

Data and Safety Monitoring at the University of Kansas Medical Center

Protocol-specific Monitoring Options

KUMC investigators engage in clinical research, interventional clinical trials and observational studies that vary in size and complexity. Data and safety monitoring is designed to ensure the safety of participants and the integrity of study data. The investigator, the HSC, and KUMC's Data and Safety Monitoring Executive Committee (DSM-EC) share responsibility to ensure the appropriate oversight and monitoring of the conduct of KUMC clinical studies.

Each protocol referred to the DSM-EC for monitoring will establish a protocol-specific monitoring body. Appropriate monitoring can vary from a single safety monitor to a full data and safety monitoring board. The investigator in collaboration with the DSM-EC will decide on which format of monitoring oversight will be implemented for the clinical study or trial. Options include a Data and Safety Monitoring Board (DSMB), a Clinical Study Oversight Committee (CSOC), or an Independent Safety Monitor (ISM). These options were developed based on NIH guidance which can be found at www.nidcr.nih.gov/GrantsAndFunding/PoliciesandGuidance/ClinicalResearch/DataandSafetyMonitoring.htm

Although each DSM Plan is individually tailored to a given protocol, generally oversight will be designated as follows:

- An ISM will oversee subject safety. This may be the only safety oversight for small clinical studies with invasive (non-drug/device) interventions. The ISM may also be a member of a DSMB or SMC for clinical trials.
- A CSOC will oversee Phase I and II clinical trials where the primary outcome is safety, and complex observational or clinical specimen studies, with a focus on study conduct and unanticipated problems.

- A DSMB will oversee phase II/III, phase III and phase IV clinical trials where the primary outcome is safety and efficacy, or phase IV trials with significant safety risks.

An overview of each of these bodies is given below, followed by more details explaining each monitoring format.

Protocol-specific Monitoring Options: OVERVIEW

Independent Safety Monitor

An Independent Safety Monitor (ISM) is an individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur, with follow-up through resolution or stabilization. The ISM evaluates individual and cumulative participant data when making recommendations regarding safety continuation of the study. An ISM could be the sole monitor for the study or may perform this role as a member of a DSMB or CSOC. An ISM is appropriate as the sole independent safety monitor for small, early phase studies of short duration. DSMBs and CSOCs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events rather than all adverse events.

Clinical Study Oversight Committee

A Clinical Study Oversight Committee (CSOC) is an independent group of experts that advises DSM-EC and study investigators on generally for Phase I and smaller Phase II trials, or other complex clinical studies, involving risk or vulnerable populations, and may be observational, specimen collection, epidemiology or surveillance studies. The responsibilities of the CSOC are to 1) monitor human subject safety by reviewing and evaluating the accumulated study data, 2) review study conduct and progress, and 3) make recommendations to DSM-EC concerning the continuation, modification, or termination of the study. The CSOC meets regularly as specified in the DSM Plan, and considers study-specific data as well as relevant background information about the disease, procedures and progress of the study.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the KUMC DSM-EC and the study investigators. These experts can be either internal faculty members at KUMC, or members of the larger scientific community. The

primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the KUMC DSM-EC concerning the continuation, modification, or termination of the trial. DSMBs meet regularly as specified in the DSM Plan, and whenever any special need arises to review study conduct and cumulative study data, and to recommend whether the study should continue without change, be modified, or be terminated. Recommendations to modify or terminate a trial may be based on any aspect of the trial it considers. A DSMB member's recommendation to terminate a trial based on finding efficacy (i.e., early rejection of the null hypothesis concerning the primary endpoint) requires statistical adjustments for interim evaluations and thus requires a pre-specified plan for interim statistical analysis. Therefore, it is essential that the DSMB for such trials include a member with appropriate statistical expertise. All NIH-sponsored Phase III trials are subject to DSMB review. DSMB oversight should also be considered for other clinical trials with associated safety risk, including Phase I and Phase II trials.

