the protocol:
        i. To preserve the study integrity and credibility; and
        ii. To facilitate the availability of timely as well as reliable findings to the broader clinical community.
    b. The DSM or DSMB should provide written documentation confirming that they have read the protocol and agree with the study design and the data safety monitoring plan (DSMP).
    c. The DSM or DSMB will review the progress of the study carefully and diligently.
    d. Each enrolled subject's research chart should be reviewed monthly for side effects and tolerability of the investigational drug.
    e. The DSM or DSMB will assure that all significant adverse events are reported to the IRB according to policies and procedures.
    f. The DSM or DSMB will be available to the Investigator for consultation concerning any untoward study events or any questions regarding consent issues.
    g. The DSM or DSMB will provide a letter of predefined frequency to the IRB, through the Investigator, summarizing the oversight activities of the DSM or DSMB during the monitoring period which should include:
        i. Results of the chart reviews;
        ii. Summary of consultations with the Investigator; and
            1. Concerns, if any, regarding subject safety or study drug tolerability.

5. **DSM or DSMB Charter**.
    The DSM or DSMB Charter should include the following:
    a. A detailed presentation of the membership composition, including qualifications and experience;
    b. Roles and responsibilities of the DSM or DSMB and if relevant, of Steering Committee members;
    c. The authority of the DSM/DSMB (e.g. advisory to the Sponsor, PI).
    d. The timing and purpose of DSMB meetings;
    e. The procedures for maintaining confidentiality;
    f. The format, content and frequency of DSM or DSMB reports;
    g. Statistical procedures including monitoring guidelines, which will be used to monitor the identified primary, secondary, and safety outcome variables; and
        i. Plans for changing frequency of interim analysis as well as procedures for recommending protocol changes.
    h. A copy of this Charter should be maintained with the research study files.

6. **DSM or DSMB Tasks**.
   Tasks may include, but not be limited to, the following:
   a. Conduct initial review of the proposed research to assure quality study conduct;
   b. Review procedures to assure quality of study conduct including data management and quality control procedures;
   c. Evaluate the quality of ongoing study conduct by evaluating the study accrual, compliance with eligibility, participant adherence to study requirements, and accuracy and completeness of data;
   d. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
   e. Recommend early termination based on efficacy results;
   f. Recommend termination due to unfavorable benefit-to-risk or inability to answer study questions;
   g. Recommend continuation of ongoing studies;
   h. Consideration of overall picture; primary and secondary analysis;
   i. Modify sample sizes based on ongoing assessment of event rates; and
   j. Review final results.

7. IND and IDE Monitoring Plans
   Existing requirements for sponsors of clinical investigations involving new drugs for human and animal use (including biological products for human use) and medical devices under 21 CFR Parts 312 and 314, and 812 and 813, respectively, require that a sponsor monitor the progress of a clinical investigation. IND monitoring should address the following:
   a. For any given study, the monitor must have proof of appropriate training and qualifications sufficient to the type and complexity of the study
   b. The sponsor or sponsor/investigator should establish written procedures for monitoring clinical investigations that address the following items:
      i. The specific schedule of monitoring
      ii The specific data and records that will be reviewed
      iii How disparities will be addressed
      iv Determination that the study plan is being followed
      v. The facilities used by the investigator continue to be acceptable for purposes of the study.
      vi. The study protocol or investigational plan is being followed.
      vii Changes to the protocol have been approved by the IRB and/or reported to the sponsor and the IRB.
      viii Accurate, complete, and current and current records are being maintained.
      ix Accurate, complete, and timely reports are being made to the sponsor and IRB.
      x. The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

B. **Procedure for Initial IRB Review of Monitoring Plans**

1. The Investigator will attach the appropriate monitoring plan to the study when it is submitted.
2. The IRB chair or designee will review the plan for appropriateness to the study.
3. If the study is being done under an IND or IDE, the IRB chair will refer the monitoring plan to ORC for a written evaluation of its regulatory compliance.
4. The IRB chair or designee may approve the plan or refer it to the full committee for approval.
5. The IRB will include in the study approval letter, the frequency of reporting required for each monitoring plan if required. Minimum reporting frequencies will be as follows:
    a. DSMPs ; yearly report filed with the study continuing review and at study closure
    b. DSMBs ; 30 days or less after the DSMB meets and issues a report
    c. IND Monitoring Reports for Industry Trials – a yearly report of monitoring activities should be submitted with the continuing review
    d. IND Monitoring Reports for Sponsor/Investigator trials; Quarterly reports should be sent to the IRB and the Office of Research Compliance. The ORC will apply its standard procedure to evaluate that the monitoring is being done according to the plan and issue a report to the IRB.

C. **Procedure for Follow-up Review of Monitoring Reports**

1. The PI will include a monitoring report as required by the IRB or DSMB reports when appropriate.
2. The IRB Chair, designee or committee will review the reports issued, the monitoring plan, safety reports and reported deviations and note:
    a. Any changes in the monitoring plan or frequency of monitoring that may be required to enhance data integrity and participant well-being and preserve the risk/benefit ratio
    b. Adherence to the monitoring plan and schedule
    c. Appropriate application of actions such as stop rules or endpoints
    d. Procedure for analysis and interpretation of the data appear correct
3. The IRB will notify the PI of their review and request changes as necessary.