

# Data and Safety Monitoring at the University of Kansas Medical Center

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KUMC Data and Safety Monitoring Executive Committee: Standard Operating Procedures

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**University of Kansas Medical Center  
Data and Safety Monitoring Executive Committee (DSM-EC)  
Standard Operating Procedures**

This document summarizes policies regarding the monitoring process, safety procedures and reporting, and institutional administrative oversight for studies referred to the University of Kansas Medical Center's (KUMC) Data and Safety Monitoring Executive Committee (DSM-EC). The Principal Investigator and the organization's infrastructure assume the responsibility of the ongoing monitoring process.

This document complies with the NIH/NCI guidelines published as *NIH Policy for Data and Safety Monitoring* as of June 10, 1998, *Policy of the NCI for Data and Safety Monitoring of Clinical Trials* as of June 22, 1999, *Further Guidelines on a Data and Safety Monitoring Plan for Phase I and II Trials* from the NIH on June 5, 2000. Additional guidance is available from the FDA's *Guidance for Clinical Trial Sponsors*, found at <http://www.fda.gov/cber/gdlns/clintrialdmc.pdf>

**I. Scope and Purpose**

- A. **DSM-EC Mission.** In July 2001 the Vice Chancellor for Research established the KUMC Data and Safety Monitoring Board (DSMB), appointed its members, selected the chair, and created its official charge. After several years of operation, the DSM-EC replaced the DSMB in 2006 as part of the revisions to KUMC compliance processes, overseen by the Associate Vice Chancellor for Compliance. The DSM-EC is charged with the mission of developing and enacting procedures to monitor safety of participants and integrity of data collected in the protocols that it oversees.
  
- B. **DSM-EC Scope and Authority.** The KUMC DSM-EC provides multi-disciplinary, independent oversight of research studies conducted by University of Kansas Medical Center (KUMC) faculty, focusing on assuring integrity of research and safety of human subjects. The DSM-EC also will monitor studies referred by the Human Subjects Committee (HSC), the Conflict of Interest Committee (COIC) and the Human Research Protection Program Director (HRPP-D). KUMC investigators may request oversight by the KUMC DSM-EC through the (HRPP-D). Data and safety monitoring is particularly appropriate for high-risk research and for studies in which the investigator and/or the institution may have a potential conflict of interest.

The DSM-EC reports the outcome of its deliberations to the referring body, and makes recommendations to KUMC's HSC with respect to continuation, modification, or termination of the protocol. For any research activities that fall within its jurisdiction, the DSM-EC has the authority to require protocol modifications related to participant safety and to recommend suspension or termination to the HSC and to the Vice Chancellor for Administration, who serves as the institutional official for human research.

## II. DSM-EC Membership and Responsibilities

**A. Identification and Selection of DSM-EC Members.** Voting members are identified in one of the following ways:

- Self-nomination by interested candidates
- Term renewal requests by members whose appointment term is ending
- Nomination by department chairs, center directors, or school deans
- Nomination by the Faculty Assembly Research Committee, the Executive Director of the Research Institute, the Human Research Protection Program Director (HRPP-D), or any of the Vice Chancellors
- Nomination by members of the HSC, DSMB, COIC, IACUC, IRSC or Radiation Safety Committee.

Prospective members must be recognized as individuals able to review and monitor research without personal bias, able to observe the strict confidentiality requirements associated with committee deliberations, and who understand the need to recuse themselves from reviews in which they may have a conflict of interest.

Nominations and requests for reappointment are submitted in writing to the HRPP-D, and shall include the following:

- Description of the nominee's qualifications for serving on the committee
- A current curriculum vita or resume
- Additional support documentation if needed

Nomination materials and reappointment requests are reviewed at regularly scheduled meetings of the Research Advisory Council (RAC). The RAC may solicit additional information at its discretion. After evaluation of the individual's qualifications and consideration of committee needs, the RAC will submit written recommendations to the Executive Vice Chancellor which specify the type of appointment that should be considered (i.e., voting, non-voting, Chair, Chair-elect), terms of appointment, and a brief explanation of the RAC's selection rationale.

The EVC is responsible for the final selection of new members and for issuing reappointments. Appointment letters which outline the committee charge, member responsibilities and terms of appointment shall be issued by the EVC through the HRPP-D.

