

DSMB Training Manual

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CTSA COLLABORATIVE DSMB WORKGROUP

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CONTRIBUTORS

Barbara N. Hammack, PhD

Colorado Clinical & Translational Sciences Institute
University of Colorado Denver
Aurora, Colorado

M. E. Blair Holbein, PhD, BCAP

Center for Translational Medicine
UT Southwestern Medical Center
Dallas, Texas

Tamsin A. Knox, MD, MPH

Tufts Clinical and Translational Science Institute
Tufts University School of Medicine
Boston, Massachusetts

Frederick W. Luthardt, D. Bioethics, MA

Johns Hopkins University School of Medicine
Institute for Clinical and Translational Research
Johns Hopkins Bayview Clinical Research Unit
Baltimore, Maryland

Jason M. Malone, MPA

Regulatory Affairs Human Subjects Division
University of Washington
Seattle, Washington

Ann J. Melvin MD, MPH

University of Washington
Seattle Children's Research Institute
Seattle, Washington

Nancy A. Needler, BS CCRC

Clinical & Translational Science Institute
University of Rochester
Rochester, New York

Marie T. Rape, RN, BSN, CCRC

NC TraCS Institute
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Carson R. Reider, PhD

The Neuroscience Research Institute
The Ohio State University
Columbus, Ohio

Susan L. Sandusky, BA

Clinical and Translational Science Institute
University of Pittsburgh
Pittsburgh, Pennsylvania

David Weitzenkamp, PhD

Colorado Clinical & Translational Sciences Institute
University of Colorado Denver
Aurora, Colorado

Laurel Yasko, MPPM, RN, CCRC

Clinical and Translational Science Institute
University of Pittsburgh
Pittsburgh, Pennsylvania

REVIEWERS

Paul Beninger, MD, MBA

Tufts University School of Medicine
Boston, Massachusetts

Lori Carter-Edwards, PhD

University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

David Couper, PhD

University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Elizabeth Geller, MD

University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Michael Green, MD

University of Pittsburgh
Pittsburgh, Pennsylvania

Sonya Heltshe, PhD

Seattle Children's Hospital
Seattle, Washington

Farzad Noubary, PhD

Tufts University School of Medicine
Boston, Massachusetts

David Weber, MD, MPH

University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

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FREQUENTLY USED ABBREVIATIONS

Frequently Used Abbreviations

COI	Conflict of Interest
CFR	Code of Federal Regulations (United States)
CTSA	Clinical and Translational Science Award
DSM	Data and Safety Monitoring (plan)
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
PI	Principal Investigator
NIH	National Institutes of Health
SMC	Safety Monitoring Committee
SAE	Serious Adverse Event

Preface

The Clinical and Translational Science Award (CTSA) program began in October 2006 under the auspices of the National Center for Research Resources with a consortium of 12 academic health centers. The program was fully implemented in 2012, comprising 60 academic medical institutions across the country and their partners. Several components of the CTSA program were defined as being crucial in supporting the overall mission to accelerate advances in health care. Each component was represented by a Key Function Committee, to share approaches that reduce or remove institutional impediments to clinical and translational research, and also enhance inter-institutional collaborations. Various workgroups within the Regulatory Knowledge Key Function Committee were established to develop recommendations for best practices and to assist consortium members to meet regulatory and human subject protection requirements in an integrated and systematic approach. This committee has worked collaboratively to share expertise and resources across the consortium including forming partnerships and liaising with other Key Function Committees. Efforts like these are particularly responsive to the recommendations put forth in the Institute of Medicine report about “engaging in substantive and productive collaborations”. One of the workgroups specifically focused on Data Safety and Monitoring Boards (DSMB), recognizing the need to develop guidance for individuals who serve on a DSMB, primarily for investigator-initiated projects. This training manual was developed through the expertise of the membership, and through review of literature and other resources.

The development of this training manual was a result of a collaborative effort of many individuals with expertise in clinical research safety oversight from various academic institutions with CTSA awards. We are indebted to our colleagues who assisted with some technical writing, particularly the sections related to statistical analysis. Additionally, we are deeply appreciative of the resources to complete this project provided by our CTSA Principal Investigators.

The purpose of this manual is to serve as a training and reference resource for individuals asked to serve on a DSMB or some other capacity of safety oversight for clinical research studies. It contains a comprehensive collection of the regulatory framework for DSMBs as well as best practices. It is written to provide both a thorough review for the novice as well as provide practical, in-depth guidance on specific topics for those with prior DSMB experi-

ence. Although sections can be read out of sequence, it will be most helpful for readers to complete one section before moving on to the next.

CHAPTER 1

Introduction

OVERVIEW

The purpose of this manual is to serve as a training and reference resource for individuals asked to serve on a Data and Safety Monitoring Board (DSMB). It contains a comprehensive collection of the regulatory framework for DSMBs as well as best practices. It is written to provide both a thorough review for the novice as well as provide practical, in-depth guidance on specific topics for those with prior DSMB experience. The intended audience is primarily individuals at academic health centers, participating in federally funded research and other non-commercial research. In addition, investigators working with DSMBs, members of Institutional Review Boards (IRB), and some in research administration may find it helpful to review this manual. While the general principles presented apply to commercial trials, the scope and focus of this manual is on investigator initiated trials. This manual presents general principles, functional guidance, definitions, and templates.

Terminology for monitoring committees can be confusing. The National Institutes of Health (NIH) communications use Data and Safety Monitoring Boards while the Food and Drug Administration (FDA) guidance uses Data Monitoring Committees. The terms are generally interchangeable. In this document we will be using the term Data and Safety Monitoring Board (DSMB).

HISTORY

External advisory committees for review of multicenter cooperative trials first started being used in the 1960s. The Greenberg report, convened by the then National Heart Institute, recommended a role for an advisory group of experts, not directly involved with a trial, to review the protocol and conduct of the trial and provide advice to the Institute. The report also included a recommendation that a mechanism be put in place for early trial closure should “accumulated data answer the original question sooner than anticipated, if it is

apparent that the study will not or cannot achieve its stated aims or if scientific advances since initiation render continuation superfluous” (Heart Special Project Committee, 1988).

As early as 1979, NIH policy recommended that “every clinical trial should have provision for data and safety monitoring”. However, there has generally been a paucity of government regulations addressing the requirements for data and safety monitoring in general or to guide the operations of DSMBs in the United States, as well as elsewhere. The only specific mention of DSMBs in the United States Code of Federal Regulations (CFR) appeared for the first time in 1996. This regulation addresses requirements for DSMBs in research studies in emergency settings in which the obtaining of informed consent from the individual to be treated or a family member is not feasible (21 CFR 50.24). The CFR formally required additional protections, including the “establishment of an independent data monitoring committee to exercise oversight of the clinical investigation” for the conduct of studies of new treatments for trauma or sudden cardiac arrest victims who were generally unconscious and for whom it was not likely to be able to contact a relative to provide informed consent.

Initially, DSMBs were used primarily for large multicenter cardiovascular trials, but their use has expanded to other disease conditions and trial types. In 1998, NIH established a policy requiring DSMBs for phase III multicenter clinical trials. Subsequently, in 2006, a guidance document was issued by the FDA entitled *Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees* directed to sponsors of new drugs, biologics, and medical devices for monitoring investigations as required by regulations (21 CFR 312.50 and 312.56 for drugs and biologics, and 21 CFR 812.40 and 21 CFR 812.46 for medical devices). It described possible approaches and discussed when and how such committees should operate but did not impose any requirements on sponsors regarding DSMB oversight. There are also references to DSMBs in the guidance documents developed through the International Conference on Harmonization (ICH). The documents in the ICH ‘efficacy’ series include: E3, *Structure and Content of Clinical Study Reports* (1995); E6, *Good Clinical Practice: Consolidated Guideline* (1996); and E9, *Statistical Principles for Clinical Trials* (1998).

Although NIH guidance specifically addresses the use of independent DSMBs only for phase III multicenter clinical trials and current FDA regulations require DSMBs only for research studies in emergency settings, both entities endorse that all clinical trials require safety monitoring and that the method and degree of monitoring should be commensurate with the risks, size and complexity of the trial. Not all clinical trials require the added complexity of additional monitoring by a DSMB; however, it has been recognized that even some smaller or early phase trials may also benefit from independent monitoring by a DSMB, such as gene therapy trials, studies involving vulnerable populations or trials with the possibility of serious toxicity.

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CHAPTER 2

Monitoring of Clinical Research Studies

PRINCIPLES OF MONITORING DATA AND SAFETY

Clinical research has numerous stakeholders with differing interests in the quality of the data and safety of the trial. These would include: (1) subjects/patients/participants in the study; (2) population at risk (potential patients); (3) funding agency; (4) scientific progress; (5) study investigators and staff. Every clinical study requires some level of monitoring for safety. The risk associated with participation in research must be minimized to the greatest extent possible. Hence, the methods and intensity of monitoring should be commensurate with the risks, nature, size, and complexity of the trial. For smaller, minimal risk or less complex trials, the monitoring can be as simple as a structured assessment and reporting by the PI as projected by the DSM plan. Sometimes a trial may warrant an outside independent observer(s), called a Safety Officer or, if additional expertise is needed, a Safety Committee. For higher risk and/or large studies, an independent monitoring committee such as a DSMB is usually required to determine safe and effective conduct and to recommend revisions and/or premature termination of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. The ultimate decision regarding the level of risk of the investigation, and therefore the monitoring requirements, will be made by the regulatory authorities (e.g., IRB, or the NIH).

The quality and integrity of the data generated and collected in a trial directly impacts the ability to interpret the work. An important part of monitoring clinical research sites includes verification of data used in analysis of the trial. A DSMB equally relies on the accuracy of the data that they are given to review. An assessment of the data integrity is also part of the monitoring responsibility.

This manual focuses on the types of studies found at academic institutions which may be smaller in the number of participants and number of sites than industry studies for the FDA.

DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring (DSM) plan establishes the overall framework for the study's data and safety monitoring. The goal is to ensure the safety of the participants, and the validity and integrity of the data. The plan should describe the entity that will be responsible for monitoring the progress and conduct of the study, and how adverse events will be reported to the appropriate institutional and federal agencies in accordance with current NIH and/or FDA and local or state regulations. The DSM plan is commensurate with the risks involved with the investigation. It can be as simple as the investigator annually submitting his/her safety and adverse event information to the IRB or as complex as having a DSMB. The DSM plan should meet institutional, IRB, and sponsor requirements.

The DSM plan should evaluate the risk inherent in the study (see **Table 2.1**) and present the appropriate method of monitoring that is commensurate with the risk, size, and complexity of the study. The DSM plan is determined by assigned level of risk, sponsor requirements, number of study sites, number of subjects, and finally the IRB.

DESCRIPTION OF THE DATA AND SAFETY MONITORING PLAN

MONITORING PLAN COMPONENTS

Monitoring entity

This identifies the person or persons who will have the primary responsibility for monitoring. Depending upon the size, complexity or inherent risk of the protocol, a plan may include the investigator, experts in the field of study, consultants (such as biostatisticians) and other specialists as needed. The PI is ultimately the one responsible for all aspects of the trial including safety. The inclusion of other reviewers does not relieve the investigator of his/her responsibility. The issue of possible conflict of interest (COI) must be taken into account, especially if the investigator assumes the role of the monitor. Use of an independent monitor can accommodate the need for an unbiased review.

Independent review can include a range of solutions. Monitoring should be conducted by persons completely independent of the investigators who have no financial, scientific, administrative or other COI with the trial. These independent assurances are important as clinical investigators have an inherent COI when conducting human subjects research. Ongoing review of the data by an independent individual or committee assures the investigators that the trial can continue without jeopardizing patient safety.

Plans for assuring participants safety, adverse event collection and reporting

A description of identified potential risks for the participants including the risks of the standard of care given in the protocol and the additional risks attributable to the intervention(s) is accompanied by a strategy for protection against the identified risks.

Plans for assuring data accuracy and security

The DSM plan should include procedures for ensuring that data are collected and analyzed per protocol and that confidentiality of study subjects is maintained.

Plans for reporting unanticipated problems

The DSM plan should include a statement of reporting problems such as serious adverse events, including required reporting entities (e.g., the IRB, FDA, sponsor, and NIH, if applicable). The urgency of reporting depends upon the issues that have led to an early termination or significant change to a study. Note that protocol violations that affect safety are considered an adverse event. If applicable some trials may include a definition, grading scale and 'study relatedness' criteria for adverse events.

Plans for monitoring

The DSM plan should indicate the monitoring process. The procedures are given for a monitor (or designee) to review, record and report information from the research record for regulatory compliance, data capture consistency and quality, process deficiencies, data irregularities, and findings of regulatory non-compliance. The process for reporting and addressing any problems discovered from monitoring should be described.

Plans for interim analysis and reporting

The plans for examining safety and efficacy data and other records from protocols on an explicitly defined schedule should be stated. The intervals are usually statistically determined, e.g., after half of the enrollment has been attained, or a specified number of participants, or set number of sentinel events. These interim analyses should be conducted and reported in such a manner as to assure that no inadvertent unblinding occurs among those engaged in the conduct of the study. The plan should include a statement of protocol stopping guidelines for overall trial conduct, safety concerns, interim boundaries, and futility. The plan should include a statement of intended scope of continuing review. This statement should include enrollment and withdrawal rates, protocol deviations, subject interview and conduct, review of subject symptoms and performance status, review of clinical

test results, physical examinations, vital signs, diagnostic tests and evaluations (e.g., in compliance with IRB required review plus any study-specific considerations). In many cases, such a summary will be a concise statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol (explicitly note any [non-] occurrence of unexpected events), the informed consent document, and any investigator brochure.

The IRB should review DSMB or independent monitor reports in a timely manner. They and the PI should act promptly on any findings indicating the need for an amendment to the protocol, informed consent form, or affecting the continuation of the protocol. Likewise, PIs and the IRB should notify the DSMB promptly of any protocol amendments they generate.

METHODS OF MONITORING

The level of oversight required for a clinical research study will vary depending on the degree of risk (described below). For studies that present a minimal or low risk to subjects, safety monitoring may be conducted continually by the PI. For studies that present a moderate degree of risk, safety monitoring may be conducted by a single independent monitor or possibly a DSMB. NIH funded phase III clinical investigations (or any multisite clinical trial) involving interventions that entail potential risk to participants are required to have a DSMB. In addition, a DSMB may be appropriate for earlier trials (phase I and II) that are: (1) multicenter; (2) blinded to the researcher; (3) employ particularly high risk interventions (gene therapy, cancer treatments, AIDS treatment); or (4) include vulnerable study populations (pediatric, pregnant, prisoners, cognitively impaired, economically or educationally disadvantaged). The NIH requires a DSMB for any investigation that places participants at significant risk of a serious adverse event.

The different entities that may monitor a study are described below. The levels of monitoring of a study in increasing intensity are:

- Minimal or low level risk: monitoring by PI in accordance with the DSM plan
- Moderate risk: monitoring by an independent Medical Monitor
- High risk, blinded study, phase III or other risk features: independent committees including study monitoring committees and DSMBs

PRINCIPAL INVESTIGATOR

The Principal Investigator (PI) is responsible for overseeing and supervising all aspects of a clinical trial. The monitoring process can be delegated but the PI is nonetheless accountable for overall study management and compliance. Basic oversight of a study's overall com-

pliance and performance can be an ‘informal monitoring’ where the PI conducts continual surveillance. At this level, the PI concurrently observes and inspects the study’s compliance with regulatory requirements (e.g., submitting study protocol changes and implementing such changes only after the IRB has approved them). In addition, informed consent, participant eligibility, protocol compliance, and data entry/quality would be examined in real-time as the above activities are occurring.