Protocol-specific Monitoring Options: DETAILS

Independent Safety Monitor (ISM) Guidelines

I. Roles and Responsibilities

The Independent Safety Monitor (ISM) is an individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

An ISM could be the sole monitor for the study or may perform this role as a member of a Data and Safety Monitoring Board (DSMB) or Clinical Study Oversight Committee (CSOC). An ISM is appropriate as the sole independent safety monitor for small, early phase studies considered to be low risk, such as some pharmacokinetics or immunogenicity studies, or other studies of short duration. DSMBs and CSOCs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events (SAEs) rather than all adverse events (AEs).

II. Selection and Invitation to Participate

The ISM should be selected based on relevant study-related or therapeutic expertise. Participation is for the duration of the study. The ISM should be able to readily access participant records in real time. He/she is generally a member of the participating institution's staff. The ISM should not be under the direct supervision of the investigator and should preferably be from a different organizational or departmental group.

Conflict of Interest

No ISM should have direct involvement in the conduct of the study. Furthermore, no

ISM should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. All ISMs will sign a Conflict of Interest certification to that effect at the time they are asked to participate.

If the ISM performs this role as a member of a DSMB or CSOC, DSM-EC staff will reconfirm that no conflict of interest exists for the ISM at the beginning of every DSMB or CSOC meeting. Interests that may create a potential conflict of interest should be disclosed to the DSMB or CSOC prior to any discussion. The DSMB or CSOC will determine how to handle such potential conflict or appearance of conflict. The DSMB or CSOC can require that an ISM with a potential conflict not vote or take other means deemed appropriate.

If the ISM is acting as the sole independent monitor, the DSM-EC will reconfirm prior to any review of data or at least annually that no conflict of interest exists. Interests that may create a potential conflict of interest should be disclosed to the DSM-EC prior to any review of data.

The DSM-EC will determine if the relationship is in conflict or gives the appearance of a conflict such that the individual should not serve as the ISM. The DSM-EC will determine how to handle such potential conflict. They can require that an ISM with a potential conflict not vote or take other means deemed appropriate. They may dismiss an ISM in the event of unmanageable potential conflict.

III. Study Materials for ISM Review

The primary focus of the ISM is to independently review all adverse events and thoroughly investigate those considered serious and unexpected. As the sole monitor, the ISM accomplishes this by evaluating all adverse events against the known safety profile of the study product. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. If necessary, special reports are prepared by the investigator or study statistician.

It is the responsibility of the PI to ensure that the ISM is apprised of all new safety information relevant to the study product and the study. This includes providing the ISM with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all CIB revisions and all safety reports issued by the Investigational New Drug application (IND) sponsor. Summary safety and enrollment data should be forwarded to the ISM at the interval specified in the DSM Plan. The ISM should also receive all protocol revisions and may receive other documents relating to the study.

IV. Reports from the ISM

The following reports are submitted by the ISM when acting as the sole independent monitor; otherwise the ISM operates under the guidelines of the DSMB or CSOC.

A. Review Report: According to the timeline specified in the DSM Plan, the ISM should communicate in writing his/her findings, any concerns and recommendations to the DSM-EC.

Unless otherwise specified, the written report will be forwarded through the DSM-EC to a designated study team representative (usually the Principal Investigator), and to the IRB. If under an IND, the IND sponsor will forward the summary report to the FDA and to any other industrial collaborators.

B. Immediate Action Report: The ISM will notify the DSM-EC Chair of any findings of a serious and immediate nature including any recommendations to discontinue all or part of the trial. The DSM-EC will convene a special meeting to review the recommendations, and the DSM-EC will immediately inform the IRB and the AVC. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to the DSM-EC in writing on the day of the ISM review and must include the ISM's rationale for the recommendations.

IX. Honoraria for ISMs

Independent safety monitors should be intellectually and financially independent of trial investigators. Honoraria paid to ISMs for their participation must be provided by funds restricted for this purpose. Honoraria are paid following KUMC guidelines found at <http://www2.kumc.edu/researchcompliance/dsmbsubprocess.htm>

Clinical Study Oversight Committee Guidelines

I. Roles and Responsibilities

The Clinical Study Oversight Committee (CSOC) is an independent group of experts that advises the KUMC DSM-EC and study investigators on clinical studies. The responsibilities of the CSOC are to 1) monitor human subject safety, 2) review study conduct and progress, and 3) make recommendations to the DSM-EC concerning the continuation, modification, or termination of the study. The CSOC considers study-specific data as well as relevant background information about the disease, procedures and progress of the study.