**B. DSM-EC Chair and Chair-Elect.** The HRPP-D shall recommend individuals for the role of DSM-EC chair and chair-elect to the Research Advisory Council (RAC) and make the appointments following RAC approval. The Chair will serve a 3-year term. At the end of the second year of the term, a chair-elect will be identified and will work with the Chair in the third year to understand the Chair's responsibility and facilitate a smooth transition following the third year. The Chair and Chair-elect shall be KUMC faculty members.

Before each meeting, the Chair meets with Office of Compliance (OC) staff to develop the meeting agenda. The protocols to be reviewed are identified, materials for members' packets are determined, and OC staff distribute packets at least one week in advance of the meeting.

The Chair facilitates each meeting and guides discussion to formalize action on each agenda item. The Chair ensures that protocol-specific monitoring results are adequately discussed, action taken, and that feedback is provided to the principal investigator within one week of committee action.

- C. **DSM-EC regular members.** The DSM-EC has a minimum of 6 voting members. Voting members will serve 3-year terms. If mutually agreeable, a member may be reappointed for an additional 3-year term for a maximum of two consecutive 3-year terms. Responsibilities include attending all DSM-EC meetings, maintaining confidentiality, making known any conflict of interest with protocols under review by the DSM-EC, and participating in all protocol discussions as appropriate.

The committee will have voting members representing the following areas:

- University of Kansas School of Medicine, Kansas City Campus
  - University of Kansas School of Nursing
  - University of Kansas School of Allied Health
  - University of Kansas School of Pharmacy, specifically clinical pharmacology
  - Professional community member
  - Patient Advocate
- D. **Ex Officio members.** KUMC Office of Compliance (OC) personnel will attend meetings to provide administrative support and will keep the DSM-EC apprised of federal regulations governing the conduct of research. OC staff are not voting members.
- E. **Guests.** Investigators may be invited to Open Sessions of meetings to provide information regarding their studies undergoing monitoring. Investigators are not present during the Closed Session when actions are determined and voting is done.
- F. **Conflict of interest.** It is recognized that an institutional monitoring system must utilize its own faculty and research staff members to enable the system to function. Inherent in this system is the potential for a conflict of interest to exist. However, no one with an indirect or direct relationship to a protocol referred for review will be allowed to participate in the monitoring of the protocol. Examples of indirect relationships would include staff members who are involved in the protocol's reports, drug dispensing and research laboratory procedures. Direct relationships would include anyone who is involved in the design, conduct, or reporting for the protocol. Financial relationships of DSM-EC members with protocol sponsors may also present a conflict of interest. DSM-EC members complete a Conflict of Interest Disclosure Form that relates specifically to their role as a DSM-EC member.

### III. The Data and Safety Monitoring Review Process

An overview of the monitoring process is provided in the document "Getting started with data and safety monitoring at KUMC", available on the Data and Safety Monitoring Executive Committee web site.

The data and safety monitoring review process has three stages.

1. In the first stage, the DSM-EC works with the investigator to develop a Data and Safety Monitoring Plan (DSMP), including a protocol-specific monitoring format (See separate document titled "Protocol Specific Monitoring Options", available at <http://www2.kumc.edu/researchcompliance/dsmbpolicies.htm>).
2. Following acceptance of the Plan by the DSM-EC, OC staff will put in place the protocol-specific monitoring format. After each review by the protocol-specific monitoring body, a summary of its deliberations and recommendations regarding the protocol's status are forwarded to the DSM-EC for consideration and review, typically at the next regularly-scheduled meeting.
3. The DSM-EC reviews the relevant materials along with the report of deliberations of the protocol-specific monitoring body and then makes a recommendation to the referring body regarding the status of the protocol.

Details regarding each of these three stages are given below.

- A. **Pre-Monitoring Approval.** All protocols must have the conditional approval of the HSC before the DSM-EC will carry out an initial review of the monitoring plan.