Formal monitoring follows a stated plan that can include the above on-going scrutiny, but more importantly involves an interim or periodic inspection mechanism that evaluates and documents compliance and study performance retrospectively.

Minimal/low risk

The PI will monitor the study with prompt reporting (typically within 24 hours or 1 business day) of adverse events and other study related information to the IRB, sponsor, and other agencies as appropriate. Team meetings by the PI and his/her staff will be conducted on a routine basis to discuss protocol issues and review adverse events. Surveillance and protections will be put in place to adequately identify adverse events promptly. The DSM plan will be revised and updated if the risk/benefit balance changes.

Moderate risk

The PI will monitor the study with prompt reporting of adverse events and other study related information to the IRB, sponsor, and other agencies as appropriate. Team meetings by the PI and his/her staff will be conducted on a routine basis to discuss protocol issues and review adverse events. Some protocols may also require well-described criteria for dose escalation, criteria defining maximum tolerated dose, and/or criteria for stopping the trial or involvement of a subject. Surveillance and protections will be put in place to adequately identify adverse events promptly. An independent Medical Monitor or Safety Monitoring Committee (SMC) may also be utilized to review adverse events as they occur and make recommendations to the protocol team. The DSM plan will be revised and updated if the risk/benefit ratio changes.

MEDICAL MONITOR

Some multicenter clinical trials will have a specifically designated Medical Monitor. This individual is responsible for real-time monitoring of reports of serious adverse events (SAEs) submitted by the clinical centers to identify safety concerns quickly and to provide regulatory bodies with case-by-case reports of the SAEs. The Medical Monitor will usually evaluate serious adverse events blinded to treatment assignment whenever possible, unless partial or complete unblinding has been approved by the DSMB. The specific role and pro-

cedures of the Medical Monitor will vary depending on the specific trial, all of which should be clarified before starting the trial. The Medical Monitor should not be a member of the study team but should have experience in the disease and population studied. The Medical Monitor reports to the PI, the DSMB, and other regulatory bodies as specified in the DSM plan. The role of the independent Medical Monitor is covered in detail in [Chapter 6, “Role of a Study Safety Officer and Study Monitoring Committees”](#).

INDEPENDENT SAFETY OFFICER

A Safety Officer is an individual independent from the study who is responsible for data and safety monitoring activities in what are typically considered low-to-moderate risk single site clinical studies. The Safety Officer advises the PI and the IRB regarding participant safety, scientific integrity and ethical conduct of a study. The Safety Officer has relevant expertise with the disease process under study, regulatory affairs, and with clinical trial methodologies. The Safety Officer provides monitoring in a timely fashion by real-time review of serious adverse events and evaluation of individual and cumulative participant data. The role of a Safety Officer is somewhat unique to smaller, single center, or non-commercial research studies.

SAFETY MONITORING COMMITTEE

In many studies, a Safety Officer alone may be insufficient to provide adequate oversight. In these cases, a small SMC can provide more effective oversight. This committee may be composed of a Safety Officer in addition to a biostatistician and/or one or two experts in the disease being studied. This type of oversight is appropriate for moderate risk studies that due to size or complexity require the on-going assistance of the statistician in the review process. The primary responsibility of the SMC is to monitor subject safety. The additional roles on the committee provide more expertise to monitor the study and answer more complex questions that may arise in larger studies which are considered to be low or moderate risk. The abbreviated monitoring of a SMC is appropriate for studies which are: lower risk, smaller, require biostatistical input (e.g., for early stopping), or additional expertise beyond what the Safety Officer can provide. One example is a relatively low risk phase I trial.

INDEPENDENT DSMB

Independent DSMBs are generally indicated in large multicenter clinical trials evaluating interventions aimed at prolonging life or reducing risk of a major adverse health outcome and where statistical comparison between treatment groups is necessary to assess on-going risk to study participants. Monitoring by a DSMB may also be useful for studies with heightened safety concerns by virtue of the population being studied or the risk of the interven-

tion. An example would be the requirement for review by an independent data monitoring committee for emergency research with exemption from the requirement for obtaining informed consent (21 CFR 50.24).

The DSMB is considered independent if the members are not involved in the design or conduct of the trial other than their role as a DSMB member and have no financial, intellectual or academic COI and no vested interest in the outcome of the trial. DSMBs are advisory to the PI and the study sponsor. Based on the on-going review of the data, the DSMB advises the PI and sponsor whether to continue, modify, or terminate the trial.

EXTERNAL DATA AND SAFETY MONITORING BOARD

An external DSMB is a group of independent (defined above) experts with no vested interest in the outcome of the study that reviews the ongoing conduct of a clinical trial to ensure continuing participant safety as well as the validity and scientific merit of the trial. The term 'external' refers to at least some, if not all, of the members not being a part of the institution where the study is being conducted. External DSMBs provide expertise beyond the walls of a particular institution, independence from COI, and augment the resources of an institution where, for example, all the biostatisticians with DSMB experience may be involved in the study itself. Based on the on-going review of the data, the DSMB advises the sponsor whether to continue, modify, or terminate the trial. An external DSMB generally includes independent data analysis verification (i.e. another separate biostatistician evaluates the data analyzed by the DSMB). The exact role, scope of authority and membership of a DSMB should be defined in a charter.

INSTITUTIONAL DATA AND SAFETY MONITORING BOARD

An institutional DSMB may be formed to handle, for example, all studies at the institution's cancer center or all clinical trials in a particular academic or clinical department. This is structured study monitoring by a group of individuals not involved in the trial's design or conduct but who may be associated with the sponsor, either industry or institute. Internal boards can be considered for trials that are earlier phase, are not blinded or do not require interim review of comparative data but for which additional monitoring beyond the study team or safety monitor would be useful to ensure participant safety or to maintain confidentiality of accumulating data.

DETERMINING RISK AND MATCHING MONITORING GUIDELINES

Minimal risk

Minimal risk is defined in the federal statutes as a risk where “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (45 CFR 46.102).

Examples: Routine physical tests; peripheral blood draws; routine X-rays; routine psychological examinations or tests when low risk to confidentiality; use of surveys or questionnaires with low risk to confidentiality; non-invasive radiology or imaging studies; observational studies; nutritional studies that do not involve radioactive isotopes; behavioral studies; gait assessments; anthropometric evaluations.

Minimal risk study monitoring: Can be monitored appropriately for safety by the investigator.

Low risk

Low risk involves a minor increase over minimal risk. The intervention or procedure presents experiences that are reasonably commensurate with those inherent in actual or expected medical, dental, psychological, social or educational situations (45 CFR 46.406).

Examples: Studies of healthy volunteers using well described research procedures such as intravenous infusions of non-vasoactive drugs; euglycemic clamp; indirect calorimetry; muscle and fat biopsy; low risk exercise tests; indwelling catheter < 24 hours; oral glucose tolerance test; minimal anticipated drug/treatment related adverse events with minimal or no anticipated medical intervention; meets the requirements for minimal risk but include special populations.

Low risk study monitoring: Can be monitored appropriately for safety by the investigator.

Moderate risk

Moderate risks are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111). Risks are recognized as being greater than low, but are not considered as serious as high risk, and their surveillance and protections are adequate to identify adverse events promptly and keep their effects minimal.

Examples: Participants treated with placebo for a recognized disease or a multiarm study where there is the potential for increased risk in one or more arms; off label use of an approved medication or drug combinations; reasonable level of baseline knowledge from which it is feasible to extrapolate risk of adverse events; only anticipated mild/moderate adverse events or low probability of serious adverse events; microneurography in healthy participants; low risk studies in vulnerable populations; procedures involving the collection of sensitive information (e.g., illegal activities); invasive sampling, invasive diagnostic testing.

Moderate risk study monitoring: Often requires a level of oversight beyond the investigator. These studies will utilize, in addition to the investigator, additional monitoring by an individual not directly involved in the study such as a Safety Officer, and may require the oversight of a Data and Safety Monitoring Board. A Safety Officer should be an expert in the field and experienced in clinical research, but independent of the study. The charter outlining the role of the Safety Officer in the study should be written by the investigator in conjunction with the Safety Officer. This charter should include appropriate study stopping criteria for safety. In moderate risk studies, a SMC may be appropriate to add additional disease-specific expertise and a biostatistician.

High risk

Studies that are of high levels of risk may result in permanent physical and/or mental changes, hospitalization, and/or death. In situations where the prospect of direct benefit to the study participant exists but the risks associated with study procedures are considered substantial; there is an increased probability for the occurrence of a study related event that is serious and prolonged or permanent, or there is significant uncertainty about the nature or likelihood of adverse events. Also studies that have large number of participants or that are very complex and that have standard-of-care-altering outcomes are included.

Examples: Interventions or invasive procedures that involve substantial risk; blinded phase I and II trials; studies involving the use of a chemical/drug/medical device for which there are little or no human toxicology data; gene transfer studies or research involving recombinant DNA; investigator-initiated phase III or multicenter clinical trials; studies where consent is waived such as in emergency circumstances or in populations unable to give informed consent (e.g., mentally incapacitated); potential anticipated for serious adverse event or frequent adverse event associated with the research requiring medical intervention; implantation of medical device with an Investigational Device Exemption; Category III radiation risk (HE (mrem) > 5000 mrem or organ limit of HT > 750/WT); surgical procedures; general anesthesia.

High risk study monitoring: Requires a level of oversight other than can be provided by

the investigator or a single independent safety monitor. These studies will utilize, in addition to the investigator, additional monitoring such as a formally established independent Data and Safety Monitoring Board that has specific oversight of the safety monitoring of the study. A DSMB will be required for multicenter trials and all phase III clinical (interventional) trials. A monitoring board may be required for certain studies to determine safe and effective conduct and to recommend termination of the study when significant benefits or risks have developed or when the trial is unlikely to be concluded successfully. Early phase studies that involve vulnerable populations, are blinded to the researcher, utilize randomization, or employ particularly high risk interventions may require a DSMB, depending on the nature of the study. The board should include a group of individuals with sufficient expertise to make safety decisions for the trial at hand. Clinicians, statisticians, ethicists, epidemiologists, scientists from other fields, and members from outside the institution not directly affiliated with the study may be needed. The investigator should provide the charter and membership of any independent DSMB for review by the IRB and other relevant regulatory authorities.

Table 2.1 Assessment of Risk for Safety Monitoring

Risk Level	Definition	Examples
Minimal Risk	Study poses no more risk than expected in daily life or in routine physical or psychological examinations.	<ul style="list-style-type: none"> • Blood draw, physical exam, routine psychological testing • Survey or questionnaire studies • Observation studies • Nutrition studies • Behavior studies
Low Risk	Involves a minor increase over minimal risk; the intervention or procedure presents experiences that are reasonably commensurate with those inherent in actual or expected medical, dental, physiological, social or educational situations.	<ul style="list-style-type: none"> • Studies of healthy volunteers using well-described research procedures (e.g., IV infusion, euglycemic clamp, indirect calorimetry) • Studies that might meet requirements for minimal review, but include special populations
Moderate Risk	Risks are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result. Risks are recognized as being greater than low, but are not considered as serious as high risk, and their surveillance and protections are adequate to identify adverse events promptly and keep their effects minimal.	<ul style="list-style-type: none"> • Participants treated with placebo for a recognized disease or a multiarm study where there is the potential for increased risk in one or more arms • Disease orientated participants exposed to non-FDA approved drug or drug combinations • Reasonable level of baseline knowledge from which it is feasible to extrapolate risk of adverse events • Only anticipated mild/moderate adverse events or low probability of serious adverse events • Low risk studies in vulnerable populations • Procedures involving the collection of sensitive information (e.g., illegal activities)
High Risk	Involves an intervention or invasive procedure with substantial risk; there is an increased probability for the occurrence of a study related event that is serious and prolonged or permanent, or there is significant uncertainty about the nature of likelihood of adverse events.	<ul style="list-style-type: none"> • Phase III clinical study • Complex multicenter study • Intervention or invasive procedure with substantial risk • Implantation of device with Investigational Device Exemption • Involves the use of a new chemical or drug for which there is little or no toxicology data in humans • A gene therapy study or research involving recombinant DNA molecules (gene transfer) • Intervention related serious adverse events that might also be due to the underlying condition or disease

RELATIONSHIPS OF MONITORING ENTITIES

RELATIONSHIP BETWEEN IRB AND DSMB

IRBs have the responsibility to protect the rights, interests, and safety of human research participants, within the federal regulations that establish and govern the operations of the IRB. Included within the responsibilities is the requirement: “When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects” (CFR 45 46.111). Thus, the protocols reviewed by an IRB will include a safety monitoring plan that reflects the size and complexity of the trial. For trials that are large, complex, multicentered, and/or higher risk, the oversight is commonly mediated by a monitoring mechanism external to the IRB, i.e. a DSMB. Both entities are charged with assuring the protection of human subject safety. Yet the IRB and DSMB serve two distinct roles in the oversight of clinical trials.

IRBs for academic health centers typically review local protocols. The focus is to protect the rights and protections afforded to human research participants in trials they have reviewed and approved. For trials directly under the purview of a local IRB, the review is local. For a single-site study, the review and scope are quite different than if the trial in question has many sites, possibly in several countries. For trials where there are subjects outside the authority of the IRB, the safety is assured by an unconnected IRB. Increasingly, multicenter trials have a single IRB of record. This means that an IRB may be reviewing safety reports from sites external to the institution. Equally, the oversight of safety of study participants at an institution is the purview of an external IRB. Thus, it can be very difficult for a local IRB to assess safety, such as occurrences of adverse events, and to get the entire scope of the trial risk and benefit balance. The role of the DSMB is to provide the larger scope of assuring the ongoing survey and analysis of large and/or complex trials. It is crucial that the two work in concert to optimize their roles in assuring human subject protection.

For institutional DSMBs that are assembled to monitor local trials (see above), the relationship is noticeably different. In this instance the DSMB should provide feedback at regular and defined intervals directly to the IRBs. The DSMB issues a report following each meeting stating the studies reviewed and the interim dates of the review period. The report should summarize the review of adverse events, performance metrics, and any interventions and any recommendations about the need for modification of the protocol. If the DSMB reports are not sent directly to the IRB, the investigator is required to transmit the report to his/her IRB. The reporting requirements are delineated in the DSMB charter for a specific study.

Inherent in the shared responsibilities is the implicit need for open communications. The information about the trial as gathered and reviewed by the DSMB is an essential component in the required oversight by the local IRB of the safety of participants in the trial. Conversely,

the local IRBs often have the best understanding of the conduct of a trial in the context of the institution and any impact that may have on the data quality as well as the protection of the participants. Any DSMB findings that have impact on the conduct of a trial should be reflected at the local site and the local IRB should be fully informed about these findings.

Communications between DSMB and IRB

Since DSMB findings have a direct impact on the conduct of a trial and the safety of the research participants, the IRB with responsibility for the oversight of a trial in their purview must receive DSMB communications and reports in a timely manner. Depending upon the structure of a trial, the IRB generally does not receive direct communication of reports from a DSMB external to the institution, e.g., transmitted from the Sponsor. Since a local IRB and an external DSMB do not typically directly communicate, the DSMB reports should be sufficiently complete and understandable for the IRB to be able to fulfill their obligation for the protection of research participants in their purview. However, the local PI is responsible for assuring that all DSMB reports received from the Sponsor or directly from the DSMB are promptly sent to the IRB. Most of the reports will be informational. Occasionally the reports require actions be taken by the Sponsor and local PI. For example, the local PI should implement any changes in the protocol recommended by the DSMB by modifications to the protocol at the research site submitted in parallel to the local IRB to match the DSMB report. The information in the DSMB reports should assure the IRB that the study is being conducted in an ethical and efficient manner across all sites.

