



The Yale School of Medicine
General Clinical Research Center
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Data and Safety Monitoring Plan

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**YALE UNIVERSITY SCHOOL OF MEDICINE
Data and Safety Monitoring Plan for
Clinical Research Utilizing the GCRC**

Background

In 1994, the National Institutes of Health's Office of Extramural Research established a Committee on Clinical Trial Monitoring to review the oversight and management practices of Phase III clinical trials. One of the outcomes of this review was a strong recommendation that "all trials, even those that pose little likelihood of harm, should consider an external monitoring body."

In 1998, NIH issued the "NIH Policy for Data and Safety Monitoring," describing its monitoring requirements for clinical trials.

More recently, the Office of Inspector General of the Department of Health and Human Services issued "Protecting Human Research Subjects: Status of Recommendations." This report, issued in April 2000, states that "problems in gene transfer trials should be a catalyst for greater attention to be directed to ensuring human-subject protection of a broader universe of clinical trials, particularly those in which patients face significant risk." The report was followed in June 2000 by additional communications from the NIH: "Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials," "Required Education in the Protection of Human Research Participants," and "Financial Conflicts of Interest and Research Objectivity."

Beginning with the October 1, 2000 grant deadline, investigators submitting proposals to the NIH were required to include a detailed monitoring plan as part of Phase I and Phase II protocols and the plan must be submitted to the local IRB for review and approval before the trials begin. Consistent with that requirement, the Advisory Committee to the Director of the (National Center for Research Resources (NCRR) has recommended that all General Clinical Research Center (GCRC) protocols have a data and safety monitoring plan (DSMP) that includes periodic review and reporting as appropriate for each study. Because the NCRR has obtained a waiver from the NIH, the local GCRC Advisory Committee (GAC) may approve the DSMP of a Phase I and II clinical trial conducted at a GCRC that is not funded by another NIH Institute. However, if the research is not funded by the NCRR, the approval of the DSMP would follow the customary approval cycle of the NIH Institute and Center (IC). The DSMP must also be approved by the local IRB. Parallel review of the DSMP of a protocol by the IRB and GAC is permitted.

Supporting Regulations/Policy Guidelines

45 CFR 46, Subparts A, B, C, D

21 CFR 50, 56, 312 and 812

Further Guidance on Data and Safety Monitoring for Phase I, Phase II, AND Phase III Trials (NIH Guide June 5, 2000).

NIH Policy for Data and Safety Monitoring (NIH Guide June 10, 1998).

Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials (NIH Guide June 11, 1999).

Recommendations to General Clinical Research Centers (GCRCs) for Patient Safety in Clinical Research. (As accepted by the National Advisory Research Resources Council [NAARC]; May 17, 2001). <http://www.ncrr.nih.gov/clinical/gcrcpatientsafety20010622.asp>

National Center for Research Resources (NCRR) Division of Clinical Research Resources Program Guidelines (March, 2004).

Definitions

Research, as defined in 45 CFR 46 (102(d)), means a systematic investigation designed to develop or contribute to generalizable knowledge. There are many different types of research studies, including studies conducting health services, educational, anthropologic, epidemiologic, and clinical research. Clinical research includes the study of the natural history of a disease or disorder.

Clinical studies or investigations, as used in the narrow sense that the Food and Drug Administration uses it, refers to the study of drug(s), biologic(s) or device(s) in human subjects with the intent to discover potential beneficial effects and/or determine its safety and efficacy. It is a systematic study designed to evaluate a product (drug, device, or biologic) using human subjects, in the treatment, prevention, or diagnosis of a disease or condition.

There are four different stages of testing drugs or biologics in humans, from the first limited experimentation with humans (Phase I) through the normally more populated and targeted population studies to broad postmarketing studies (Phase IV).

Phase I studies include the initial introduction of an investigational agent or treatment to humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. *Phase I* studies are designed to determine the metabolic and pharmacological actions of the investigational agent or treatment in humans, the side effects associated with increasing doses (to establish a safe dose range), and if possible, to gain early evidence of effectiveness. The primary purpose of Phase I studies is to determine if the investigational agent or treatment is safe for use in humans and what are the side effects that limit treatment dosage levels. Normally, Phase I studies are conducted with a small number (20 – 80) of volunteer participants.