The CSOC will review the protocol in conjunction with the data and safety monitoring plan, and identify any major concerns prior to implementation. During the study the CSOC should review:

- Real-time and cumulative safety data for evidence of study-related adverse events
- Unanticipated problems involving risks to subjects or others (for additional information, see Office for Human Research Protections <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>)
- Adherence to the protocol; and
- Factors that might affect the study outcome or compromise the study data, such as protocol violations, losses to follow-up, breach of subject confidentiality)

- Unexpected barriers, if any, to study progress or completion, such as slow enrollment new data or findings, other milestones, change in resources, and futility of endpoints, etc.)

The CSOC should conclude each review with a recommendation to the DSM-EC as to whether the study should continue, be modified, or be terminated. Recommendations regarding modification of the design and conduct of the study may include corrective actions when performance is unsatisfactory, recommendations to suspend or terminate enrollment, or recommendations to modify consent documents. Votes will carry by simple majority.

Confidentiality must always be maintained during all phases of CSOC review and deliberations. The CSOC is responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

II. Membership

The membership of the CSOC should reflect the disciplines and clinical specialties such as medical, nursing or behavioral sciences, necessary to interpret the data from the clinical study and to fully evaluate subject safety. The CSOC generally consists of at least three voting members. Membership usually includes an Independent Safety Monitor (ISM), expertise in the clinical aspects of the disease/subject population being studied or procedure being performed, and expertise in current clinical research conduct and methodology.

Consideration should be given to including other voting or ad hoc members such as a biostatistician or a bioethicist if the study design or subject population would benefit from their expertise. CSOC and *ad hoc* members may be from the principal investigator's institution or from other participating sites but should not be directly involved with the trial or under the supervision of the study investigator. Furthermore, the CSOC members should generally be in a different organizational group than the Principal Investigator.

DSM-EC members may participate as *ex officio*, non-voting members. Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the CSOC as *ex officio* or voting members.

Conflict of Interest

No member of the CSOC should have direct involvement in the conduct of the study. Furthermore, no member should have or appear to have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the CSOC. All CSOC and *ad hoc* members will sign a Conflict of Interest certification to that effect at the time they are asked to participate.. At the beginning of every CSOC meeting, DSM-EC program staff will reconfirm that no conflict of interest exists for CSOC members. Interests that may create a potential conflict of interest should be disclosed to the CSOC prior to any discussion. The CSOC will determine how to handle such potential conflict. The CSOC can require that a member with a potential conflict not vote or take other means deemed appropriate. The DSM-EC may dismiss a member of the CSOC in the event of unmanageable potential conflict or appearance of conflict.

Selection and Invitation to Participate

The principal investigator is responsible for developing the roster of potential CSOC members. Recommendations for proposed members may be solicited from many sources. The proposed roster of members must be submitted to the DSM-EC as part of the DSM Plan for review and approval. Office of Compliance staff then contact potential CSOC members, invite them to participate on the CSOC, and obtain confidentiality and conflict of interest agreements.

III. Meetings

The structure and operating procedures for a CSOC are usually less formal than that of a DSMB. The initial CSOC meeting should occur before the start of the trial or as soon thereafter as possible. DSM-EC staff may discuss KUMC's perspective on and

expectations for the study at this initial meeting. At this meeting the CSOC should discuss the protocol, review and approve or modify the investigator's proposed DSM Plan, and establish guidelines for monitoring the study. The CSOC should decide which member(s) should receive reports of serious adverse events in real time and determine if on-site review of clinical records might be needed. Teleconference calls may often be an appropriate means for conducting meetings. Scheduling of meetings will follow the timeline proposed in the DSM Plan, and are initially based on the magnitude of the perceived risks. Meeting frequency may change as a function of rate of subject enrollment, or problems that occur during the progress of the study. Meetings also may be requested for cause by any member of the CSOC, the investigator, or IRB. The Office of Compliance will be responsible for ensuring the distribution of materials for review to CSOC members and other meeting participants.