- B. The DSM Plan.** Once a protocol has been referred to the DSM-EC for monitoring, the DSM-EC Chair or designee contacts the principal investigator and requests that a DSMP be submitted to the Office of Compliance. The DSMP template including required plan elements can be found at <http://www2.kumc.edu/researchcompliance/dsmbforms.htm>.
- a. As part of the plan, the principal investigator must first propose a protocol-specific monitoring body (Independent Safety Monitor; Clinical Study Oversight Committee; or Data and Safety Monitoring Board). The investigator must also nominate the individual(s) with protocol-specific expertise to serve on the protocol-specific monitoring body. These protocol-specific members must have relevant expertise and must be free of conflict of interest with the to-be-monitored protocol. They may be from any institution as long as they have the appropriate expertise and are willing to serve. The principal investigator must contact the proposed experts prior to nominating them to assure their willingness to serve. Nominations should be forwarded to the Office of Compliance using the monitoring body nomination form found at <http://www2.kumc.edu/researchcompliance/dsmbforms.htm>
  - b. Honoraria for these experts will be the responsibility of the principal investigator. Details on these costs and methods of payment are given in the DSM Honoraria Information Sheet, found at <http://www2.kumc.edu/researchcompliance/dsmbforms.htm>.

Additional plan components to be specified by the DSM-EC:

- i. The DSM-EC may request that the HRPP's Quality Assurance Program conduct a periodic quality assurance (QA) reviews to confirm that data are being collected and recorded according to protocol. The reports coming out of these record reviews will be reviewed by the protocol-specific monitoring body as part of its regular protocol review. If the results of the QA reviews indicate the need for a further review, a detailed evaluation by an independent monitor may be required.
  - ii. The protocol specific monitoring body or the DSM-EC may also identify additional variables that they wish to review as part of the monitoring process, and the investigator will be required to provide those data.
  - iii. The DSM-EC and the protocol-specific monitoring body will work with the investigator to develop reporting forms for use when requesting information from the investigator.
- C. Initial Review of the DSMP.** Once the investigator submits a DSMP to the Office of Compliance, the plan and supporting materials are circulated to the DSM-EC. Committee members will inform the DSM-EC chair of any questions or concerns or requests for additional information regarding the proposed DSMP within one week of receiving the materials. The DSM-EC chair will then integrate these comments and write a *Report of Initial Review* to the protocol PI, documenting any concerns with the DSMP including any requests for changes or additions. This report will be written within one week of receiving initial feedback on the proposed plan.

If no issues are raised in the initial review processes regarding the protocol specific experts, these individuals will be contacted by Office of Compliance staff as part of the initial review to confirm their willingness to participate in the on-going protocol review process and if so, to obtain their signed confidentiality agreement and Committee Conflict of Interest Disclosure before reviewing any protocols. If concerns or conflicts are identified during the initial review phase regarding the proposed protocol-specific experts, the principal investigator may be asked to supply additional names or the DSM-EC may recruit additional experts. Once confirmed, the protocol-specific experts will also be consulted for an opinion regarding the proposed DSMP.

Principal investigators are encouraged to work closely with the Office of Compliance during this period of initial review so that Plan approval can be accomplished in a timely manner.

- D. **DSM-EC Plan Review And Approval.** Following the initial review, the plan is scheduled for full review at the next scheduled DSM-EC meeting, and is distributed to all DSM-EC members prior to the scheduled meeting date.

If any Plan changes are requested by the DSM-EC, the DSM-EC will not recommend initiation of the protocol until those changes have been made or negotiated to the satisfaction of the DSM-EC.

When the recommendation is that the protocol be initiated, a *Letter of Agreement* is sent to the protocol PI stating that the DSMP has been accepted and monitoring has begun following the terms of that Plan. The protocol PI is required to sign a copy of the letter and return it to Office of Compliance staff for their records.

- E. **Investigator's Reporting Responsibilities.** In advance of each scheduled protocol-specific monitoring meeting, the Investigator will be required to submit an Interim Monitoring Report to the OC (found at <http://www2.kumc.edu/researchcompliance/dsmbforms.htm>), current enrollment data, adverse event summary data, and any other data requested by the monitoring body or DSM-EC. Deadlines for the submission of materials will be determined by the scheduled monitoring meetings and will be communicated to the investigator by OC personnel.
- F. **Ongoing Protocol Review.** The protocol-specific monitoring body will meet at regularly scheduled intervals to review trial progress, adverse event data, and any other relevant information such as significant amendments or reviews from HSC submitted by the principal investigator. The DSM-EC chair will attend protocol-specific monitoring meetings to facilitate the review process, but will not have a vote in any of the proceedings.