Guidance for IRB members

The IRB reviews the DSM plan at time of the initial review, at continuing review, upon receipt of communications issued by the DSMB, and if needed at times dictated by the project itself. In all of these cases, the review is based on the communications either from the Investigator or the DSMB and the clarity of the information is paramount.

Initial IRB review of a Data and Safety Monitoring plan

A description of the DSM plan is included for all studies. This includes the rationale, risk assessment, and approach to assure subject safety and data validity. The components are:

- Monitoring entity
- Assuring participants safety, adverse event collection and reporting
- Assuring data accuracy, data security, and protocol compliance
- Plans for reporting unanticipated problems

- Plans for interim analysis and reporting

IRB review of an interim Data and Safety Monitoring report

As an essential component of the oversight required of an IRB, the safety monitoring is reviewed as a part of the Continuing Review submission to the IRB or at more frequent intervals, if needed. Importantly the review should confirm that indicators of safety monitoring are included. Namely, reporting of unexpected and serious adverse events and forwarding any reports for the monitoring entities (e.g., DSMB) are completed as required. The finalized report from the DSMB is sent to the PI who subsequently submits it to the IRB. The investigator should be aware of his/her IRB's procedures and sequence for submitting DSMB reports (e.g., the report could be tendered to the IRB at Continuing Review, or sent at the time of DSMB review).

- For minimal and low risk studies the PI reports ongoing analysis and event reporting
- For moderate risk studies with independent review, the independent reviewer provides a statement regarding review of any serious and unexpected adverse events or protocol deviations and any recommendations regarding the continuing conduct of the protocol
- For moderate and high risk studies requiring a DSMB (FDA or NIH regulations), the PI provides a copy of the DSMB report (or minutes of the most recent meeting, if applicable)

All interim analyses should include an assessment of on-going operational feasibility. If the enrollment rate in the previous year is not sufficient to reasonably reach planned enrollment, a plan should be offered to assure completion of the study.

Table 2.2 Summary of IRB Review of Data and Safety Monitoring Plans

Single Site				
Risk Category	Minimal	Low	Moderate	High
Monitoring Entity	PI	PI	PI + Independent review or DSMB	Independent DSMB
Plan Filed with IRB	No	Yes	Yes (+ DSMB charter)	Yes + DSMB charter
Safety Monitoring Interim	Annual	Annual	Annual + stated plan additional frequency	Annual + stated plan additional frequency
Safety Summary in Continuing Review	Yes	Yes	Yes	Yes + DSMB report
Multicenter Secondary Site				
Risk Category	Minimal	Low	Moderate	High
Monitoring Entity	PI	PI	PI + External review or DSMB	PI + External review or independent DSMB
Plan Filed with IRB	Yes	Yes	Yes (+ DSMB charter)	Yes + DSMB charter
Safety Monitoring Interim	Annual	Annual	Annual + stated plan additional frequency	Annual + stated plan additional frequency
Safety Summary in Continuing Review	Yes	Yes	Yes + DSMB report	Yes + DSMB report
Multicenter Lead Site				
Risk Category	Minimal	Low	Moderate	High
Monitoring Entity	PI	PI	PI + Independent review or DSMB	Independent DSMB
Plan Filed with IRB	Yes	Yes	Yes	Yes + DSMB charter
Safety Monitoring Interim	Annual	Annual	Annual + stated plan additional frequency	Annual + stated plan additional frequency
Safety Summary in Continuing Review	Yes	Yes	Yes	Yes + DSMB Report

RELATIONSHIPS BETWEEN DSMBs AND SPONSORS, FUNDING AGENCIES, AND INVESTIGATORS

A DSMB may need to interact with other organizational components of the clinical trial it is monitoring, on a regular or an occasional basis. In addition to the IRB the DSMB may need to interact with and have a relationship with study sponsors, funding agencies, and investigators. Communication with each of these components may vary depending on the nature of the relationship and the need to limit access to interim or unblinded data.

The DSMB functions as an independent advisory group. The reporting structure should be carefully specified in the charter as to whom the DSMB reports to. This may be only to the PI, to the PI and IRB, or to the PI and sponsor (usually in Federally supported research grants). All communications should be from the chairperson of the DSMB to the appropriate person or committee.

Communications between DSMBs and sponsors, funding agencies, and investigators

The process for communication between the DSMB and the study team should be described in the DSMB charter. The DSMB's primary communication is often with the study PI and/or the study Steering Committee, as applicable. In larger trials, the communication may occur between the DSMB and the chair of the study steering committee. Both written and oral communications are valuable; and yet it is best for the results of any action-related communications to be documented. Non-confidential information such as study recruitment status, baseline population characteristics, and relevant new external data is generally presented and discussed during the open session of the DSMB meetings. A written report of the DSMB recommendation(s) should be provided to the PI after each meeting in a timely fashion. In order to maintain the confidentiality of study data, the DSMB report should provide the minimum amount of information required for the PI to make a reasoned decision in response to the Board's recommendations. The rationale for both the DSMB's recommendation(s) and the PI's response(s) should be clear and concise (FDA guidance).

DSMB members should not individually communicate with the PI directly beyond any joint DSMB and PI interactions. Any individual communication with the PI should be through the DSMB Chair unless otherwise detailed in the DSMB charter.

Mechanisms should be in place for secure transfer of study data and any intra-DSMB member communication such that the integrity of study data would not be compromised. [See Chapter 3, "DSMB Membership Issues, Confidentiality"]

Communication with local IRBs is generally the responsibility of the local site PI. IRBs should be provided the initial monitoring plan including information on the operating pro-

cedures of the DSMB. This can be accomplished by providing the IRBs with the DSMB charter prior to initiation of trial activities. Additionally, DSMB reports should be provided to individual site investigators (if applicable) for distribution to the local participating IRBs. For trials involving Investigational New Drugs or Investigational Device Exemptions, the DSMB report may be provided to the IRB directly by the study PI or sponsor.

For industry sponsored multicenter trials, the primary communication may be between the DSMB and the sponsor/study steering committee. Communication with the local IRB is the responsibility of the site PI. For multicenter NIH-funded studies a DSMB is usually set up by and advisory to the NIH sponsoring institute/center and there are communications directly between the DSMB and the NIH. In some such instances the NIH requires communication between the DSMB and the PI to be through the NIH Project Officer. The PI is responsible for assuring the IRB is informed.

Guidance on content and process for communication between the DSMB and the sponsor/investigators is provided in the policy statements in **Box 2.1**.

Box 2.1 Policy Statements on Communication between DSMBs, Investigators and Sponsors

- **National Institutes of Health Policy for Data and Safety Monitoring, June 12, 1998 and Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multicenter Clinical Trials, June 11, 1999**

“...each IRB should be informed of the operating procedures with regard to data and safety monitoring (e.g., who, what, when, and how monitoring will take place).”

“The DSMB’s summary report should provide feedback at regular and defined intervals to the IRBs.”

“The Institutes and Centers should assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB.”

- **European Medicines Agency Guideline on Data Monitoring Committees**

“The proper communication of its recommendations is a major responsibility for a DMC. If changes in the study conduct are recommended by a DMC, sufficient information should be provided to allow the sponsor to decide whether and how to implement these recommendations. The implementation of any DMC recommendation is solely the responsibility of the sponsor who is also free to neglect (in whole or in part) recommendations of a DMC.”

- **Food and Drug Administration Guidance for Clinical Trial Sponsors**

“Under 21 CFR 56.103, 21 CFR 312.66, 21 CFR 812.40, and 21 CFR 812.150, individual investigators (or the sponsor of investigational devices) are responsible for assuring that IRBs are made aware of significant new information that arises about a clinical trial. Such information may include DMC recommendations to the sponsor that are communicated to IRB(s), either directly or through individual investigators or sponsors.”

“Although FDA typically expects that confidentiality of the interim data will be maintained, the DMC may interact with the sponsor and/or trial lead investigators to clarify issues relating to the conduct of the trial, potential impact on the trial of external data, or other topics. In order to permit such interaction without compromising confidentiality, many DMC meetings include an ‘open’ session in which information in the open report is discussed.”

“We recommend that a DMC document its recommendations, and the rationale for such recommendations, in a form that can be reviewed by the sponsor and then circulated, if and as appropriate, to IRBs, FDA, and/or other interested parties.”

Chapter 2 Key Points

- All human research studies require some level of monitoring for the safety of participants. The extent of monitoring depends on the degree of risk to participants from study participation.
- The DSM plan establishes the overall framework for monitoring a study.
- The successive levels of monitoring of a study for safety are: monitoring by the PI according to the DSM plan (low to minimal risk studies); monitoring by an independent Medical Monitor/Safety Officer or a small SMC (moderate risk); and independent DSMBs (high risk, phase III, or blinded study).
- The DSMB provides information about safety events and the overall conduct of a study to the PI. The PI is responsible for providing the IRB with DSMB recommendations, thus, helping the IRB monitor a study.

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CHAPTER 3

DSMB Organization and Member Responsibilities

SO, YOU'VE BEEN ASKED TO SERVE ON A DSMB

This chapter is meant to be an introduction for new DSMB members.

EXPECTED TIME COMMITMENT

The amount of time you can expect to commit will vary depending on the frequency of scheduled DSMB meetings, the possibility for unscheduled meetings due in part but not limited to unforeseen risks and/or unexpected problems, and the complexity of the study. Most DSMB meetings include both an open and closed session which combined can last from 60-120 minutes. For every one (1) hour of meeting time expect to also spend one (1) hour of preparatory time to review the study and safety data. The frequency of meetings will also vary from study to study and might be enrollment dependent. Typically, you can expect a DSMB to convene 1-4 times per year until the study is complete but no less than once a year. The DSMB charter outlines the expected frequency of the meetings, the type of data to be reviewed, and the format for presentation. If drafted and available, you should request and review a copy of the DSMB charter to understand the time commitment or, solicit this information up front prior to agreeing to serve. At minimum a review of the protocol is necessary to guide your decision to participate. Additional time may be required (approximately 1 hour) to complete general orientation and training for a DSMB program.

YOUR EXPERTISE

Being asked to serve on a DSMB means you're expected to impart your knowledge, expertise and opinions in reviewing the study data. Make sure you understand what the expectations are. For example: are you a biostatistician being asked to interpret an interim statistical

analysis? Are you a physician with clinical and/or research experience with the disease under study?

You should make sure that you understand your role on the DSMB and feel comfortable in the capacity requested of you (e.g., scientific expert, biostatistician, ethicist, chairperson). The DSMB charter outlines responsibilities and expectations along with the composition of the rest of the committee. Prior to making your decision, you should receive and review a copy of the protocol (even a draft) so you understand the study and type of data to be collected. You should be able to determine if you understand the study, have the necessary expertise to participate and have no conflicts of interest (financial or otherwise) before agreeing to serve. You should feel the study has scientific validity and is feasible to conduct. Typically, a DSMB reviews the protocol at their first meeting (along with the DSMB charter) and makes any suggestions for improvement prior to final IRB review and approval. Ultimately you should feel comfortable being associated with this project before agreeing to serve.

PRINCIPAL INVESTIGATOR/SPONSOR EXPECTATIONS OF YOU

The PI and Sponsor will expect that you are prepared for all meetings and that you have conducted a thorough review of any data and safety information provided. If there are general questions or missing information that is needed, you should request this from the PI or Sponsor as soon as possible and before the DSMB meeting. Because continuation of the study is often predicated on the DSMB review, it is important that you and the DSMB are responsive and conduct your reviews in a timely manner in accordance with the schedule laid out in the DSMB charter. All findings or determinations that you render are to be conveyed clearly to the DSMB membership, and all in-person open- or closed meetings and any written interactions between you and the DSMB are expected to be professional and constructive, in keeping with the overall aims of the DSMB's charge.

You will be expected to make the DSMB meetings and reviews a priority in your schedule. It is very difficult to schedule a meeting with experts from different institutions and often in different time zones. Making DSMB work a priority is necessary to have timely review of material and timely responses to crucial decisions for the study. You will need to be responsive to emails from the Chairperson, and to editing and signing reports needed for the study to proceed.

Recommendations by the DSMB's consensus should be communicated in writing, be clear and concise, and distributed to the PI/Sponsor as soon as possible. If there are questions about the DSMB's recommendations or appeals to the DSMB's decisions, you and the rest of the Board should make yourselves available and respond to the PI and/or Sponsor's requests. Note that the DSMB Chair serves as the contact point for communications

between the Board and any member of the research team including the PI. Most importantly, you are obliged to keep all communications private, according to any applicable confidentiality provisions to which you have agreed.

ROLES AND RESPONSIBILITIES OF DSMB MEMBERS

GENERAL AND EXPERT MEMBERS

DSMBs must be multidisciplinary in composition. The breadth of expertise among the DSMB's membership is to be commensurate with the complexity of the protocol and the inherent risks of its procedure(s) and intervention(s). Much as Team Science is the current approach to address, engage, conduct and analyze scientific inquiry, so too do the activities of the DSMB require a team approach. It is most common for DSMBs to be composed of experts in the scientific field of study as well as in applied statistical methods to meet the study objectives. Additional knowledge and experience in clinical trials, ethics, research subject advocacy, epidemiology, and/or recruitment/retention are valuable to not only preserve but also quite possibly to heighten the integrity of a study.

At minimum, a DSMB should be composed of three persons with required areas of expertise in the medical specialty being studied, and in statistics. A DSMB for more complex, higher risk studies may benefit from more members so that additional areas of expertise and a broader perspective can be represented. Regardless, for voting purposes it is preferable to have an odd number of members, e.g., 3, 5, 7, etc. It is important to realize that the larger the number of members the more operationally difficult administration of a DSMB becomes.

At least one member is to have specific knowledge of the disease and patient group that are to be enrolled in the study. Representation of other disciplines on the DSMB provides complementary perspective(s) by which to evaluate the conduct of a study and its purpose, design, population, procedures and analysis. Skill sets which lend unique perspectives include clinical trial specialists, statisticians, ethicists, research subject/patient advocates, epidemiologists, pharmacologists, toxicologists, patient representatives, nurses, and/or other related health care professionals. The broader the scope of expertise, the wider the inclusion of unique perspectives by which oversight can be provided; lending a more comprehensive consideration of issues, responses and recommendations.

Should an unanticipated issue arise that is perceived by the Board to be beyond its expertise, ad hoc experts may be invited to provide the necessary insight for the DSMB to better respond to the issue(s) of concern. These identified individuals would serve in a limited capacity, offering expertise but not as a voting member of the DSMB. Beyond expertise, it is imperative that all DSMB members are free from any conflicts of interest including but not limited to financial, scientific or administrative, with either the PI(s), Co-Investigators,

Key Personnel, and/or the study sponsor. Finally, it is imperative that each member of the DSMB be a cooperative participant, offering up his/her insights and perspectives as well as being respectful of those of the other members. Where possible, consideration should be given a priori to the personalities and the inherent dynamics of the DSMB. Open and respectful dialogue is essential to the successful operations of a DSMB, and the ability to achieve this should be periodically reviewed by the DSMB.