CSOC meeting format

The recommended meeting format may consist of two sessions: an Open Session and a Closed Executive Session.

A. Open Session: Occurrences of adverse events, unanticipated problems involving risks to subjects, and enrollment are reviewed. Issues relating to the general conduct and progress of the study will also be considered. CSOC members, voting and *ex officio* members, DSM-EC members, and *ad hoc* experts attend and participate in this session. The lead investigator and study statistician, if applicable, may in some cases attend part of this session to present results and respond to questions.

B. Closed Executive Session: A second session, if necessary, involves only voting members to ensure complete independence for making decisions and formulating independent recommendations.

Voting

A simple majority of CSOC members must be present to vote either in person or by conference call. After a thorough discussion of CSOC members' opinions and rationale a vote is taken. A consensus opinion is not required. The final recommendations are recorded and either identified as majority or minority positions or are accompanied by actual vote tallies for each divergent recommendation, i.e., as number of votes for or against a particular action, such as continuing or terminating a study, etc.

IV. Study Reports for CSOC Review

It is the responsibility of the PI to ensure that the CSOC is apprised of all new safety and risk information relevant to the study. Summary safety, enrollment data, and other progress reports (e. g.: protocol deviations, site monitoring summaries) should be forwarded periodically to the CSOC, on a schedule specified in the DSM Plan. The CSOC should receive all protocol revisions and may receive other documents relating to the study.

Reports are prepared by the study statistician or the investigator. The general content for reports to the CSOC is as determined by the CSOC at the initial meeting. The CSOC and DSM-EC must also review and approve the actual data elements to be presented. At each meeting, additions or modifications to these reports may be directed by the CSOC on a one-time or continuing basis. Distribution of written reports should allow sufficient time for review.

Reports for meetings of the CSOC will consist of the Open Session Report and, if required, a Closed Session Report. Open Session reports are distributed to CSOC members, selected DSM-EC staff, and other appropriate persons as directed by the CSOC. Closed Session reports are distributed only to CSOC members and others as designated by the CSOC.

V. Reports from the CSOC

A. Summary Report: At the conclusion of a CSOC meeting, the CSOC will issue a written summary report that identifies topics discussed by the CSOC and describes their individual findings, overall safety assessment, and recommendations. The rationale for recommendations will be included when appropriate. This report will not include confidential information. OC staff who attended the meeting are responsible for preparing and distributing the report. Unless otherwise specified, the summary report will be forwarded through the DSM-EC to a designated study team representative (usually the Principal Investigator) and to other appropriate DSM-EC members.

B. Closed Session Minutes (optional) The CSOC may also prepare confidential minutes that include details of closed session discussions. Meeting minutes are to be held in strict confidence, accessible only to voting members of the CSOC until a) such time when the study is closed, b) if the CSOC recommends early termination, or c) if the minutes are requested by the FDA or DSM-EC for patient safety or regulatory purposes.

C. Immediate Action Report: If there are any findings of a serious and immediate nature, such as if the CSOC recommends that all or part of the study be discontinued, the DSM-EC will immediately inform appropriate Compliance staff, including the AVC for Compliance. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to the DSM-EC in writing on the day of the CSOC meeting. This written, confidential briefing may contain supporting data and should include the CSOC members' rationale for its recommendations. The written briefing should be submitted to the DSM-EC.

IX. Honoraria for CSOC Members

CSOC members should be intellectually and financially independent of trial investigators. Honoraria paid to CSOC members for their participation must be provided by funds restricted for this purpose. Honoraria are paid following KUMC guidelines found at <http://www2.kumc.edu/researchcompliance/dsmbprocess.htm>

Data and Safety Monitoring Board (DSMB) Guidelines

I. Roles and Responsibilities

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the KUMC DSM-EC and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to DSM-EC concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;

- Data quality, completeness, and timeliness;
- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The DSMB should conclude each review with their recommendations to DSM-EC as to whether the study should continue without change, be modified, or terminated.

Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subject safety, inadequate performance or rate of enrollment;
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines;
- Optional approaches for the DSM-EC and investigators to consider when the DSMB determines that the incidence of primary study outcomes is substantially less than expected such as recommendations to increase the number of trial centers or extend the recruitment period; and,
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious.

Confidentiality must always be maintained during all phases of DSMB review and deliberations. Usually, only voting members of the DSMB should have access to interim analyses of outcome data by treatment group. Exceptions may be made when the

DSMB deems it appropriate. The reason and to whom the exceptions for access to interim analyses is granted will be documented in the Closed Session Report. DSMB members must maintain strict confidentiality concerning all privileged trial results ever provided to them. The DSMB should review data only by masked study group (such as X vs. Y rather than experimental vs. control) unless or until the DSMB determines that the identities of the groups are necessary for their decision-making. Whenever masked data are presented to the DSMB, the key to the group coding must be available for immediate unmasking.

II. Membership

The membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. The number of DSMB members depends on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk but generally consists of three to seven members including, at a minimum:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- One or more biostatisticians; and,
- Investigators with expertise in current clinical trials conduct and methodology.

Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired. Some trials, depending on the population and nature of the intervention, may well be served by inclusion of a bioethicist on the DSMB, Steering Committee, or Advisory Panel.

Representatives of the manufacturer (industrial collaborator) of the test substance(s) or any other individual with vested interests in the outcome of the study are not eligible to serve on the DSMB although they may attend open sessions of the DSMB meetings.

Conflict of Interest

No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have financial, proprietary, professional, or other

interests that may affect impartial, independent decision-making by the DSMB. In addition, all DSMB and ad hoc members will sign a Conflict of Interest certification to that effect at the time they are asked to participate. At the beginning of every DSMB meeting, DSM-EC staff or the DSMB Chair will reconfirm that no conflict of interest exists for DSMB members. Interests that may create a potential conflict of interest should be disclosed to the DSMB prior to any discussion. The DSMB will determine how to handle such potential conflict. The DSMB can require that a member with a potential conflict not vote or take other means deemed appropriate. The AV-C, on advice from the DSM-EC, may dismiss a member of the DSMB in the event of unmanageable potential conflict or appearance of conflict.

Selection and Invitation to Participate

The study investigator is responsible for developing the roster of potential DSMB members. Recommendations for proposed members are solicited from many sources. Study investigators and the industrial collaborators should have the opportunity to review the list of proposed members before the candidates' interest and availability are confirmed by the Compliance Office). The proposed roster of members must be submitted to the DSM-EC for review and approval before invitations are issued.

Terms of membership are also determined by the DSM-EC. Participation is generally for the duration of the study. Participation for standing DSMBs convened to monitor multiple protocols or lengthy studies may be for fixed terms. As continuity of review is essential, the duration of fixed terms should be staggered so that no more than one third of the membership changes at any one time.

III. Meetings

The frequency of DSMB meetings is specified in the DSM Plan. The frequency may change depending on several factors including the rate of enrollment, safety issues or unanticipated adverse events, availability of data, and, where relevant, scheduled interim analyses. The DSM-EC is responsible for convening meetings, selecting a venue when the meeting is not convened by teleconference, and coordinating the

distribution of meeting materials to DSMB members and other meeting participants. The agenda for each meeting is generally developed by the DSM-EC Chair.

The initial DSMB meeting should occur preferably before the start of the trial or as soon thereafter as possible. At this meeting the DSMB should discuss the protocol and the DSM Plan which includes triggers set for data review or analyses, definition of a quorum, and guidelines for monitoring the study. Guidelines should also address stopping the study for safety concerns and, where relevant, for efficacy based on plans specified in the protocol. OC Staff and the DSM-EC chair may also discuss KUMC's perspective on the study at this initial meeting.