Monitoring reviews assess protocol elements as described in the monitoring worksheet (found at <http://www2.kumc.edu/researchcompliance/dsmbforms.htm>). Following their review, the protocol-specific monitoring body makes a recommendation to the DSM-EC regarding continuation of the study. This recommendation will be forward to the PI as the initial review outcome, pending approval by the DSM-EC.

A summary of protocol-specific monitoring body deliberations and their recommendation in the form of meeting minutes is drafted by the OC member who attends their meetings. If the protocol specific monitoring body raises any questions for the PI or requests any additional information from the PI, those questions or requests will be sent immediately to the PI for response. The protocol specific monitoring body recommendation, along with any additional relevant information, will be reviewed by the DSM-EC at the next regularly-scheduled meeting.

If there are significant concerns raised by the protocol specific monitoring body, the DSM-EC chair will notify the PI and call a special DSM-EC meeting to consider the monitoring review and to make a recommendation to the HSC or other referring body about modifying, suspending, or terminating the protocol.

- G. **DSM-EC Ongoing Protocol Review.** Before each DSM-EC meeting, summaries of protocol specific monitoring body deliberations and recommendation will be distributed to all DSM-EC members.
- H. **Monitored protocol elements.**
- i. **Scientific progress and accrual:**
    - a. All studies referred to the DSM-EC are monitored for scientific progress, accrual, and protocol compliance. Protocol compliance is reviewed and summarized and accrual is reported on a schedule determined by the DSM-EC for each protocol. These reports are then reviewed by the protocol-specific monitoring body for any necessary actions.

b. The protocol specific monitoring body reviews accrual rate forecast relative to the characteristics of the protocol participants and estimated duration of the protocol. The general principles followed by the protocol specific monitoring body in its recommendations regarding scientific progress and accruals are as follows:

1. **Under-accrual.** At the end of the first year following activation, the protocol-specific monitoring body reviews accrual to the protocol. Based on the PI's accrual forecast, if there is less than 25% of the accrual projected, a letter to the investigator would call attention to the original projection and remind the investigator that the accrual is being monitored. Accrual and scientific progress are reviewed regularly thereafter and if accrual continues to lag behind the predicted rate, the protocol may be suspended unless there are extenuating circumstances. To make this determination, the investigator may be asked to justify continuing the protocol.
2. **Overaccrual.** Over-accrual within the range of 10-15% is not a deficiency. However, beyond that, assessment of reasons is required.

ii. **Adverse events:**

For each protocol, the DSM Plan will specify criteria (negotiated with the protocol PI and approved by the DSM-EC and the protocol-specific monitoring body) to terminate the protocol before the scheduled end date. These stopping rules will be put into effect if significant risks have developed, or if compelling ethical concerns arise.

If significant concerns about safety arise in a double-blind study, the protocol-specific monitoring body or the DSM-EC can request that an analysis of adverse events be done. This analysis can be done first by study arm without breaking the blind. If adverse events are found to differ by study arm, the DSM-EC or protocol-specific monitoring body may then ask that the blind be broken to further assess safety issues.

I. Level of Monitoring.

At the time of initial review of the DSMP, a determination of the level of monitoring is made commensurate with the phase, endpoints, level of intervention, degree of risk, size (single site vs. multiple sites) and complexity of the trial. Protocols may be reviewed 1, 2, 3, or 6 times per year.

i. **Initial review considerations.**

At the time of initial review, the protocol is reviewed to ensure that the items below are adequately addressed. If any of these items is not adequately addressed, the PI must provide the required information before monitoring will begin. Protocols must address:

- a. Procedures to ensure the safety of subjects in accord with the degree of risk.
- b. Validity and integrity of the data (an adequate biostatistical design must be present and procedures to ensure adequate data capture and how the data will be evaluated).
- c. Expected duration of the protocol based on a realistic predicted enrollment rate based on the characteristics of the participants.
- d. Data management systems that will ensure subjects' eligibility for the trial.
- e. Adverse event reporting (to the HSC, protocol-specific monitoring body, funding agency, sponsor) is adequate. The protocol must contain a grading system for adverse events (i.e. Common Toxicity Criteria); reference the reporting forms to be used and describe oversight by the investigator for

grading and attribution to the protocol intervention. The investigator is responsible for submission of adverse event reports to all agencies described in the protocol in accordance with federal regulations. These would include the pharmaceutical or device sponsor, and/or FDA, HSC and protocol-specific monitoring body.

ii. **Changes in a monitoring plan.**

Studies are automatically scheduled for more frequent monitoring if any review identifies any aspect of the protocol or its outcomes as unsatisfactory. Each protocol and its review findings are judged on a case-by-case basis and follow-up actions are taken in accord with the type and degree of the deviations or violations, and the investigator's response in terms of corrective actions. If a corrective plan of action has been proposed, its impact will be assessed at a follow-up review.