CHAIRPERSON

The DSMB Chairperson must have experience in clinical trials and have previously participated in other DSMB(s), ideally in related research. The Chairperson should have knowledge in the primary scientific field in which the study population arises. Often the Chairperson is a recognized expert or senior scientist with commensurate research experience. The communication and administrative skills of the Chairperson are salient to the success of the Board, allowing varied perspectives to be voiced and heard, reaching a consensus for its recommendation(s), and relaying those requests to the PI, study leadership and/or sponsor. The Chairperson may be appointed by the sponsor (and/or investigator), but is to be independent of the sponsor and trial organizers to avoid any conflicts of interest. The Chairperson should be able to commit to participation in the DSMB for the duration of the trial. [Note: Independence does not require that a Chairman nor the DSMB to be external from the sponsor's and/or investigator's institution. What is critical is that there are no financial and/or administrative conflicts of interest between the DSMB and its Chairman with the Sponsor and/or investigator.]

The Chairperson is the primary contact for the DSMB and provides both administrative and scientific leadership for the Board. The Chairperson assists with the selection of DSMB members, assuring their appropriate expertise and independence. Along with the DSMB members, the Chairperson reviews and approves the DSMB charter.

The DSMB Chairperson is responsible for facilitating the meetings and develops the agenda in consultation with the PI. The Chair assures that all members are able to provide input into the DSMB discussion and decisions, and that the meeting conduct maintains the confidentiality of the trial. The Chair or designee takes minutes at the DSMB meetings and drafts the meeting reports for review and approval by the DSMB members. The DSMB Chairperson communicates the DSMB recommendations to the study PI and sponsor.

EXECUTIVE SECRETARY

The executive secretary (or administrator) is the person who is responsible for writing and transmitting minutes and recommendations to the PI, or Sponsor, or other individuals as identified in the DSMB charter. This person may have other administrative responsibilities

such as scheduling the meeting, arranging telecommunications for the meeting (telephone, video or web conferencing), as well as distributing data and serious adverse event reports prior to the meeting. A degree of computer and communication skills is an asset for this position.

BIostatistician

Biostatisticians participating on a DSMB should be knowledgeable about statistical issues in clinical trials. It is preferred that this experience be actual than purely theoretical, i.e. the individual has been involved in the design and analysis of clinical research and optimally, in the area of medical specialty under immediate concern of the DSMB. Biostatistical expertise is essential to the meaningful function of the DSMB. As clinical trials have increased in complexity and size, so too has the involvement of statisticians in the design and analysis phases of clinical investigations. The participation of a biostatistician is critical at every stage of the function of the DSMB.

The charter should state the role(s) of the statistician(s). This will include voting status, independence, accountability, and committee structure. The initial organizational meeting will include a review of the protocol for study design, intended statistical approach to analysis, proposed monitoring plan, and study structure. Any recommendation for modifications necessary prior to study implementation should be made at the initial meeting. Depending upon the study structure, there may be one or more statisticians with differing expertise or role in the study. Some DSMBs will have both an independent statistician as well as the trial statistician.

The interim meetings of the DSMB will include presentation and review of the interim efficacy/safety analyses and interpretation provided by the statistician. The statistician should assure that distribution of unblinded information is strictly limited to DSMB members to assure confidentiality. They instruct the DSMB on the statistical component of subsequent reports issued to the Steering Committee, the Sponsor, or the institutional study sites. The reports will include interim statements on the study progress, recommendations regarding any proposed changes to the primary outcome variable, duration of trials recruitment and follow-up, modifications necessitated by safety or enrollment concerns, or analysis plan.

SPECIALTY MEMBERS: ETHICISTS, PATIENT ADVOCATES, COMMUNITY MEMBERS

In 1998, the NIH issued a data and safety monitoring policy for clinical trials:

Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians,

bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available if warranted.

Specialty members who could be considered to provide expertise for specific trials include ethicists, patient community representatives, epidemiologists, lawyers, pharmacists or individuals with niche scientific expertise who could be included to provide advice on an ad hoc basis.

An **ethicist** may serve on the DSMB to provide the viewpoint of the society at large. The ethicist may serve as a consultant through the life of a trial. In the protocol development phase prior to IRB submission, an ethicist can help frame the protocol design by identifying potential recruitment concerns (equity) or other issues that may potentially arise from what and how safety data is collected and reviewed. It is the role of the ethicist to “ensure that the scientific goals of the study...do not lead to actions that are unacceptable from the perspective of the study patient.” An ethicist can assist in “framing the issues” when “unanticipated decision points” occur during the course of the study. Throughout the study an ethicist reviews safety data, helps to ensure that the subject’s rights are respected and preserved, and makes recommended changes to the protocol and informed consent if new information is presented that impacts the subject.

The **participant advocate community representative’s** role on a DSMB is to share information based on personal experience. A DSMB may benefit from including such a member when demonstration of a collaborative relationship between the study’s targeted patient population and the researchers conducting the study is required, or when there is a need to provide the representative’s unique perspective, the patient experience. Since a patient community representative may be chosen on the basis that he/she shares knowledge readily, often in advocacy groups, this specialty DSMB member may require custom training to ensure study-related data is kept confidential, including within the confines of the DSMB. This may be difficult if study results appear to be significant as the representative may wish to ‘share the news’. In order to have the skills to interpret study data, the patient community representative may also need added training on the understanding and the principles and methodologies of conducting clinical research. Since the primary criteria for this member is the possession of the patient experience, this specialty member’s role may be filled by the actual patient community representative or by close relatives of a patient; yet, the principles and good practices of clinical research must be known and respected. The FDA and NIH are increasingly calling for community representatives as participants at various stages of the clinical research process.

A DSMB may require the expertise of a variety of professionals who have the knowledge that may be needed to fulfill the needs of a particular trial. **Epidemiologists** have expertise in patterns and causes of disease and injury in human populations which would contribute to the DSMB review and be able to recommend methods to reduce the risk of events that have

a negative health outcome. The presence of an epidemiologist on a DSMB complements the statistician's role. **Attorneys** may be considered as specialty members for their legal expertise. The expertise of a **pharmacist** or **toxicologist** may be required for a DSMB member if preliminary pharmacological data collected before study initiation is less than routinely available or if issues of drug interactions may be expected due to the specific of the study or the characteristics of the study population. If the study's intervention is filed under an Investigational New Drug or Investigational Device Exemption, a **regulatory specialist** may be required to help ensure compliance with study-related federal obligations. For interventional studies involving devices, the DSMB may benefit from an **engineer**. Additionally, the need for other ad hoc specialty members (non-voting) may arise and can be considered. Finally, **clinical trialists** are investigators who by their experience and training in research can provide a depth of understanding of the clinical trial process from inception through each progressive step of a clinical trial to publication of results. Their expertise in trial design, implementation and administration, risk/safety assessment, and analysis of efficacy or other endpoints can give a comprehensive perspective for the DSMB that is often essential in monitoring larger or more complex trials.

RESEARCH PARTICIPANT ADVOCATE

A research subject advocate can provide very helpful expertise on a DSMB. This person usually has expertise in regulatory science, as well as clinical studies and the ability to see the study from a participant's viewpoint. In this way, the research subject advocate can provide some of the same expertise that a patient community representative provides along with the experience of clinical trials.

MEDICAL MONITOR

Some multicenter clinical trials will have a specifically designated Medical Monitor who is *not* a member of the study team. This individual is responsible for real-time monitoring of reports of serious adverse events submitted by the clinical centers to identify safety concerns quickly and to provide regulatory bodies with case-by-case reports of the serious adverse events. The Medical Monitor will usually evaluate serious adverse events blinded to treatment assignment whenever possible, unless partial or complete unblinding has been approved by the DSMB. The specific role and procedures of the Medical Monitor will vary depending on the specific trial, all of which should be clarified before starting the trial. This individual however should not be considered to participate as a member of the DSMB, despite potential active interaction with the study.

DSMB MEMBERSHIP ISSUES

CONFLICT OF INTEREST

The reliability and credibility of the DSMB requires that its members are independent and unbiased in their work. Many of the trials that DSMBs review are large, complex, and extremely costly projects. In the case of pharmaceutical companies these trials may represent the final step in attaining approval for the very costly drugs that are in development. Thus, the findings of the DSMB can have substantial impact beyond the actual trial itself. Avoiding a COI, or even the appearance of a COI, is an essential step in serving on a DSMB.

Most oversight agencies and funding institutes (Office for Human Research Protections, NIH, FDA) as well as academic institutions have standing COI policies in place. Most of these policies address financial COI. Some consideration should be given to intellectual, scientific, and emotional issues as well. While it may not be possible to completely eliminate all possible or inferred conflicts of interest when assembling a DSMB, each member should be able to attest to their independent and unbiased assessment of the information they review and the recommendations that they make.

DSMB charters will usually include a statement of the intent to assure all members are free of any apparent significant COI. The items addressed usually include financial involvement with the companies involved or their competitors, including ownership or stock, consulting or financial agreements. This is not limited to the Sponsor of the trial. This may include contract research organization, diagnostic services with an interest in the outcome of the trial, or financial service companies such as investment brokers. The COI extends to the immediate families or other significant financial relationships of the member.

There is a difference in industry sponsored and publicly funded trials. Sometimes the DSMB will, by necessity, include individuals associated with the Sponsor when their expertise and familiarity with the project will be needed. Conversely, for publicly funded trials, the COI is less often problematic since the financial interests are quite different. Depending on the type of trial, the rigor of delineating any COI on the part of members will differ.

At the opening of each DSMB meeting every DSMB member will be asked to disclose any COI with a study being discussed. If a member has a COI, this should be explicitly noted in the minutes. Members with a conflict should recuse themselves from any discussion and voting regarding the study for which they have a conflict. Their recusal should also be noted in the minutes.

See **Box 3.1** and [Appendix C, “DSMB Charters”](#) for sample COI statements. Some trials may have specialized issues that need explicit statements regarding special circumstances. The

overarching principle is to assure that there is no actual or perceived COI on the part of any committee member.

Box 3.1 Sample Conflict of Interest Language

- The DSMB membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DSMB.
- The DSMB members should not own stock in the companies having products being evaluated by the clinical trial. The DSMB members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organization for the trial (if any), or with other sponsors having products that are being evaluated in the trial. The DSMB will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.
- The DSMB members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DSMB member who develops significant conflicts of interest during the course of the trial should resign from the DSMB.
- DSMB membership is to be for the duration of the clinical trial. If any member leaves the DSMB during the course of the trial, the sponsor, in consultation with the steering committee and/or investigators will promptly appoint their replacements.

CONFIDENTIALITY

Every DSMB member must keep information about trial data, content of discussions held at DSMB meetings, and possibly even the names of other board members completely confidential. Any breach of confidentiality may ruin a trial. The ramifications for failure to maintain confidentiality can collapse on-going trials and possibly result in harm to participants, can create misperceptions about the trial or the treatments being tested, or may have economic repercussions for pivotal trials in industry-sponsored trials. This then jeopardizes the study's potential for proper regulatory review for approval by the FDA or other applicable regulatory office(s).

The scope of confidentiality extends to the deliberations and statements made within the closed session of the committee, as well as to recommendations of the committee outside the official communications issued by the committee. Many committees will require signed

agreements to adhere to stated confidentiality requirements. Assurance of confidentiality is crucial for the integrity of the DSMB. The essential nature of this assurance is emphasized in policy statements regarding the standards for confidentiality made by several research governance entities (see **Box 3.2**).

Box 3.2 Policy Statements on Confidentiality

- **National Institutes of Health Policy for Data and Safety Monitoring**

“Confidentiality must be maintained during all phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations...usually only voting members of the DSMB should see interim analyses of outcome data. Exceptions may be made under circumstances where there are serious adverse events, or whenever the DSMB deems it appropriate.”

- **World Health Organization Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards**

“The DSMB should ensure confidentiality and proper communication to enhance the integrity and credibility of the study. It is recommended that each DSMB meeting be divided into two sessions: an open and a closed session. This will enable the DSMB to interact with groups and individuals who assume responsibilities for the study while ensuring the independence and integrity of the Board’s recommendations.”

- **European Medicines Agency Guideline on Data Monitoring Committees**

“A critical point in all DMC activities is to ensure the integrity and credibility of the ongoing trial. Thus, it is within the responsibilities of the DMC and the sponsor to have appropriate policies in place to ensure the integrity of the study. As an example, policies to avoid the dissemination of interim study results prior to unblinding have to be in place.”

- **Food and Drug Administration Guidance on the Establishment and Operation of Clinical Trials Data Monitoring Committees**

“Knowledge of unblinded interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trial...Therefore, the interim data and the results of interim analyses should generally not be accessible by anyone other than DMC members. Sponsors should establish procedures to ensure the confidentiality of the interim data.”

LIABILITY AND COMPENSATION

Participating members should also be aware of and resolve any potential liability issues. In many cases direct compensation for service is considered outside of institutional duties. In those instances, then, a directly financially compensated member would potentially be liable for any damages that may be incurred as deemed to have resulted from the study. Service that is not [directly] compensated usually is considered as being within the scope of one’s

usual institutional duties and therefore the individual would be protected by his/her home institution. It is best for the potential DSMB member to discuss any liability concerns with the Risk Management Office of the home institution before fully agreeing to and executing the role as a member of a DSMB.

Institutes within the NIH require DSMBs for various clinical research studies. As such membership is composed of various individuals often at the invitation of the PI, liability for service on the DSMB is not provided by the NIH; nor is it provided by the lead institution unless the DSMB member is faculty and/or staff of that same institution. Liability coverage may be provided by the member's home institution; however, direct compensation to the individual for service on the DSMB may be considered outside of the scope of institutional duties. Therefore, a member who receives direct compensation may be liable for any damages that may be incurred during the course of the study, particularly as brought forth by any study participant(s); with responsibility for payment of those damages resting with that member.

This scenario also holds true should a DSMB be composed by an industry sponsor. Therefore, should direct compensation be provided, the DSMB member needs to pursue insuring him/herself in the event any such damages and/or other legal action occur; else be at potentially significant risk of liability.

If compensation by a sponsor is provided, then it is possible to indirectly receive compensation for service by establishing an account within the DSMB member's home institution. This would be best pursued with the member's home institution's Office of Risk Management, and Office of Sponsored Programs/Research Administration.

Possible scenarios:

- Internal DSMB: possibly covered by institutional malpractice
- Internal DSMB – biostatistician: doesn't have individual policy but covered by institutional policy as part of scope of work
- External DSMB with compensation: may not be covered
- DSMB member accepts compensation and risk
- DSMB member doesn't take compensation
- DSMB member takes compensation sent to an institutional fund that is not for salary support

An additional and related aspect that may also arise is that if there is a financial COI identified that involves both an investigator and his/her employing institution, a management plan may be directed by COI officials to convene an independent DSMB (not affiliated with the institution) to perform data and safety assessments. If the DSMB membership is to be compensated, it will be the responsibility of the investigator to secure an independent

source of funding (i.e. the investigator and institution cannot directly remunerate the DSMB members), in order to maximize the independence of the DSMB.