In **Phase II studies**, the investigational agent or treatment is given to a larger group of participants to see if it is effective and to further evaluate its safety. Normally the participant population used is the population for whom the investigational agent or treatment is intended. Phase II studies usually involve no more than several hundred subjects.

Phase III studies involve the administration of the investigational agent or treatment to a larger number of participants to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the investigational agent or treatment to be used safely. Phase III studies usually test the investigational agent or treatment as compared

to a placebo or an existing (approved) treatment. Several thousand participants may be part of Phase III studies.

Phase IV studies, or postmarketing studies as they are known, are used to collect additional information about the drug's risk, benefits, and optimal use. Often, Phase IV studies are requested by the FDA concurrent with marketing approval. Phase IV studies may involve studying different doses or schedules of administration, use in different patient populations or other stages of a disease or disorder, or use over a longer period of time.

An **Adverse Event (AE)** is any untoward event that occurs to the subject while participating on a research protocol or clinical trial.

A **Serious Adverse Event (SAE)** as defined by federal regulation (21 CFR Part 312.32) is any adverse event that:

- is fatal or life-threatening (i.e., results in an immediate risk of death).
- is permanently or substantially disabling.
- requires or prolongs hospitalization (only if related to an unexpected complication).
- is a congenital anomaly, new cancer or medication overdose.

This definition also includes any other event the investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution.

The **Yale University School of Medicine Institutional Review Board (IRB), known as the Human Investigation Committee**, is the predominant Institutional Review Board that reviews research at the Yale University School of Medicine, Yale New Haven Hospital, the Yale University School of Epidemiology and Public Health (EPH) and certain research at other organizations (for which Yale has agreed to provide IRB review) that involves the use of human subjects. Some behavioral research protocols are reviewed by the Faculty of Arts and Sciences (FAS) IRB. The Yale IRB's are charged with assuring that trials meet ethical standards and comply with all federal regulations and relevant guidance.

The **General Advisory Committee (GAC)** is Yale University's local GCRC Advisory Committee. As the primary internal review and monitoring committee, it is responsible for the evaluation of the scientific quality of research and the allocation of resources conducted within the Yale GCRC (NCRR, 2004). The GAC is also responsible for approving the DSMPs of all GCRC protocols prior to study initiation.

The GCRC appoints a **Research Subject Advocate (RSA)** to assure that GCRC protocols are performed in accordance with the approved protocol and Data Safety and Monitoring Plan (NCRR, 2004).

The Yale University Human Investigation Committee (HIC) Executive Director or Deputy Director appoints the **HIC liaison to the GCRC**. The liaison is an integral member of the GCRC Protocol Pre-Review Committees and the GAC. The liaison advises these committees and collaborates closely with the RSA to ensure that applicable regulations, guidance, and ethical principles are consistently followed throughout the process of HIC and the GAC review and approval. This interaction includes close collaboration on the development and implementation of DSMPs.

Yale University School of Medicine Policy on Data and Safety Monitoring Plans

Effective June 20, 2001, Yale University formalized a policy requiring data and safety monitoring plans (DSMP) for all therapeutic and non-therapeutic research studies involving human subjects. The policy, highlighting 45 CFR 46.111(a)(6), is an important component of the human subject protection program and consistent with the National Institutes of Health Policy for Data and Safety Monitoring.

Recognizing the need for the development of guidance to assist investigators in identifying the crucial components of the DSMP, the Yale School of Medicine HIC/IRB implemented this regulation in August 2001. The DSMP specifies the assessment of risk of participating in a study; how adverse events are defined, graded, tracked and reported to relevant parties; the process for conducting data and safety monitoring; and who will perform the data and safety monitoring.

The DSMP is written by the principal investigator, reviewed by the IRB/HIC, and in the case of studies conducted at the GCRC must be approved by the GAC. The investigator, GAC or IRB have the authority to determine whether someone other than, or in addition to, the principal investigator should conduct the review of safety and adverse events and/or conduct the data monitoring. This may include the use of internal and independent data and safety monitoring boards.