J. **Data and Safety Monitoring Recommendations**

The protocol-specific monitoring body recommends continuation, modification, suspension, or termination of the protocol to the DSM-EC, which in turn recommends continuation, modification, suspension, or termination of the protocol to the HSC and the referring body (if different than the HSC) following each review meeting. The DSM-EC recommendation is conveyed to the investigator by letter following each review meeting. Final action for each review will be determined by a simple majority of the members present. *A quorum is comprised of a simple majority of all current voting members.* Minority reports may be filed.

i. **Factors influencing monitoring recommendations**

- a. The monitoring recommendations are a composite of scientific progress, accrual, and the safety findings relevant to the conduct of the protocol.
- b. In making a recommendation regarding the protocol, the protocol-specific monitoring body and DSM-EC exercise reasonable judgment in determining if serious adverse events, problems or protocol deviations affect the integrity of the study.

ii. **Recommendations: Continuation, Modification, Suspension, or Termination**

- a. If a protocol receives a recommendation for continuation, it will continue to be reviewed for scientific progress, safety, and accrual on the schedule determined in the DSMP or as otherwise specified in the protocol.
- b. If problems are noted in a protocol during monitoring, the monitoring bodies may elect to recommend corrective actions, more frequent monitoring, suspension or termination of the protocol if the level of unacceptability warrants it.
- c. Grounds for recommending suspension or termination of a clinical trial include, but are not limited to:
  1. Zero accrual for 1-2 years or long-term low accrual.
  2. Stopping rule triggering.
  3. Major violations in the conduct of the protocol
- d. The decision to recommend suspension or termination of a protocol is carefully considered and takes into account whether corrective actions had been requested at previous reviews and were not implemented, or had insufficient impact to justify continuation. Imminent threat to safety or welfare of participants is also considered in recommending suspension or termination of a protocol.

1. If the decision is made to recommend suspension or termination of a protocol, the recommendation will be made in a letter to the HSC, sent simultaneously to the Vice Chancellor for Administration, the referring body (if different than HSC), and to the investigator.
2. The HSC and the Vice Chancellor for Administration share final authority to effect termination or suspension of a protocol. The determinations of the Vice Chancellor for Administration are reported to the PI, the HSC, the referring body (if different from HSC), the DSM-EC, and the federal Office for Human Research Protections (OHRP).

#### **IV. DSM-EC Meetings.**

- A. Meeting schedule. DSM-EC meetings will be held during the second week of even-numbered months. Materials to be reviewed at the meeting will be distributed a week prior to the meeting.
- B. Meeting structure. Meetings will follow the agenda established and distributed to the group with other packet materials in advance of the meeting date. Meetings may include an Open Session to allow investigators and/or investigative teams to present information relevant to the review and to answer questions raised by the EC. A Closed Session of the DSM-EC will follow that includes only EC members and OC staff.
- C. Confidentiality. Deliberations of the DSM-EC are confidential and will not be disclosed to outside individuals. Each DSM-EC member must submit an annual confidentiality agreement and Committee Conflict of Interest Disclosure, which shall be retained in official OC files. Discussions from the Closed Session will not be revealed to the investigator, except as authorized by the DSM-EC.
- D. Administrative coordination. OC staff provide administrative support to the DSM-EC and each protocol-specific monitoring body. This includes database management, report generation, meeting coordination, and minutes preparation. Minutes reflect members present, substantive issues discussed, voting results, and members abstaining due to conflict of interest. OC staff are also responsible for ensuring that follow-up activities occur in a timely manner. All records of DSM-EC activities are maintained in the OC by OC staff.

#### **V. Data and Safety Monitoring Executive Committee Annual Report and Review**

- A. The DSM-EC will conduct an annual self-review to evaluate workload, policies and procedures, efficiencies and inefficiencies, membership, and overall contribution to research compliance at KUMC. Quality improvement measures will be implemented as needed.
- B. The DSM-EC will provide an annual report of its activities to the Vice Chancellor for Administration..