DSMB MEMBER TRAINING

There is no regulatory requirement for DSMB member training nor are there national standards or guidance published to date. This manual is an attempt to provide a comprehensive resource for DSMB members to study and for reference, whether they are an experienced member or serving on a DSMB for the first time. Some institutions that have an established data and safety monitoring program offer or mandate institution-specific training. The World Health Organization, in its guidelines on DSMBs, recommends that provisions for training should be included in any DSMB appointment. It is highly recommended that if you have never served on a DSMB that you seek out some sort of basic training. In general, a comprehensive training program would include:

- General information on DSMBs including their role, function, and regulatory basis
- Role and responsibilities of each DSMB member (including your own)
- Institution-specific training
- COI and Confidentiality policies
- Accessing/receiving, secure storage and confidential disposal of materials (e.g., electronic, paper)
- Meeting conduct (phone conferencing, online presentations, meeting order)
- Expedited adverse event reviews
- Sponsor/PI and DSMB dispute resolution process
- Protocol-specific training
- Study objectives & design
- Study population

In addition to the above, each DSMB member is to be familiar with all applicable federal guidelines regarding DSMBs. General and institution-specific training should occur prior to serving on a DSMB. Protocol-specific training should occur before or as part of the initial DSMB meeting. Training may be provided as part of an in-person or online course, in written materials for self-review, and/or as part of the first DSMB meeting. Training may be provided by institution program staff, the DSMB chairperson, or another experienced DSMB member, or the study Sponsor. If you have never served on a DSMB it is recommended that you be provided with an experienced mentor (typically the chairperson) whom you can consult regarding questions or concerns. While many elements of training occur early in the formation of the DSMB, training on DSMB related topics and topics related to the trial under

review should continue throughout the span of DSMB oversight. All formal training should be documented in writing and maintained for future reference.

Assessment of member training

Just as it is important for DSMB members to receive training, it is equally important for that training to be documented. Ideally, any institutionally provided training should include an assessment tool (e.g., online post-module questions, written self-assessment) with feedback on comprehension. Any formal training should be documented in writing and available for Sponsor or institution review.

RESIGNATION OR REMOVAL OF A DSMB MEMBER

DSMBs that operate over a span of years can experience a change in the original membership. A member may resign or may not be able to serve for a number of reasons. More problematic is the removal of members. This can be viewed with suspicion especially if those who express opinions or vote contrary to the Sponsor's wish are the ones who are removed or who resign. In these circumstances, the Sponsor (or the Board) may want to replace the departing member with an individual with comparable expertise. They may even determine a need for additional expertise. A reasonable strategy is to invite people, with the consent of the Board, to join as a non-voting consultant to the DSMB.

Chapter 3 Key Points

- DSMBs should have multiple disciplines represented among its membership.
- The size and breadth of specialty representation is to be commensurate with the risks and complexity of the study that the Board is to provide oversight.
- The DSMB Chairman should have prior DSMB experience as well as understand the scope, purpose and dynamics of the Board which he/she is to lead.
- DSMB members should have no personal, financial, or scientific COI with the study or with the sponsor of the study.
- DSMB members must maintain strict confidentiality about the trial, the results, and the content and decisions of DSMB meetings.
- Personal liability is an important risk that members should resolve prior to serving on a DSMB.

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CHAPTER 4

DSMB Meetings and Documents

ORGANIZATIONAL PRINCIPLES

While the composition of a DSMB and the requirements of a particular study may vary greatly, the organization of a DSMB, the sequence of meetings, and the tasks that the DSMB must accomplish are common to all studies. These are the general tasks:

Form the DSMB

The PI and/or sponsor decide on the expertise, size, and scope necessary to adequately monitor the trial and then invite members to serve on the DSMB. [See Chapter 2, “Monitoring of Clinical Research Studies”] It is important to appoint the chairperson early in this process so that the chair can communicate with the DSMB members as they join. As the members agree to serve on a DSMB, it is helpful to have them send their curriculum vitae (CV) and contact information directly to the chairperson. Depending on the requirements of the Sponsor, the Chairperson may send a letter to the PI and Sponsor confirming the formation of a DSMB for a study as well as the composition and expertise of the membership.

The DSMB functions as an independent advisory group. The reporting structure should be carefully specified from the beginning as to whom the DSMB reports to. This may be only to the PI, to the PI and IRB, or to the PI and sponsor (usually of federally supported research grants).

Write the charter

The chairperson and PI write a charter to define how the DSMB will operate. The chairperson will need to have the protocol, the manual of operations and/or investigators’ brochure, and the DSM plan in order to draft the charter. This may take several iterations between the chair, the PI, and the study biostatistician to arrive at a satisfactory initial version of the charter. This will be reviewed and possibly modified at the initial DSMB meeting.

Conduct meetings

A DSMB starts with the initial organizing meeting, followed by appropriate meetings at set intervals (with additional ad hoc meetings as needed) and ends with a final end-of trial meeting.

Issue documents and reports as defined by the charter

DSMB CHARTERS

INTRODUCTION TO DSMB CHARTERS

The charter is the guiding document for the DSMB actions and responsibilities. An Independent Safety Monitor or Data and Safety Monitor should also have a charter or guidance document. [See Chapter 6, “Role of a Study Safety Officer and Study Monitoring Committees”] The DSMB acts in an advisory capacity to the PI and its functions are dependent on the requirements of the study, the risk of the study, and the requests from the PI, funding agency, and sponsor. It is important to consult with the funding agency which may have specific DSMB and/or charter requirements. An outline of the sections of a typical charter is shown in **Box 4.1**.

The charter’s introduction explains why a DSMB, Independent Safety Monitor or Data and Safety Monitor was convened (appointed) and what the overall purpose of this monitoring entity is for the study. The DSMB works with the PI to protect the welfare and safety of participants in the trial. The DSMB members have individual and collective responsibilities which are detailed in the charter. [See also Chapter 3, “Roles and Responsibilities of DSMB Members”] Lastly, the DSMB charter is a living document which should be reviewed prior to study initiation, at the initial DSMB meeting, and at least annually. If a charter is amended during the course of the study, it should be reviewed and accepted by the DSMB membership. The new charter should have an updated number (e.g., version 1.3) and a new effective date. The acceptance of a new charter should be documented in the minutes of the DSMB meeting in which the new charter was approved. All versions of the charter should be kept for regulatory documentation. A charter is often seen as a confidential document, shared by the PI with the IRB and DSMB members. Some charters will include a protocol summary of the study in the introduction.

Box 4.1 Outline of a Typical DSMB Charter

1. Title page
 - a. Includes version, version date, study title, PI
 - b. Page footers should include: DSMB charter version and date, study title or abbreviation, and page number (e.g., x of y pages)
 - c. A table of contents is helpful for longer documents
2. Introduction
 - a. Optional protocol summary
3. DSMB responsibilities
 - a. Safety monitoring
 - b. Monitor performance of the trial
 - c. Stopping rules for safety, efficacy, and/or futility (if applicable)
4. Principal Investigator responsibilities
5. Sponsor responsibilities – if applicable
6. DSMB membership and role-specific responsibilities
 - a. All members: COI, confidentiality, communications
 - b. Responsibilities of the chairperson
7. Structure and Conduct of DSMB meetings
 - a. DSMB meetings
 - b. Quorum and voting
 - c. DSMB recommendations
 - d. Ad hoc meetings
8. DSMB Operations
 - a. Disbanding the DSMB and destruction of documents
 - b. Procedures for replacing a member
9. Reports

- a. Minutes
 - b. DSMB Recommendations
 - c. Reports to PI for IRB review
10. Signature page
 11. Appendices
 - a. DSMB membership, affiliations and contact information
 - b. Template for recommendations from the closed (executive) DSMB session
 - c. Stopping rules

DSMB FUNCTIONS

This section of the charter defines the responsibilities of the committee in contrast to those of individual members and specifies the tasks the DSMB must carry out. A DSMB may have some but not all of the tasks listed below. Initially, the PI and the DSMB chairperson should determine the function(s) of the DSMB. The IRB and the sponsor may also request that the DSMB have additional tasks. This section should be carefully discussed at the initial meeting of the DSMB to be sure that the committee's scope-of-work is clear and agreed upon by all committee members, the PI, and co-investigators.

The three functions of a DSMB are:

Safety monitoring

- To monitor the study for the safety of the participants
- To examine adverse events and serious adverse events for relationship to study participation
- To conduct interim analyses as specified in the protocol

Performance monitoring

Monitoring the performance of the study for: enrollment, improper entry criteria, slow accrual rate, low participation rate, failure of randomization, data quality, adequacy of follow-up, protocol violations, inadequate treatment adherence, and severely compromised validity.

Stopping rules

Reasons to stop a study early:

- Safety concerns
- Efficacy (optional)
- Futility (if applicable)

For ease of reviewing and amending, the stopping rules may be detailed in an appendix to the charter. If so, each stopping rule must be detailed in the charter's appendix and referenced in the charter under DSMB responsibilities.

PRINCIPAL INVESTIGATOR RESPONSIBILITIES

For PI initiated studies, the PI has primary responsibility for the welfare of participants in the study. In addition, the PI is responsible for creating the DSMB and for the development and management of the charter. In industry-sponsored studies, the charter may be developed in conjunction with the sponsor.

The PI has responsibilities in relationship to the DSMB which should be detailed in the charter. The PI is responsible for:

- Investigating and reporting safety events to the DSMB and to the IRB in a timely manner as specified by the DSMB charter and IRB guidelines
- Conveying relevant recommendations from the DSMB to the IRB, sponsor, and funding agency in a timely manner
- Determining the relationship of adverse events and serious adverse events to study participation and adjudicating the cause(s) of death
- Providing study data to the DSMB chairperson and biostatistician for DSMB meetings and upon request

SPONSOR RESPONSIBILITIES

If a sponsor is involved, some of the PI's responsibilities may shift to the sponsor. The sponsor is responsible to the DSMB for making resources available as necessary to carry out the DSMBs designated functions. It is optional to include the sponsor's responsibilities in the charter.

For NIH-funded multicenter studies it can be the NIH's responsibility to appoint the DSMB and manage development of the charter.

DSMB MEMBERSHIP AND ROLE-SPECIFIC RESPONSIBILITIES

The charter delineates the responsibilities of the DSMB members. [See also Chapter 3, “Roles and Responsibilities of DSMB Members”] The names, affiliations, roles, and contact information for DSMB members are given in an appendix to the charter. These responsibilities should be stated in the charter.

Responsibilities of all members (including Chairperson)

Conflict of interest

Members are free of apparent COI involving financial, scientific or regulatory matters. NIH standards should be used in determining COI.

Confidentiality

Confidentiality should be maintained about participants in a study and about DSMB meeting deliberations. Members should maintain all DSMB related documents (paper and electronic) securely and destroy or shred the documents when the DSMB disbands as specified in the charter.

Communication

Members should communicate study issues only with the Chairperson or other DSMB members.

Training

Members should have DSMB experience or receive training for their role(s). This training may be provided by the Sponsor or the Institution.

Responsibilities of the Chairperson

The Chairperson is responsible for:

- Convening DSMB meetings
- Providing written minutes of the meeting and recommendations based on the committee’s deliberations and voting
- Providing information to the PI for IRB review
- Communicating the views of the DSMB to the PI, as well as sponsor or funding agency as specified in the charter

- Documenting that DSMB members have received training [See also Chapter 3, “DSMB Membership Issues, DSMB Member Training”]

STRUCTURE AND CONDUCT OF DSMB MEETINGS

The charter should specify the process of conducting and documenting open and closed meetings including who may attend the meetings and the matters for discussion at the meeting.

The following items should be included in the charter:

DSMB meetings

Specify the minimal number and frequency of DSMB meetings (yearly, at a minimum). The timing of interim analyses may also determine the frequency of DSMB meetings, for example, after a specified number of participants are enrolled, after completion of low dose intervention prior to increasing the dose, or, in a high risk study, after each participant receives therapy.

Quorums and voting

- Voting and non-voting members should be specified
- Define a quorum of members needed for a meeting to be convened and voting to occur (a quorum is further defined below under “Structure of Meetings”)
- Define whether votes must be unanimous or by majority consensus
- Define what happens if consensus cannot be achieved or a tie occurs

DSMB recommendations

The charter should specify the types of recommendations the committee may make. These may include:

- To continue the study
- To continue the study with suggestions
- To modify the study
- To suspend or terminate the study depending on the findings at the meeting.

Ad hoc meetings

To address emergent issues, the charter should specify who can call an ad hoc meeting and the format of the meeting (e.g., email, teleconference, webinar).

DSMB OPERATIONS

This section includes topics which pertain to specific operating procedures of the DSMB. These items may be written into other sections of the charter. Some charters also include content pertaining to the specific study, similar to a manual of operations.

Data and reports to be reviewed at DSMB meetings should be specified in the charter. [See “Reports” in this chapter, and Chapter 5, “Data and Safety Review Process”]

The charter should specify how the DSMB will be disbanded at the end of the study. This should occur by consensus vote and be documented in the last meeting minutes. The chairperson should hold a copy of the DSMB regulatory documents and DSMB meeting minutes according to institutional policy. All other documents (paper and electronic) should be destroyed.

If a DSMB member is unable to continue serving on the DSMB or does not fulfill his/her responsibilities as a DSMB member, the PI and Chairperson should agree on a procedure to replace that member which is specified in the charter. [See Appendix C, “DSMB Charters”]

REPORTS

The charter should specify the types of reports which the DSMB will produce and to whom reports are distributed. Generally, DSMB reports include:

- Minutes for both open and closed (executive) meetings
- DSMB Recommendations to the PI after each meeting
- Reports to the PI as requested (e.g., for annual IRB renewal)

SIGNATURE PAGE

A charter delineates a set of processes the DSMB and chairperson will follow for the course of a study. The signature page attests that the charter has been approved by the chairperson, who signs the page, and all members of the DSMB. Individual signatures may not be necessary as approval is documented in the initial DSMB meeting minutes.

APPENDICES FOR A DSMB CHARTER

Some information is best placed in the appendices if this information may change frequently or for ease of referral. The appendix should be referenced in the body of the charter. Common appendices include:

- DSMB membership, affiliation, role, and contact information
- Template for DSMB recommendations to the PI from the closed (executive) session
- Stopping rules

The documents below are referenced in the charter but are kept with regulatory documents for the DSMB files including:

- COI statements
- Members' CV
- Training documentation

STRUCTURE OF MEETINGS

INTRODUCTION TO DSMB MEETINGS

Most DSMB meetings will follow a similar format as described in this section of the manual. However, the format may vary somewhat depending on the nature or purpose of the meeting. An initial meeting to review a new protocol may differ in some ways from a meeting to review interim data or an ad hoc meeting to discuss safety events. In cases where a DSMB serves multiple studies, this common sequence is helpful, as well. A DSMB meeting is usually divided between an open session, which includes DSMB members and the PI/study representatives, and a closed session in which only DSMB members participate. Common variations in practice are noted in each section below.

The set of procedures for a DSMB meeting is defined by the DSMB charter for that particular study. Thus, the first step in planning an initial DSMB meeting is to prepare the DSMB charter. The charter should lay out the membership of the committee, voting and non-voting members, quorum rules, frequency of the meetings, procedures for convening additional meetings, and the reporting function of the DSMB. In addition to specifying the structure of the meetings, the charter lays out the responsibilities of the DSMB, which may include planned interim analyses and may require additional meetings or meetings at pre-specified times in the study. The charter is the essential document for the DSMB to refer to for all procedural matters.

TIMING AND FREQUENCY OF DSMB MEETINGS

The frequency of the DSMB meetings is determined by the assessment of risk for a participant involved in the study. This assessment may be made in advance and specified in the

study protocol or in the study DSM plan. In this case, the charter will reflect the need for meetings at specified intervals (e.g., quarterly, yearly) or at particular times in the progress of the study (e.g., prior to dose escalation, after a certain number or percentage of participants are enrolled). In general, the minimum meeting frequency is yearly since annual review is needed to appropriately monitor the study and to ensure recertification of the study with the IRB.