The review of the data and safety monitoring of clinical trials and human research protocols conducted at the Yale School of Medicine fall within the purview of a number of other campus committees as well, depending upon the clinical content of the protocol and where the research will be conducted. These committees include: the Yale Comprehensive Cancer Center's Protocol Review Committee, the Pediatric Protocol Review Committee (PPRC), the GAC Pre-Review Committee, the Radiation Safety Committee, and the Biosafety Committee. In addition, additional guidance regarding data and safety monitoring is required for clinical protocols involving gene transfer. A Subcommittee on Gene Transfer Protocols has been established at Yale University to monitor and approve all such protocols and any of the on-campus laboratory facilities that are involved. (This review supplements the Yale University School of Medicine Biosafety Committee and the IRB/HIC review and approval of these protocols.)

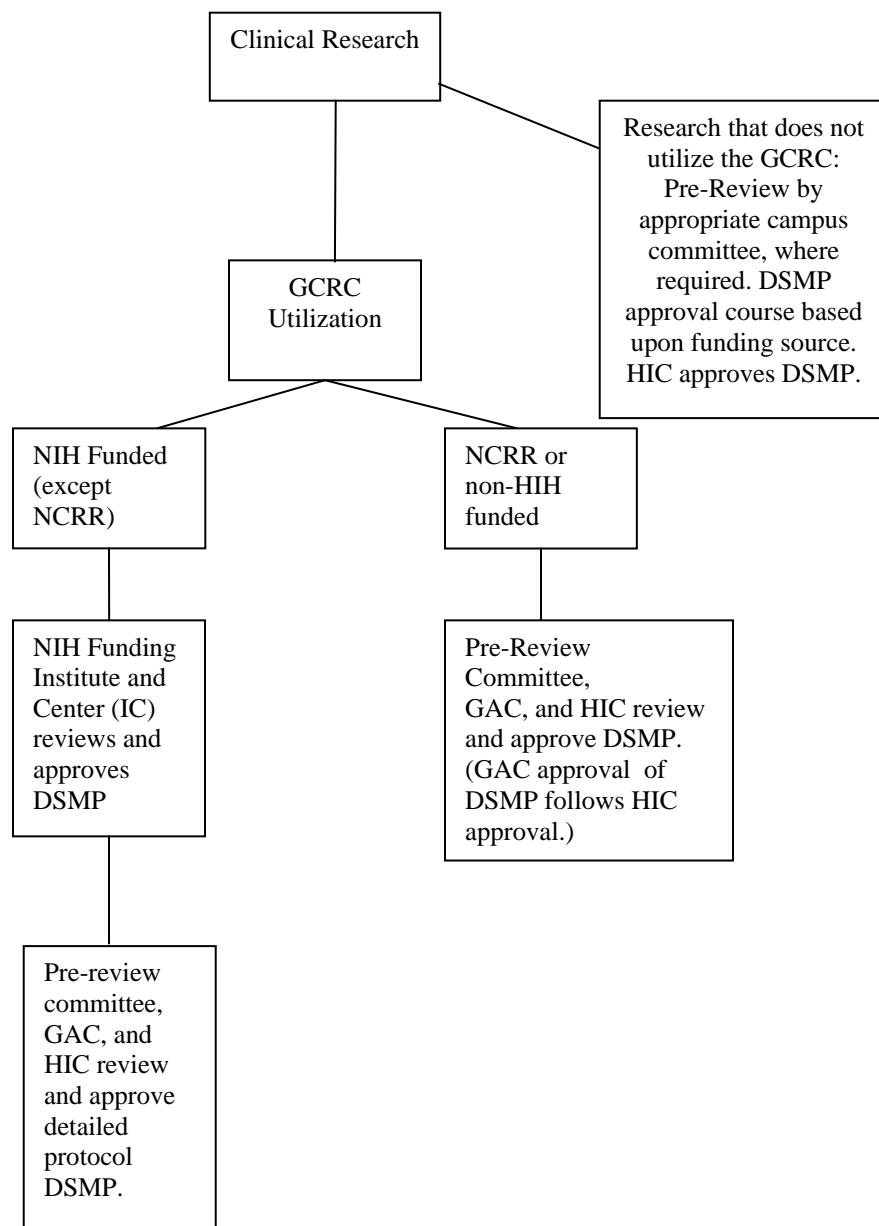
An integral part of the School of Medicine's strategy for data and safety monitoring is a commitment to the ongoing education of key clinical research personnel and the implementation of policies and procedures that maintain subject confidentiality and secure databases. Key personnel involved in the conduct of research are required to complete training on human subjects protection and on the requirements of the Health Insurance Portability and Accountability Act (HIPAA). In accordance with the HIPAA Security Rule, the University will properly secure its databases with password protection, access restrictions, and/or encryption as appropriate. Paper and other non-electronic records are also secured via access restrictions.