Once a study is implemented, the DSMB should convene as specified in the DSM Plan, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might affect continuation of the study as designed. A DSMB meeting may be requested by DSMB members, the DSM-EC, industrial collaborator, IRB, or study Principal Investigator at any time to discuss safety concerns. Decisions to hold ad hoc meetings will be made by the DSM-EC and DSMB. Meetings may be held by conference calls or videoconferences or as face-to-face meetings. In the event a DSMB member cannot attend a meeting, he/she may receive a copy of the closed session DSMB report (see below) and either participate by conference call or provide written comments to the DSMB Chair for consideration at the meeting.

DSMB Meeting Format

The recommended meeting format consists of three sessions: Open Session, Closed Session, and Closed Executive Session.

A. Open Session: Issues relating to the general conduct and progress of the study are discussed including adverse events and toxicity issues, accrual, demographic characteristics of enrollees, disease status of enrollees (if relevant), comparability of

groups with respect to baseline factors, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up. Any data provided must be presented without grouping by treatment assignment or otherwise by preserving the masking of all subjects. Outcome results must not be discussed during this session. DSMB members, voting and *ex officio* members, DSM-EC staff members and ad hoc experts attend this session. The lead investigator and the study biostatistician may be in attendance in order to present results and respond to questions. This session is open to study investigators, coordinating center staff, representatives for industrial collaborators, representatives from the Food and Drug Administration (FDA), and DSM-EC program and regulatory staff.

B. Closed Session: Grouped safety data and, if appropriate, efficacy data are presented by the study statistician(s) at this session. Grouped data should be presented by coded treatment arm. This session is normally attended only by voting members, study statisticians, and invited *ex officio* members. The DSMB may invite the participation of other individuals for all or part of the session.

C. Closed Executive Session: This final session involves only DSMB voting members, OC staff, and the DSM-EC Chair, to ensure complete objectivity as they discuss outcome results, make decisions, and formulate recommendations regarding the study.

Voting

A simple majority of DSMB members must be present to vote either in person or by conference call. After a thorough discussion of DSMB members' opinions and rationale a vote is taken. A consensus opinion is not required. The final recommendations are recorded and either identified as majority or minority positions or are accompanied by actual vote tallies for each divergent recommendation, i.e., as number of votes for or against a particular action, such as continuing or terminating a study, etc.

IV. Study Reports for DSMB Meetings

It is the responsibility of the PI to ensure that the DSMB is apprised of all new safety information relevant to the study product and the study. This includes providing the DSMB with a copy of the Clinical Investigator's Brochure (CIB) in advance as well as promptly providing all CIB revisions and all safety reports issued by the IND sponsor and manufacturer. The DSMB should receive all protocol revisions and may receive other documents relating to the study.

Summary safety and enrollment data should be submitted to the OC by the study investigator in anticipation of each DSMB meeting. OC staff then forwards the information to the DSMB. The DSMB must review and approve the suggested formats or templates for data presentation for the initial meeting of the DSMB and all data elements to be presented. At subsequent meetings, additions or modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Written reports should be sent to DSMB members prior to the meeting and should allow sufficient time for review.

Reports for meetings of the DSMB consist of two separate parts: Open Session Report and Closed Session Report. Open Session reports are distributed to DSMB members, selected DSM-EC members and staff, and other appropriate persons as directed by the DSMB at least one week prior to a scheduled meeting. Closed Session reports are distributed on the same schedule but only to DSMB members and others as designated by the DSM-EC Chair. The data presented in the reports must reflect both the need for the fullest possible information on trial results and the need to assure reliability and accuracy of the information included.

A. Open Session Report: This report provides information on study conduct, as outlined above in Section III, such as accrual, appropriate demographic representation, baseline characteristics, protocol compliance, site performance, quality control, and currency of follow-up. General (ungrouped) adverse events and toxicity issues are also included in the open report.