The initial meeting of the DSMB, which occurs before or at study initiation, should independently review the protocol, study documents, and discuss the potential risk to participants. The degree of projected risk for study participants will determine the frequency of regularly scheduled DSMB meetings. Factors which commonly influence the assessment of risk are given in **Table 4.1**. [See also Chapter 2, “Methods of Monitoring”] These factors do not necessitate DSMB monitoring or determine a set monitoring frequency but will provide guidance in the frequency of monitoring a study. The frequency of meetings may change if a study proves to have more or less risk than expected based on outcomes and events.

Table 4.1 Considerations in Assessing the Risk of a Protocol for Participants

Study Feature	Criteria with Increased Risk
Type	<ul style="list-style-type: none"> • Phase I or II study • Pilot study • Complex protocol (e.g., multiple intervention arms, different sequential treatments) • Multisite study • International study • Complex data collection or use of new technologies for data collection
Population	<ul style="list-style-type: none"> • Co-morbidities in the study population (e.g., cancer, cirrhosis, or other conditions that may have a higher risk for poor outcomes) • Vulnerable populations (e.g., children, prisoners, women of child-bearing potential, decision-impaired) • Other risk to participants (e.g., HIV testing with loss of confidentiality, language barriers)
Intervention	<ul style="list-style-type: none"> • Gene transfer studies • Known risk of study agent or procedure (e.g., anaphylaxis with administration, major surgery) • Novel technologies • Study with high public scrutiny
Investigator	<ul style="list-style-type: none"> • Inexperienced (< 2 previous clinical trials) • Investigator held Investigational New Drug/ Investigational Device Exemption • Institution faculty developed the agent, device or process • Other conflicts of interest by the investigator or institution

Additional DSMB meetings may be necessary in addition to the regularly planned yearly, bi-annually, or quarterly DSMB meetings. These meetings may be scheduled in advance at

specified times in the study time-line for a planned interim data review or analysis. For example, a study protocol and the DSMB charter may specify that the DSMB will review unblinded data to look for early evidence of efficacy when half and, again, when two-thirds of the study population have completed the study (using an early stopping principle). A DSMB may be asked to review the study at specified times to ensure adequate enrollment or randomization. Alternatively, in a dose-escalation trial, the DSMB may be convened to examine the data for safety in each cohort before an increase in the dose is administered. In very high risk studies, a DSMB meeting may be convened to assess the outcome of each participant before the next subject is enrolled. This type of meeting may replace a regularly scheduled DSMB meeting and review both safety and efficacy at the same meeting.

DSMB meetings may be convened in response to a safety event as an ad hoc meeting. This emergency meeting may be due to an unanticipated problem, a serious adverse event, or a protocol violation which affects the safety of participants. The PI is responsible for notifying the DSMB chairperson of any safety event. The DSMB chairperson will communicate the details of the event with the DSMB committee and determine whether there should be an additional committee meeting or whether the discussion of the event may appropriately occur by phone or email. The DSMB chairperson will convey the recommendations of the DSMB committee to the PI. If the event warrants a change in the protocol or suspension of enrollment, in general, a formal meeting should be convened.

Finally, the DSMB should convene at the end of the study to review all the cumulative study data. If requested by the PI, this may also serve as a time for the DSMB committee to review any manuscripts from the study for descriptions of adverse events. After this meeting, the DSMB chairperson should ensure that all documents are handled in accordance with the DSMB charter and institutional policy.

In summary, DSMB meetings occur at the following times:

- An initial meeting before or at study initiation.
- Regularly scheduled DSMB meetings at a frequency determined by the risk assessment of the study. These meetings commonly occur at quarterly, bi-annual, or yearly intervals. The minimum meeting frequency is yearly to ensure adequate monitoring and recertification of the study by the IRB. The frequency of meetings may change depending on safety events (or lack of events) which occur during the course of the study.
- The charter may specify planned DSMB meetings for review of the data at specified times in the study time-line to examine: adequacy of enrollment or randomization; safety in the cohort at specified enrollment numbers or intervals; safety in a cohort prior to dose escalation; or early evidence of efficacy at specified enrollment numbers (planned interim analysis).

- Urgent, ad hoc emergency meetings in response to safety events.
- A final DSMB meeting after the close of a study.

QUORUM

A quorum is typically defined as an adequate number of voting members present and able to vote at DSMB meetings. A quorum is required at both scheduled and ad hoc meetings. In order for a meeting to occur, the number of members defined for quorum must be present. If quorum is not met, the meeting cannot occur. Note that a COI identified during a meeting may reduce the quorum needed for a vote. Guidelines on how this will be addressed should be included in the DSMB charter.

The number of members and the expertise of members needed for a quorum should reflect the complexity and level of risk of the study. The quorum should be clearly defined in the DSMB charter and/or established at the initial meeting. Each DSMB should have a minimum of 3 voting members. While valuable to DSMB discussions, non-voting and ad hoc members are typically not considered part of a quorum. Study information (i.e. modifications, adverse events) that is being reviewed by DSMB members via email also requires quorum. Each voting DSMB member should review the study information and provide their vote and/or comments.

A quorum of the DSMB may be determined by the following:

- A majority of DSMB members present at the review meeting, i.e. 3 of 5 members
- Adequate representation of essential scientific expertise of the members present

Voting members

May include physicians, laboratory scientists, statisticians, ethicists and patient advocates who have appropriate expertise in the scientific area of the study and/or safety monitoring and without COI for the protocol(s).

Non-voting members

An individual directly involved with the conceptual design or analysis of a particular study may not be a voting member of the DSMB. However, inclusion of such individuals as non-voting members will be at the discretion of the Chair of DSMB.

Sponsor representatives are typically non-voting members.

DSMB members with a possible COI of concern for the issue at hand should not vote.

Ad hoc specialists may be invited to participate as either voting or non-voting members at any time if additional expertise is desired. They should be added to the charter membership list.

VOTING

Rules for voting should be clearly established and described in the DSMB charter and/or presented during the initial meeting. Voting members are expected to be present to hear and participate in the discussion prior to their vote. Being present at the meeting may include participating via video or teleconference. Voting members who are not present at the meeting but have reviewed the data and provided opinions and rationale may be considered eligible to vote. One way to accomplish this is to hold the final vote after the members review the minutes of the meeting. These instances should be clearly established in the DSMB charter.

The items that need to be voted on should be described in the charter. These may include: acceptance of previous meeting minutes, whether responses from the PI are appropriate to DSMB inquiries, suggested modifications to the protocol, and recommendations on halting the study.

After a discussion of the issues during the closed session, a vote will be solicited. In general, the chairperson should seek consensus from the DSMB on a particular voting issue. Some DSMB charters recommend or require a consensus vote particularly to amend or terminate a study. Others may not require consensus, but a majority vote will determine the outcome.

Recommendations from the DSMB are made by majority consensus. For this reason, it may be useful to have an odd number of voting members on a DSMB. Procedures for handling a tie vote in the setting of an even number of voting members should be specified in the DSMB charter. These procedures could include the referral of the issue to an external ad hoc new member of the DSMB agreed upon by the entire DSMB, or that both recommendations (for and against) will be conveyed to the PI along with the rationale for each opinion. Once voting has occurred, the final votes are counted, identified as majority or consensus vote, and reported to the study PI as the final determination from the DSMB meeting.

At the conclusion of each DSMB meeting in a closed session, a quorum of voting members will vote on the final recommendations of the DSMB. The recommendations for outcome are the following:

- Continue the study
- Continue the study with suggestions
- Continue the study with mandatory changes
- Suspend further enrollment in the study *or*

- Terminate the study

FORMAT OF THE MEETING

Scheduled DSMB meetings are conducted via in-person, teleconferencing, or web conferencing. In-person is often preferred especially for the initial meeting, but when travel is limited, teleconferencing or web conferencing can work well, allowing all board members to communicate with one another. Having a dedicated teleconference line or web conference meeting can help prevent technical problems. Interim reporting or study status updates for planned data reviews that occur in between formal meetings can be sent via secured email or shared web-based system (many universities have document sharing systems available). Members can comment amongst themselves about the interim study data within a designated period of time. The Data and Safety Monitoring Administrator in concert with the Chair can compile the board's determination and send it onto the Investigator for response.

The topics to be reviewed at the initial Data and Safety and Monitoring Board meeting are usually more comprehensive than subsequent meetings and more time should be allotted for this meeting. See **Table 4.2** for the topics that initial and subsequent DSMB meetings should include.

Table 4.2 DSMB Initial and Subsequent Meeting Topics

Topic	Initial Meeting	Subsequent Meeting(s)
Review of protocol, IRB risk level, study status	X	X
Review of protocol modifications, IRB approval, IRB updates		X
Assessment of risk to participants	X	X
Definitions of adverse events, SAEs, unanticipated problems (protocol deviations)	X	
Define outcomes of interest	X	
Discussion of early stopping principles, if any	X	
Review conflict of interest	X	X
Vote for a DSMB Chairperson (may be done prior to meeting)	X	
Review/modify DSMB charter	X	X
Data		
Format of data for DSMB meetings	X	
Data on recruitment, screening, enrollment (expected vs. actual)		X
Participant eligibility, follow-up, withdrawals		X
Articles pertaining to new developments		X
Missing data information		X
Safety		
All adverse events, SAEs, unanticipated problems (protocol deviations)		X
Breaches of participant privacy and/or study data confidentiality		X
Other		
Outcome data, if any		X
Industry updates and data from other sites		X
Administrative		
Vote to begin, continue, halt study	X	
Formal requests and recommendations	X	X
Vote on frequency of meetings	X	X
Select date of next meeting	X	X

PREPARATION FOR THE MEETING

The Chairperson and PI in conjunction with a DSMB Executive Secretary (Administrator), if there is one, will create an agenda for the meeting to make sure all points are covered for the current review period. Materials that should be covered are included in **Table 4.2** under subsequent meetings. COI issues should be considered in creating the agenda and ensuring a quorum. [See Appendix D, “Sample Meeting Agendas”]

The DSMB will look for trends in the data, so it is important to not only report current data in the review period but also to show the cumulative data. This can be achieved by showing all the cumulative data in a specific report and highlighting the data that has occurred in the current reporting period. [See “Reports” in this chapter]

Ad hoc meetings may be assembled as needed either in-person or via teleconference dependent upon the urgency of the situation. The emergency meeting may only address one issue, but the PI should send the board all pertinent documents that the board may need to see in order to make a decision such as the current protocol, consent, detailed description of the event, risk involved, participant outcomes and all IRB documentation concerning the event. The board should formally decide the severity of the event, relationship to study participation, and document their recommendations to the PI.

All data, reports and communications should be considered confidential. Data can be shared via secure email (behind a firewall), secure web-based system (many universities have document sharing systems available). Paper copies can also be mailed or distributed at a meeting. It is important for the members to have adequate time to review and prep for the meetings, usually 7-14 days. Often, the DSMB Administrator will give the deadline for document submission, usually just over two weeks prior to the meeting. This will give the DSMB Executive Secretary (Administrator) and Chairperson enough time to review the documents for completeness and ask for any additional documents or clarification prior to sending the material onto the board for review.

OPEN AND CLOSED SESSIONS

The DSMB meeting is generally divided between an **open session**, which includes DSMB members and the PI/study representatives, and a **closed session** in which only DSMB members participate. Additionally, the structure of a DSMB meeting may differ whether the DSMB covers one study or is established to review multiple studies. Most meetings will follow a similar format as described in **Table 4.3**.

The meeting will be called to order by the DSMB Chairperson. Attendance of the DSMB members will be taken, noting the presence of any visitors (i.e. PI or study representatives). The DSMB Administrator and/or Chairperson should determine that there is a voting quo-

rum present. The first order of business will be to review the minutes from the previous meeting. Any discrepancies with the minutes or corrections that are needed will be noted. The DSMB will discuss any administrative issues. This may include educational issues such as DSMB training requirements or updates on specific topics of interest to DSMB members. Another administrative issue includes the continual assessment of COI. DSMB members will be reminded of the Conflict of Interest Policy and to recuse themselves if they have a COI with any of the protocol(s) under review. Changes in the DSMB charter or scope of the DSMB will also be addressed.

Any correspondence from a PI in response to contingencies identified during a previous meeting will be reviewed by the DSMB membership. A vote will be taken on the acceptability of the PI response to the contingencies (i.e. did the response satisfactorily address the contingencies raised?).

The next component of the DSMB meeting will consist of the review of the clinical protocol(s) on the agenda. If the meeting consists of more than one protocol, the meeting will start with a brief protocol review. The meeting will begin with an open session which may include the PI of the clinical study under review and other members of the study team. The PI will provide an update on the study since the time of the previous review. He/she will provide the DSMB with new literature pertaining to the study and how it impacts the current protocol. The DSMB members will review blinded study data tables (enrollment numbers, follow up, outcomes) and review adverse events and serious adverse events that have occurred in study participants since the time of the previous review. The PI will be asked to address any questions from the DSMB members related to the data provided in the reports and tables. The review and discussion with the PI during the open session will not involve unblinded data and care will be taken to avoid disclosure of treatment assignments or any indication of whether one arm of the study is trending toward a better/worse outcome. Once the DSMB members are satisfied that all questions have been answered, the PI and other study representatives will be asked to leave the room to allow the closed session of the DSMB meeting to begin.

For the **closed session**, only the DSMB Members and the presenting statistician will be in attendance. Some DSMBs request only the DSMB biostatistician and recuse the study statistician from the closed meeting. In this case, the DSMB biostatistician must communicate with the study statistician in advance to obtain unblinded data if that will be needed to address safety concerns or interim analyses. At this time, the DSMB may consider data by treatment arm (e.g., arm A or arm B) or, if needed, unblinded comparative data. This may include a review of tables detailing the treatment assignments per participant (coded) and statistical reports related to outcomes and adverse events or serious adverse events. It may be useful to re-review the adverse events or serious adverse events in the absence of the study team for any comments. The DSMB members will consider any study-wide stopping rules in place for the protocol as defined in the charter and whether the data presented indi-

cates a stopping rule for the study has been met. The DSMB members will also discuss any issues that were identified during the course of the open session.

After the data has been reviewed and a full discussion by the DSMB members has taken place, the DSMB will come to a consensus on a list of recommendations and vote on whether the study should continue. The outcome of the DSMB vote will consist of one of the following:

- Continue the study
- Continue the study with suggestions
- Continue the study with mandatory changes such as suspending or terminating the involvement of one or more centers (while the other centers continue), because of poor performance (enrollment, quality of data, deviations from protocol, etc.)
- Suspend further enrollment in the study or suspend activity in the study
- Terminate the study for early efficacy, futility, lack of enrollment, safety issues, violations, etc.

Once the closed session has ended, a **final open session** with the PI, study representatives and DSMB membership may be held. This final open session is optional. The DSMB chair will review any concerns with the PI and outline action items/recommendations for the PI to address. The DSMB may answer any questions from the PI or study team. The PI will be advised that a formal letter detailing the recommendations by the DSMB will be forthcoming.