The Provost's Office, General Counsel's Office and Dean's Offices have significant roles in research compliance. The Yale University Research Compliance Committee, co-chaired by the Deputy Provost for Biomedical & Health Affairs and the Deputy General Counsel, is the overarching body responsible for compliance with all research-related federal regulations at the University. A DSMP Subcommittee is responsible for overseeing and coordinating all of the

Data and Safety Monitoring Plans developed at the Yale School of Medicine, including the GCRC and other centers. The membership of this subcommittee includes: the Executive Director of the HIC; GCRC Associate Director; Executive Director Grant and Contract Administration; Deputy Director of the HIC; Pediatric and Adult GCRC RSAs; Director of Compliance and Training for the Cancer Center; and the HIC Compliance Manager.

Pathway For Data and Safety Monitoring

A Pathway has been established for the review and approval of data and safety monitoring plans, including two pathways for trials that utilize GCRC resources. These pathways are illustrated below; the remainder of this document deals exclusively with studies involving the GCRC.



If a study conducted at the GCRC receives primary funding from an NIH Institute or Center (IC) other than NCRR, it is the responsibility of that funding IC to approve and monitor the data and safety monitoring plan and establish a data and safety monitoring board (DSMB) if deemed necessary. The study should conform to data and safety monitoring and interim analysis algorithms in effect within the NIH IC.

Content and Review of GCRC Data and Safety Monitoring Plan

The GCRC's strategy for the DSMP continues to evolve. As federal data and safety monitoring rules are established, DSMP procedures are developed at NIH Institutes and Centers, and best practices and standards are identified and better understood, we anticipate the creation of new models that will allow our own strategy to be modified and strengthened. As well, we draw from existing grading and attribution scales such as the National Cancer Institute [NCI] guideline on expedited adverse event reporting requirements for NCI investigational agents [<http://ctep.info.nih.gov>]).

Despite plans for continual improvement and enhancement, a comprehensive strategy for developing and approving DSMPs, which are required for all GCRC clinical trials regardless of the level of risk involved, is already in place.

The Role of the IRB/HIC: The IRB/HIC is charged with assuring that Yale School of Medicine research studies involving human subjects meet ethical standards and comply with applicable regulations and that the DSMP written by the principal investigator is appropriate to the level of risk associated with the protocol.

The IRB/HIC assesses all protocols and reviews the principal investigator's assessment of "minimal risk" or "more than minimal risk." Protocols carrying minimal risk are those that are commensurate with everyday experiences and risks and where there is adequate protection of confidentiality. Examples would include protocols that are non-invasive, questionnaire driven, observational, or involve blood drawing in manners and amounts that correlate with normal blood donations for healthy individuals. In the event that there is disparity between the funding institute, the GAC, and/or the IRB/HIC in assessing level of risk, the most conservative assessment will prevail and the most aggressive monitoring plan will be implemented.

The Role of the GAC: The GAC is required to evaluate all studies utilizing GCRC resources and will approve all data and safety monitoring plans for GCRC protocols. The GAC will evaluate and approve the DSMP based on the assessment of risk and the size and complexity of the trial or the research protocol. It will also evaluate the need for a DSMB based upon the size, complexity, and level of the clinical trial and approve the DSMB membership and responsibilities in instances where a DSMB is required.

The GAC has assigned the preliminary review of GCRC protocols to a Pre-Review Committee for protocols involving adult subjects while the Pediatric Protocol Review Committee (PPRC) continues to serve in this capacity for protocols involving children. Each Pre-Review committee is chaired by a Research Subject Advocate. (Dr. Rosa Hendler for the adult Pre-Review and Dr. Thomas Carpenter for the PPRC.) Recommendations to the PI with regard to the DSMP are discussed at these meetings. These meeting minutes/notes will also be made available to the NCRR.