B. Closed Session Report: This report may contain data on study outcomes, including safety data and, depending on the study, efficacy data coded by group. It may also contain data from the Open Session report but presented separately for each study arm. Interim analyses of efficacy data are presented only when planned in advance and appropriate statistical criteria for assessing evidence of efficacy have been clearly addressed. If an exception has been made to provide the Closed Session Report to non-voting members, the reason and to who will be included in the Report. Supplemental information may need to be furnished immediately after the meeting if the DSMB decides that such follow-up is needed in order to conclude their deliberations.

The Closed Session Report is **confidential** and marked accordingly. Copies of reports distributed prior to and during a meeting are collected by OC staff at the end of the Closed Session. Procedures for securing closed reports distributed to telephone and videoconference participants should be specified in advance of the meeting.

V. Other Reports of Study Progress

Masked safety and enrollment data may be forwarded periodically to all DSMB members or to the member who serves as the Independent Safety Monitor. The DSMB receives all protocol revisions and may receive other documents relating to the study, such as annual reports, manuscripts, and newsletters. Appropriate follow-up procedures, such as for directing concerns or requests for further information to the DSM-EC staff, should be identified in advance.

VI. Reports from the DSMB

A. Verbal Report: At the conclusion of a DSMB meeting, the DSMB should discuss its findings and recommendations with DSM-EC representatives and OC staff.

B. Summary Report: The DSMB will issue a written summary report that identifies topics discussed by the DSMB and describes their individual findings, overall safety assessment and recommendations. The rationale for recommendations will be included

when appropriate. This report will generally not include confidential information. The DSM-EC Chair or designee is responsible for drafting, circulating and obtaining approval from other DSMB members within two (2) weeks of the meeting. The final summary report will be forwarded through the DSM-EC to a designated study team representative (usually the Principal Investigator) and to other appropriate KUMC staff. If under an IND, the IND sponsor will forward the summary report including routine and nominal findings to the Food and Drug Administration (FDA) and to any other industrial collaborators.

C. Closed Session Report: (optional) The DSMB may also prepare confidential minutes that include details of closed session discussions. Meeting minutes are to be held in strict confidence, accessible only to voting members of the DSMB and DSM-EC until such time when the study is closed or the DSMB recommends early termination or in the event the minutes are requested by the FDA for participant safety reasons or for regulatory purposes.

D. Immediate Action Report: If the DSMB reports any findings of a serious and immediate nature or recommendations to discontinue all or part of the trial, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to DSM-EC in writing by e-mail, fax, or courier on the day of the DSMB meeting. This written, confidential report may contain unmasked supporting data and include the DSMB member's rationale for their recommendations. The DSM-EC will convene to review and act on the DSMB's recommendation.

VII. Communication Between DSMBs and IRBs

NIH policy has explicitly identified required communications that must occur between DSMBs and Institutional Review Boards (IRBs) (Guidance on reporting adverse events to IRBs for NIH-supported multicenter clinical trials dated June 11, 1999 (<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>)). At KUMC, this communication will be mediated by the DSM-EC. The DSM-EC will provide feedback at

regular and defined intervals to the IRBs, after each meeting of the DSMB. This feedback will include DSMB members' conclusions with respect to progress or need for modification of the protocol.

VIII. OC and DSM-EC Chair Role

OC staff and the DSM-EC chair collaborate to provide support for the DSMB. Their responsibilities include:

- Coordinating communications between DSMB members and other meeting participants such as *ex officio* and *ad hoc* members;
- Overseeing meeting logistics including: selecting meeting dates and locations, providing reimbursement for per diem and DSMB honorarium, and assisting with other travel arrangements;
- Preparation and dissemination of meeting summary reports and other appropriate non-confidential documents;
- Obtaining conflict of interest statements; and,
- Preparing thank you letters/letters of appreciation to recognize and acknowledge DSMB members' contributions.

IX. Honoraria for DSMB Members

DSMB members should be intellectually and financially independent of trial investigators. Honoraria paid to DSMB members for their participation must be provided by funds restricted for this purpose. Honoraria are paid following KUMC guidelines found at <http://www2.kumc.edu/researchcompliance/dsmbsubprocess.htm>