Table 4.3 General Meeting Structure

DSMB Meeting Session	Attendees	Items Addressed
Administrative Session	<ul style="list-style-type: none"> • Administrator • DSMB Chair • DSMB members • Ad hoc members 	<ul style="list-style-type: none"> • Attendance and confirmation of quorum • Review of previous minutes • DSMB training and educational updates • Conflicts of interest • Changes in the DSMB charter, if needed • Review of PI correspondence / response to contingencies
Open Session	<ul style="list-style-type: none"> • Administrator • DSMB Chair • DSMB members • Ad hoc members • Principal Investigator • Study representatives 	<ul style="list-style-type: none"> • Review of protocol(s) • PI update on study and relevant literature • Review of enrollment, blinded study data, and safety events • Question and answer between PI and DSMB members
Closed Session	<ul style="list-style-type: none"> • DSMB Chair • DSMB members • Statistician • Ad hoc members • [Administrator] 	<ul style="list-style-type: none"> • Review of unblinded comparative data, if appropriate • Consideration of study-wide stopping rules • Develop list of recommendations • Vote on continuation of study
Final Open Session (Optional)	<ul style="list-style-type: none"> • Administrator • DSMB Chair • DSMB members • Ad hoc members • Principal Investigator • Study representatives 	<ul style="list-style-type: none"> • Review DSMB concerns and action items with PI • Answer questions by the PI

INTERIM MEETINGS

Interim Meetings are planned periodic reviews of the study data after the initial meeting. The frequency of interim meetings is usually based upon risk, rate of enrollment, and volume of expected data. The projected frequency should be outlined in the DSMB charter with the notation that the Board may vote to change the frequency as they deem fit.

If one arm of the study is high risk but another study arm only enrolls standard of care participants or is a control arm, the data may be reviewed separately on different schedules. For example, the data from the subjects enrolled in the high risk arm can be examined within 30 days of enrollment but the reports of all study participants, including the control arm, could be examined every 3 to 6 months.

Table 4.4 Expected Frequency of DSMB Meetings

Risk Level	Frequency of Interim Meeting
Minimal Risk	Annual DSMB meeting
Greater than Minimal Risk	Every 6 months
Greater than Minimal Risk, high enrollment	Every 3 months
High Risk, high enrollment	Every 3 months
High Risk, first in humans, high profile	Within 30 days of subject enrollment or study procedure completion If no enrollment, minimum annual meeting

AD HOC MEETINGS

Ad hoc or emergency DSMB meetings are called by the PI, the DSMB Chairperson, or by a DSMB member in response to a trigger. Triggers may be: an expected or unexpected serious adverse events including death; an unanticipated problem; a protocol deviation; or an event of a critical nature which may affect subject safety or the study. Such events should be reported to the DSMB Chair and Administrator based on criteria set out in the DSMB charter usually within 24 hours of learning of the event.

The necessity of an ad hoc or emergency meeting cannot be predicted, however, the DSMB charter should outline how such meetings will be handled. Once a triggering event is identified, the DSMB Administrator or Chairperson sends out the de-identified reports to the committee. The reports can be submitted either via email or fax and should include not only the event, but all supporting documents that the Board may need to make an informed decision (e.g., MedWatch Form, IRB forms, de-identified lab reports, current IRB approved protocol and consent).

The DSMB Chair or PI can either call an ad hoc meeting as soon as it is reported or once the Board members have a chance to review the initial issue via email. Any DSMB board member may make the recommendation to meet. The ad hoc meeting can be held either in-person or via teleconference. While there are no restrictions, PIs are typically not invited to participate. However, if the DSMB feels their presence would help, then the meeting should be divided into an open and closed session. If the study has an appointed Medical Monitor, it would be appropriate to invite them.

At the end of the meeting (or closed session) the DSMB should come to a consensus as to whether they require more information from the PI to make a determination. If the DSMB is able to make a determination without additional information, the DSMB should make a for-

mal vote as to whether or not the study should continue with or without modification. The DSMB should also vote as to whether the event will trigger more frequent interim meetings due to increased risk. The results of the vote and recommendations will be conveyed to the PI who is responsible for communicating with the IRB and Sponsor, if applicable.

EMAIL/TELEPHONE REVIEWS

There may be instances where DSMB members may review study information via email, sent using secured email or shared web-based system. These instances may include a minor modification to the protocol or correspondence from the PI in response to DSMB request for further information, adverse event, etc. In these instances, each voting DSMB member should review the study information and provide vote and/or comments. If any DSMB member feels that the study information should be discussed further, an ad hoc meeting should be scheduled.

FINAL DSMB REVIEW

The final meeting of a DSMB is held when the study has closed to enrollment and follow-up. The study should have collected and cleaned all of the data needed for analysis of the major outcomes in the study design. The purpose of a final DSMB meeting is to review the data for overall safety events and trends which may not be evident until the full data is available.

If the study has been terminated early due to stopping rules for safety, efficacy, or futility, a final DSMB meeting should still be held. If the study is stopped early, the DSMB should receive a formal memo or letter from the PI indicating that enrollment has ceased, all follow-up visits have been completed, and no more data will be collected.

The structure of the final DSMB meeting follows that laid out in this chapter (“Structure of the Meeting”) and **Table 4.3**. Interim safety events are reviewed first. Most of the attention of the meeting is then focused on a review of the cumulative data by treatment arm, which may be unblinded at this point. Input by the DSMB and study biostatisticians is very important so that data needs to reach them well before the meeting to allow time for review and analysis.

In addition to the study data, the PI should submit any abstracts, papers, or manuscripts in preparation which concern the study results. Some PIs may request input from the DSMB on manuscripts from a scientific viewpoint. DSMB members asked to review manuscripts should particularly focus on accurate portrayal of the adverse events and risks of the study.

At the closed meeting, the DSMB should vote on their final conclusions about any safety concerns or trends noted in the study. The DSMB should consider data quality including enrollment targets, follow-up goals, and missing data for important end-points. Finally, the

DSMB should vote to disband. Note that a DSMB may disband when a study is still open to data analysis, but patient participation has ended. Some DSMBs may disband when the intervention is completed, the final data pertinent to major outcomes have been obtained, and only survival data is being collected.

At the conclusion of the final DSMB meeting, the DSMB Chairperson sends out the minutes for approval to all DSMB members. The DSMB Chairperson sends a final letter to the PI stating the conclusions of the final DSMB meeting and that the DSMB has disbanded. The PI is responsible for communicating this to the IRB.

After the final DSMB meeting, DSMB Chairperson should ensure that all necessary documents are preserved in accordance with the DSMB charter and institutional policy. These documents may be stored by the DSMB Chairperson, by the IRB office, or returned to the PI as instructed by institutional policy and the DSMB charter. The DSMB chair should remind members to shred all paper copies and permanently delete any electronic copies of documents.

REPORTS

The DSMB uses and generates several different types of reports. The DSMB charter specifies the types of reports generated by the DSMB. Examples of sample reports may be found in the appendices.

STUDY DATA FROM THE PI

The PI and study staff prepare a report of the study data for the DSMB in a format that the DSMB agrees upon at the initial meeting. There are two types of data the DSMB needs to review. The first type is specific reports of specific adverse safety events or protocol deviations. This information should be de-identified as much as possible and tracked by study ID number. Sometimes some identifiers such as date of birth must be given for important study information and identification or the DSMB may request to review certain radiologic exams with names on the images.

The second type of data is that on enrollment, follow-up, and outcomes. The DSMB will look for trends in the data, so it is important to not only report current data in the review period but to also show the cumulative data. This can be achieved by showing all the cumulative data in a specific report and highlighting the data that has occurred in the current reporting period. The DSMB Administrator or Chairperson may provide the PI with a format for data to be presented at the meeting.

The study data should be sent to the DSMB Administrator or Chairperson 7-14 days before

the meeting to allow them to look for any inconsistencies or missing information and to get the data to the DSMB with adequate time to review before the meeting.

MINUTES

Minutes of the DSMB meeting are prepared by the DSMB Administrator and Chairperson. They should include who was present, and topics discussed in the open and closed meeting. The minutes conclude with the results of voting on recommendations for study continuance, timing of the next meeting, and with a list action items for the PI or other members of the meeting. In some DSMBs, the minutes of the open meeting may be reviewed by the PI for accuracy about study data. In some DSMB committees, minutes of the open meeting may be shared with NIH non-voting members, hospital oversight committees, the sponsor, the PI, and/or the IRB.

The minutes of the closed meeting are restricted to the members of the DSMB committee. The purpose of confidentiality of the minutes of closed DSMB meetings is to preserve the frank nature of discussion at the meetings.

LETTER TO THE PI

The DSMB Chairperson should send a letter to the PI with a brief summary of the meeting, a list of action items requested by the DSMB, if any, and the recommendation of the DSMB about study continuance.

At the end of the closed DSMB meeting, the committee votes on recommendations. These are possible recommendations:

- Continue the study
- Continue the study with suggestions
- Continue the study with mandatory changes
- Suspend further enrollment in the study
- Terminate the study

If the DSMB makes suggestions or mandatory changes, these should be concisely stated in the letter.

The PI is responsible for communicating with the IRB and the study sponsors which may include industry, or the NIH, for example. However, some DSMB committees as a courtesy will also send a copy to the IRB. This is institution and study specific but should be documented in the charter at the start of the DSMB.

IRB RECERTIFICATION LETTER

The PI and study staff may request an annual letter to the IRB for study recertification depending on institutional practices. This may be a brief, formal letter stating the dates on which the DSMB met to review the study and the DSMB recommendation to continue or halt the study. This recertification letter should be limited to dates of the meetings and final DSMB recommendations.

Chapter 4 Key Points

- The work of a DSMB is to: convene the DSMB by inviting expert members to serve; write the charter for the DSMB; conduct meetings at least annually; and to issue reports of the recommendations.
- The DSMB charter is the guiding document for DSMB actions and responsibilities. It is written at the time of DSMB formation but may be modified during the course of the study by the committee.
- DSMB meetings follow a similar format whether they are regularly scheduled meetings or ad hoc meetings in response to a safety event or new information. An open meeting is held with the PI and invited study staff. This is followed by a closed meeting of the DSMB committee only.
- A quorum of voting DSMB committee members (as specified in the charter) must be present for the meeting to occur.
- After a DSMB meeting, the committee issues reports which may include separate minutes of the open and closed meetings, DSMB recommendations to the PI, and annual reports to the PI/IRB for the annual IRB approval.

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CHAPTER 5

Data and Safety Review Process

INITIAL DSMB REVIEW

The initial meeting of the DSMB should plan to review the following documents. It is important that the DSMB members have a detailed knowledge of the protocol, the major expected outcomes of the study, the study timeline, the DSM plan, types of expected adverse events, and the method of reporting adverse events to the DSMB and other regulatory entities.

ITEMS TO BE REVIEWED

Protocol

A good monitoring plan begins with a comprehensive, well-written protocol. Elements of a well-written protocol include the following:

Study design

Should be adequate to answer the research question, including pilot or small feasibility trials; review of appropriateness of eligibility criteria; clear delineation of endpoints.

Feasibility and site performance

The site and staff are adequate to: recruit, retain, and follow up participants, case report form tracking, protocol adherence and quality of data; infrastructure adequate for data management (case report form, electronic medical record integration, information technology security).

Eligibility criteria

The inclusion and exclusion criteria must be clearly defined, rigorous enough to allow accrual of a defined population, and yet not so restrictive as to deter enrollment. Issues such

as severity of disease, concomitant medications, language comprehension, ability to comply with the study regimen and confounding factors should be considered when formulating inclusion and exclusion criteria.

Assessments and timeline

The study assessments, including lab and imaging, are clearly specified and adequate to determine possible adverse events in a timely manner.

Statistical plan

The protocol should justify sample size, describe and define the study endpoints, analytic procedures, and any plans for interim analyses.

Treatment modification or discontinuation

For dose escalating studies, procedures for modifying or discontinuing treatment must be specified.

Study termination

Procedures for reviewing enrollment, safety events, and outcomes must be specified to allow for early stopping or suspension of the study.

Ongoing adverse event review

Procedures must be specified for identification and reporting to all appropriate organizations and staff of adverse events.

Monitoring entity

This identifies the person or persons who will have the primary responsibility for monitoring. Depending upon the size, complexity or inherent risk of the protocol a plan may include the investigator, experts in the field of study, consultants (such as biostatisticians) and other specialists as needed. The PI is ultimately the one responsible for all aspects of the trial including safety. The inclusion of other reviewers does not relieve the investigator of his/her responsibility. The issue of possible COI must be taken into account, especially if the investigator assumes the role of the monitor. Use of an independent monitor can accommodate the need for an unbiased review. Independent review can include a range of solutions. Monitoring should be conducted by persons completely independent of the investigators who have no financial, scientific, administrative or other COI with the trial. These independent assurances are important as clinical investigators have an inherent COI when conducting human subjects research. Ongoing review of the data by an independent individual or

committee assures the investigators that the trial can continue without jeopardizing patient safety.

Data and Safety Monitoring plan

The DSM plan is reviewed for completeness, reporting responsibilities, adequacy of safety oversight and review, and accountability. This is distinguished from the DSM plan review done by the IRB where the DSMB formation and structure is part of the DSM plan.

INTERIM REVIEW

During the trial, at the study-stated intervals the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. The review includes adequate information that the timeliness, completeness, and accuracy of the data submitted 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.

For each DSMB meeting, the board should consider, at a minimum, a detailed reporting of safety-related data. A study statistician or a specially designated unblinded statistician should provide a report covering enrollment, study progress, dropout, protocol violations, serious adverse events (SAE), adverse events, and any specially designated safety outcomes.

ITEMS TO BE REVIEWED

Items reviewed by the DSMB include at least all of the following:

- 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; many small studies will not have statistical interim evaluations
- Data quality, completeness, and timeliness
- Adequate recruitment and retention sufficient to meet study endpoints
- 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.)
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study

Safety

One of the primary responsibilities of a DSMB is to determine significant safety signals that emerge from its formal analysis of safety-related data. The DSMB reviews are meant to determine if a study's risk-benefit ratio remains acceptable or not. The DSMB reviews accumulated adverse events or SAEs by study arm to determine whether these events occur more commonly in one arm or if there is a pattern of adverse events which may be due to the study intervention.

The FDA has established a definition of an adverse event as any untoward medical occurrence associated with the use of the intervention, whether or not considered related to the intervention. A SAE is an undesirable experience associated with the use of an intervention in a study participant, such as death, a life-threatening event, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or birth defect, or required intervention to prevent permanent impairment or damage. An unanticipated problem is a SAE that is unexpected, related to a study process or investigational agent and that may place a participant at greater risk. Such events must also be reviewed as part of the DSMBs analysis in the regular meetings or in ad hoc meetings which may be called to review a new event of concern.

For SAEs it is important to independently evaluate if the events are related to the intervention(s) being evaluated. A related event would indicate that there was a reasonable possibility that the event may have been caused by procedures involved in the research. In addition, it is also important to evaluate if the SAE is expected. Expected events are typically included in any package insert, investigator brochure, and from safety profiles of similar drugs/devices/interventions and are included in the informed consent documents.

The reporting of SAEs may vary by study. In addition to the cumulative summaries mentioned earlier, DSMB members may want to see individual reports of all or a subset of SAEs (e.g., deaths) as they are informed of the event.

Data reports

At a minimum, data should be presented in summarized tables reporting frequencies. To allow for efficient follow up of observed problems, the data should also be listed and sorted by treatment and subject. The tables are to be used to identify patterns and the listings must be of sufficient detail to allow for quick assessment of the patterns and to inform any subsequent follow up questions. In general, these tables and listings as well as figures are best included in a text document, but, for a sophisticated DSMB, may also be provided as a supplementary dataset including only the information presented in the listings.

Data quality

The quality of the study data can directly impact the conclusions of the study. For example, if the primary outcome is missing in a large number of participants, the study may not be able to address the hypothesis which it was designed to test. As a result, it is important for DSMBs to monitor data quality. Data quality can be monitored in two areas: completeness and accuracy. The highest level is endpoint information. Although this is sometimes obtained at visits, when the endpoints involve death and/or particular types of hospitalizations (such as for a myocardial infarction) there need to be other ways to obtain the information. It may be much more difficult to assess completeness of such information.