DSMP Content: A DSMP will, at a minimum, include:

- The assessment of risk as described by the Principal Investigator.
- A plan for addressing the grading of adverse events and the attribution of adverse events.
- Plans for reporting serious unanticipated and anticipated (where appropriate) adverse events to other researchers, the IRB/HIC, GCRC RSA, funding agency and regulatory bodies.
- A plan for reviewing and reporting non-serious anticipated and unanticipated adverse events.
- Identification of the individual(s) who will perform the data and safety review.
- A plan for conducting data reviews at a frequency commensurate with risk and progress of study.

The IRB/HIC, the GAC and RSA may conduct concurrent reviews of data and safety monitoring plans to maximize the efficient review of protocols.

As appropriate, the GAC may require additional information to assist in examining and analyzing such data as dropout rates, the frequency and severity of adverse events, violations of enrollment criteria, hypothesis validation and analysis of the main outcome data and its relationship with potential changes in study design. The evaluation (approval, deferral, or approval contingent based upon recommendations of the GAC and RSA) of the DSMP for each protocol will be documented in the GAC meeting minutes. These minutes will be made available to the NCRR or other NIH program staff responsible for oversight of specific clinical trials or protocols conducted at the GCRC.

Criteria for the requirement of a DSMB: Phase I and II clinical trials, in which the intervention is considered to pose minimal risk and the investigators and institution have no actual or potential conflicts of interests, frequently may be monitored by the PI with regular reporting to the IRB/HIC and to the GAC. The method and degree of monitoring for Phase I and II clinical trials that present greater than minimal risk will be appropriate to the nature of the study, its size and complexity, the subject population, the research environment, and the degree of risk involved. Trials that are blinded, and particularly those that involve vulnerable populations (i.e., pediatric, pregnant, prisoner, or decisionally impaired subjects), require a more intensive level of monitoring than studies involving minimal risk and are likely to require an external Data and Safety Monitoring Board. The organization, responsibilities, and operation of the DSMB, whose monitoring activities are distinct from those of the IRB/HIC, are described in detail later in this document.

In summary, a DSMB is established if the proposed study meets any of the following criteria:

- The study is a Phase III clinical trial.
- The study includes a high risk intervention.
- The study is a blinded and/or a high risk intervention Phase II multi-center study.
- The study may include management of conflict of interest issues.

When a DSMB is required, it is the GAC and the HIC that determine how to constitute the Board and the appropriateness of its membership.

DSMP Roles and Responsibilities

Role of the Principal Investigator (PI): The PI is responsible for protocol design, the overall safe conduct of the study, and the assessment of risk as well as a justification of that risk. The PI is also responsible for knowing the policies of the Yale University HIC with regard to adverse event reporting (reference: HIC DSMP template at <http://www.info.med.yale.edu/hic>) as well as any additional requirement specified by the DSMP. Required reporting includes, but may not be limited to, the documentation, investigation, follow-up of adverse events, and annual reporting of these events.

A principal investigator will report any serious and unanticipated adverse event to the IRB/HIC within 48 hours, via HIC Form 6a, which will, in compliance with federal regulations [45 CFR 46.103(b)(5)(i); 21 CFR 312.32(c)(1); and 21 CFR 56.108(b)] additionally report to the Department of Health and Human Services and the FDA. In many studies, investigators have additional obligations to report adverse incidents to funding agencies or industrial sponsors and to inform other sites involved in a multi-center trial. The GCRC should receive serious adverse event reports no later than 15 calendar days after the event.

The principal investigator is required to perform safety reviews at a frequency commensurate with the size and complexity of the study. It is the principal investigator's responsibility to notify the IRB/HIC and the RSA of any new information considered relevant to the safety or efficacy of any GCRC protocol, whether it involves minimal or greater than minimal risk. Finally, the PI is responsible for communication of any serious adverse events and DSMB reports to the Yale University HIC and the GCRC RSA.

Research Subject Advocate: The GCRC has appointed a Research Subject Advocate (RSA) to advise investigators as to the design of a DSMP that is commensurate with the level of risk of the protocol. In addition, the RSAs assure that GCRC protocols are performed in accordance with the approved protocol and monitoring plan. Any serious violation or systematic misrepresentation of data or failure to meet established criteria will be reported by the RSA to the GAC and the IRB/HIC for disciplinary or other action.

Data and Safety Monitoring Boards

Where a DSMB is required, the principal investigator and/or the HIC (in certain circumstances, such as conflict of interest) will select participants with appropriate scientific and biostatistical expertise and, as noted, will seek GAC and HIC approval for the composition of the board.

Members of a DSMB will be responsible for:

1. Familiarizing themselves with the clinical research protocol and plans for data and safety monitoring.
2. Reviewing interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data. The DSMB may also review trial performance information, such as accrual data, and determine whether and to whom results should be released prior to the final reporting of study results.

3. Reviewing reports of related studies to determine whether the monitored study needs to be changed or terminated.

4. Reviewing major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

5. Following each DSMB meeting, providing the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. The responsible principal investigator must promptly provide a copy of this information to the IRB/HIC, GAC and funding agency as appropriate.

Membership: The principal investigator may appoint DSMB members for a fixed term in cases where an internal DSMB is appropriate, i.e. where the HIC/IRB and University Conflict of Interest Committee determine that there are no associated actual or apparent conflicts of interest. In certain high greater than minimal risk studies and in cases where a potential for a conflict of interest exists, the DSMB will be appointed by a neutral party. The Chair of the DSMB will be selected from among the voting members. Voting members of a DSMB may be from within or outside the institution and are likely to include physicians, statisticians, non-physician scientists, and lay representatives. Staffs affiliated with the institution who are members of the DSMB should view themselves as representing the interests of subjects and not that of the institution. Criteria for selection include experience, reputation for objectivity, and knowledge of clinical trial methodology. DSMB members may be compensated for their expenses, including lost compensation, unless there is a conflict of interest with this payment.

Individuals invited to serve on the DSMB will disclose any potential conflicts of interest, whether real or apparent, to the principal investigator and the appropriate institutional officials. Conflicts of interest can include professional interests, proprietary interests, and miscellaneous interests as described in the NIH Grants Policy Statement, Pages 11-12 and 45 CFR Part 94. Any conflicts that develop during a member's tenure on a DSMB must also be disclosed and the member excluded from future DSMB participation. Members with real or apparent conflicts of interest will be excluded from DSMB participation.

Meetings: DSMB meetings will be held at least annually and in some instances, more often, depending on the nature and volume of the trials being monitored. Each meeting will be divided into three parts. First, there will be an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. The focus in the open session will be on accrual, protocol compliance, and general toxicity issues. Outcome results must not be discussed during this session. Following this session, a closed session of DSMB members will be held. The statistician(s) will be present and discuss the outcome results with the DSMB. A final executive session involving only DSMB members will be held to allow the DSMB an opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, to develop recommendations, and to take votes as necessary. Legitimate concerns about subject safety or early conclusions may require premature dissemination of results.

Release of Outcome Data: In general, outcome data will not be made available to individuals outside the DSMB until accrual has been completed and all subjects have completed their

treatment. At that time, the DSMB may approve the release of outcome data on a confidential basis to the principal investigator to expedite manuscript preparation and to a small number of other investigators planning future trials. Any release of collective outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

Confidentiality Procedures: Any communication, either written or oral, of the deliberations or recommendations of the DSMB will be made only in compliance with this policy. Each member of the DSMB must sign a statement of confidentiality.

Recommendations from the DSMB

Any recommendations from DSMB meetings will be given to the principal investigator, with copies provided to the IRB/HIC, the GAC, and as required to appropriate funding and regulatory agencies.

If the DSMB recommends that a study be changed for subject safety or efficacy reasons, or closed early due to futility, apparent positive/negative results or slow accrual, the principal investigator must obtain seek IRB/HIC approval for and, if approved, act to implement the change as expeditiously as possible. In the unlikely situation that the PI does not concur with the DSMB recommendations, he/she must inform the IRB/HIC, the GAC, and the funding agency of the reason for disagreement. The IRB/HIC will be responsible for reaching a final decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with selected trial investigators and funding staff in order to reach a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy or slow accrual, the DSMB will provide an adequate rationale for its decision. In the absence of disagreement, policies of the funding center whose award supported the trial will be followed prior to amending the protocol or changing the award.