The completeness of data can be thought of looking for missing data or anomalous (out of range) data. A hierarchy of missing data can be envisioned for a study. At the highest level are missing visits and drop outs. In each instance, it is important to record the reason for the event (e.g., patient dropped out because moved to a new area). The next level would be the completion of a visit, though specific instruments or forms were not completed during the visit. For example, a follow-up visit was completed, but the participant did not complete the quality of life instrument. Once again, in these instances it is important to collect the reasons for the missed visit. At the next level is the completion of a measure or instrument, but a specific item is missing (e.g., on a depression measure the suicidal ideation question is skipped).

It is important for the DSMB to review the overall frequency of these events as well as the frequency by important characteristics. Examination by treatment/intervention would indicate potential biases in the data. Examination by study characteristics (clinical center in a multicenter trial or by interviewer) may reveal differential implementation approaches that can be remedied during the course of the trials.

Recruitment, screening, enrollment, retention, withdrawals

Beyond the science involved in clinical research, there are important regulatory and ethical issues that need to be considered. How these issues are addressed impact the overall value, validity and integrity of the conduct, and results of a study. These considerations are meant to create a robust environment for human subject research that not only meets the applicable rules and regulations, but promotes the conscientious conduct of that activity.

Such ethical requirements for clinical research include but are not limited to fair subject selection, informed consent and respect for enrolled subjects; each having influence on the validity of the study; and its design, conduct and analysis. These specific criteria are relevant when critiquing recruitment, screening, enrollment and retention during the develop-

ment and implementation stages as well as subsequent aggregate data review by members of a DSMB.

Regarding fair subject selection, the chosen sample population is driven by science not by convenience, and should avoid exploitation of a particular population. Historically, certain populations such as the elderly, prisoners, minors and those with diminished capacity for decision-making, have been taken advantage of and have been deemed as vulnerable populations. It could be argued that any population could be labeled as vulnerable, especially for those refractory patients identified to participate in clinical investigational with therapeutic intervention studies. It is a responsibility of the DSMB to take into consideration which sample population is being considered for inclusion in order to answer the study question; as representative of the study population. Moreover, it is just as important for the Board to consider which population(s) is (are) considered to be excluded due to reasons beyond scientific rationale. Lastly, the DSMB may be asked to review/approve changes in inclusion/exclusion criteria, especially for trials with lagging enrollment. These should be reviewed carefully to ensure the decision is driven by science, not by expediency.

Informed consent is a process and not merely an event. As clinical investigational drug and device trials are FDA governed, rarely is there any waiver for this process not to occur. As such, consideration must be given to the initiation and continuation of the process, and the environment in which that process is initiated and continued. During the course of the study as procedures are modified, and/or new risks and/or benefits identified, it is important that the consent document be revised. Once approved by the appropriate IRB(s), that information should be imparted to currently enrolled as well as candidate-subjects. Another domain of the consent process to consider is individual autonomy in the decision to (not) participate and to continue to (not) participate in the study. It is important as a member of the DSMB to consider whether or not that autonomy is and remains as objective of an environment and process as possible. In fact, for high risk studies including those in which the PI is a key stakeholder in the technology being investigated and/or any other significant COI, an independent party, e.g., Research Subject Advocate, is a viable option to consider to preserve objectivity of decision-making. It is always recommended to suggest that the process of consent be initiated prior to the initial study visit.

The consent document is a proxy for the actual conduct and content of those conversations that occur and are to occur between the candidate-subject/subject and research team. Consent should be inclusive of the study purpose, procedures, risks, benefits, inducements, options, voluntary nature of participation, and contact information, during the initiation and course of a subject's participation. Moreover, it is to be reflective of any changes that occur in the study, e.g, procedures, or as a result of the study, e.g., unanticipated adverse events deemed to be at least possible-related to the study, its procedures and/or intervention(s). This process must be communicated clearly and constantly in the study protocol,

and should be revisited as felt to be appropriate by the DSMB during its meetings concerning the progress of the study.

Related to that process, the protocol should be critiqued for retention measures in order to promote and preserve compliance and valid study results. This may involve consideration of the timing, frequency and duration of study visits as well as the overall length of participation, as well as the extent of the proposed study procedures. It may be necessary to balance these against the ability to answer study objectives beyond the primary purpose.

Data regarding enrollment, progress, and dropout should follow the kind of flow expected in CONSORT (Consolidated Standards of Reporting Trials) and, at each stage, provide reasons for participants to not progressing as planned. In addition, a demographic breakdown of actual enrollment data is important to assure the study is sufficiently generalizable. While not essential, this same demographic breakdown can be repeated at various stages in the study. In studies with relatively large dropout at particular stages, a repeat of this demographic breakdown and subsequent study stages would assure representativeness continues. When study completion is spread out over many years, an occasional demographic workup of those who have completed up to the date of record for the meeting could prove of further use.

Data for protocol violations should describe the protocol violations in sufficient detail to assure DSMB members that the study's validity has not been fundamentally threatened. This includes information describing the violation, the impact of the violation, and any actions taken to remedy the violation.

Finally, safety outcomes should be described in some detail and, in randomized studies, with some sort of breakdown by arm (with arm identified generically by, for example "Arm A", "Arm B"). SAEs and (closed session) study-specific safety outcomes should be reported by arm with information specifying the time, seriousness, attribution to treatment, hospitalization or death status, resolution and any action taken to remedy the condition. Non-SAEs may be treated in a similar fashion, but may not be essential to the DSMB. Any unblinded data should be reviewed in the closed meeting even if this data is given only by study arm, not by treatment.

Review of a randomized clinical trial, balanced by baseline characteristics

For randomized controlled trials, the DSMB should consider tracking several factors related to stratification and randomization balance. In stratified trials, potential subjects are first placed in well-defined groups (males/females, older/younger than 50, etc.) and then randomized within that group. For a trial to reach its aims each stratum needs to be filled and each arm needs to be roughly similar in terms of demographics, baseline health, and other

factors that may predict a successful outcome. On average, randomly assigned arms *are* balanced, but in any specific trial, it is possible for arms to be imbalanced from chance alone.

In trials using stratified random assignment, the participants are randomized separately within each stratum. The strata represent important subgroups that the researchers wish to either assure adequate representation or for which there is plausible reason to believe the treatment may act differently. For example, males and females under age 40 may have different risk factors for heart disease. If so, it might improve the design for the researchers to stratify by gender in order to assure both that genders are equally balanced between groups and that the study is sufficiently powered for gender-specific subgroup analyses. However, the introduction of strata complicates study enrollment, sometimes requiring extra recruiting effort for hard-to-fill strata. DSMB monitoring should ensure that recruitment has a realistic chance of filling the strata within the allotted time. If it appears that a stratum is unlikely to be filled, the DSMB can suggest changes in the study design to, for example, collapse multiple strata into one, to expand inclusion criteria, or to more aggressively recruit subjects in under-populated strata.

Among the advantages of randomized trials are that all relevant covariates (like gender or age) are, on average, balanced between the arms such that the only true difference between the arms is the treatment itself. However, being balanced on average over many such trials is not the same as being actually balanced in any specific trial. A lack of balance is not necessarily a threat to safety in a trial. It can threaten the analysis and require the analysis to account for imbalances in the randomization. However, a periodic report showing certain key factors by allocated arm is extra assurance that the risk undertaken by the study subjects is likely to result in the intended advance in scientific knowledge. An egregious imbalance, while theoretically possible by chance alone, may require careful attention to assure that treatment allocation procedures are appropriately followed. In general, an imbalance only requires monitoring by the DSMB and not actual DSMB action. It is prudent, though, to be sure that the researchers are aware of the imbalances.

Interim analyses and outcomes

In a well-constructed protocol, interim analyses or procedures to trigger interim analyses should be specified in advance. Any interim analysis, pre-planned or not, should have a clear and narrow goal that would inform a decision to continue or halt a trial. These goals can be grouped into either safety or efficacy goals. Analysis of efficacy requires an end-of-trial analysis plan that sufficiently accounts for multiple testing of study aims, so as to avoid type I statistical errors (concluding a difference where, in fact, there is no true difference).

Interim safety analyses will generally be focused on several targeted safety events as well as patterns of unexpected serious events, particularly on differences between groups. If the

event itself is fairly common, the interim analysis may take the form of a statistical analysis of adverse event rates, trying to detect differences between arms or participant subgroups. More likely, the event itself will be uncommon enough to require more qualitative comparison between arms. However the comparison is made, the DSMB should attend most specifically to indicators of risk and not to the potentially publishable scientific implications of the observed risk patterns. The DSMB needs to be particularly careful attending to and reporting differences in adverse events that may be related to the study outcome or may, inadvertently suggest efficacy results.

Interim efficacy analyses are variations on end-of-trial efficacy analyses. The protocol may specify certain early-decision rules for early proof of efficacy or lack thereof. For these pre-planned analyses, the DSMB may simply serve as a body that can look at unblinded results and decide accordingly using the statistician-provided algorithm. For trials with particular risk or rarity, the DSMB may oversee a futility analysis where results are periodically analyzed to determine whether a final finding of efficacy is now impossible (or futile) and, thus, supporting the end of the trial. This early stopping should be balanced against the utility of continuing the trial for other reasons such as to measure safety or pharmacokinetic outcomes.

The DSMB should conclude each review with their recommendations to the Sponsor or PI as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study include any or all of these action items:

- 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 subjects' 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 (less likely for small trials)
- Corrective actions if needed

SINGLE CENTER OR SMALL- TO MEDIUM-SIZED TRIALS

Responsibility for review by the DSMB of small to medium-sized trials, early phase studies, non-therapeutic, or single site trials is structurally similar to review of larger or more complex trials. However, for such trials the review and analysis may not be as statistically driven as for larger trials. Timeframes may be much shorter and the acuity and safety concerns may even be greater, for example as in phase I trials. For small trials with lower risk, the PI

can fulfill the monitoring role. Institutional DSMBs are typically involved in the oversight of small trials with higher risk.

Typically, these trials do not have a dedicated DSMB. An institutional DSMB would not have a separate charter for each study it reviews. Nonetheless, there may be a steering committee or clinical study oversight committee for some trials. In this case, the communications from the DSMB and the oversight committee are an essential component of the review process. Small trials will often use Independent Medical Monitor (distinct from Medical Monitor in large multicenter trials) to serve as part of the monitoring function.

Early studies (non-therapeutic, phase I, phase II) usually are allowed great flexibility in monitoring; it is not uncommon that the PI does the monitoring. 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.

STATISTICAL TOPICS

Perhaps the most fundamental decision concerning any one study is what criteria and/or rules govern its continuance or its termination. Such decisions may be made purely upon review of the data and the collective wisdom of the DSMB. In other cases, there may be more formal statistical rules to govern such actions of continuation or termination. Such criteria may be applied to efficacy and/or safety parameters. Their primary intent is to minimize bias when such decisions regarding continuation or termination of a study are made; i.e. creating a priori determination criteria, as bounded by statistical rules. There is no single model or rule applicable across studies, regardless of scope and complexity. It is the collective wisdom of and collaboration by both the research team and the DSMB to determine the appropriateness of the inclusion or exclusion of such statistical boundaries as well as the scope of their application. Hence prior DSMB experience for a statistician serving on a DSMB is particularly important when only one statistician is serving on that Board, as is that person's independence from the study statistician.

STOPPING RULES

Stopping rules of all types should be described in both the study protocol and the DSMB charter. These stopping rules come in one of two types: study stopping rules and individual

stopping rules. In addition to the stopping rules themselves, there should be a procedure describing any restart or to shut down the study or remove a subject from study treatment.

Study stopping rules themselves come in three flavors: safety-based, efficacy and futility. Safety-based criteria stop the study when a certain amount, even just one, of serious events occur such as deaths or people needing to be medically withdrawn from study treatment. Often, study stopping rules are based on the most serious of individual stopping rules, but, unlike the individual stopping rules, a study stopping rule affects the entire study. Each study stopping rule should have a specific scope of 'stop' such as whether enrollment stops, treatment stops, or some other study procedures stops.

Individual stopping rules are defined at the patient level based on safety or, less commonly, compliance measures. As much as possible, these rules should include specific criteria such as clinical characteristics or outcomes. In order to address unanticipated problems, one stopping rule should be more general and defined based on seriousness of an adverse event or clinical experience.

Chapter 5 Key Points

- Initial DSMB review of the study includes careful review of the study protocol, the DSM plan and the study DSMB charter.
- In subsequent, interim reviews by the DSMB the committee reviews: interim safety events as well as cumulative safety events; data quality and completeness; recruitment and retention rates; protocol violations; and external factors such as scientific advances which may impact the study or participant safety.
- The DSMB charter specifies when the DSMB should review unblinded data. This may occur for safety review or on a pre-specified interim review of outcome data.
- An experienced biostatistician is key in guiding DSMB review of interim and cumulative data.
- Stopping rules for safety, efficacy, or futility should be specified in the charter at the beginning of the study.

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CHAPTER 6

Role of a Study Safety Officer and Study Monitoring Committees

SELECTION OF THE SAFETY OFFICER

The Safety Officer is an individual independent from the study who is responsible for data and safety monitoring activities in what are typically considered low to moderate risk single site clinical studies. The Safety Officer advises the PI, the IRB, and other regulatory authorities regarding participant safety, scientific integrity and ethical conduct of a study. The role of a Safety Monitor is unique to smaller, single center, or non-commercial research studies.

The Safety Officer should have experience with clinical research, clinical expertise relevant to the study, and a commitment to serve for the duration of the study. All COI should be disclosed before becoming a Safety Officer. The Safety Officer should be as free of COI as possible such as financial connections with sponsor or investigators, as well as professional or institutional affiliations.

Typically, the PI proposes an independent Safety Officer with knowledge of research in the clinical area, and submits the individual's name for review and approval by the IRB or other relevant regulatory bodies.

The Safety Officer must maintain independence from the study and the investigators in order to remain objective. Therefore, the Safety Officer should not be directly involved in the conduct of the study nor have scientific, proprietary, financial or other interests that may influence independent decision-making.

SAFETY OFFICER CHARTER

The Safety Officer charter is a set of predetermined guidelines that define the role of the Safety Officer, describe the purpose, frequency, and structure of reviews and meetings,

define the data to be reviewed, and outline the content of the Safety Officer reports. It is important for all parties to agree on all issues at the onset of the study. Operating procedures should be clearly set in the charter. Consideration should be given for COI, such as how determinations will be initially defined, how they will be continually monitored, and how COI will be managed.

RESPONSIBILITIES OF THE SAFETY OFFICER

The primary role of the Safety Officer is to provide independent safety monitoring in a timely fashion to assure the safety of research participants and scientific integrity of the study.

PROTOCOL REVIEW

At the beginning of the trial, the Safety Officer is expected to review and comment on several aspects of the study and safety monitoring including the: protocol, monitoring plan, manual of procedures, study forms, and reports that will routinely be prepared by the research team. The Safety Officer should not write these documents. The goal is that the Safety Officer should be comfortable with and support the protocol including the definitions of adverse events, SAEs, and reporting structure. The monitoring plan should describe the role of the Safety Officer and the procedures for his/her data review and reporting.

SAFETY MONITORING

SAEs are generally reviewed as they occur. For unanticipated and/or related serious events, the Safety Officer may request additional information such as laboratory data or other study related data, to evaluate these events against the known safety profile of the study treatment and the disease. The Safety Officer may recommend actions including partial or complete unblinding, and/or modifying or terminating the study. Typically, the Investigator will notify the IRB and other regulatory authorities if a pattern of events occurs and will suggest prevention measures (e.g., changes in inclusion/exclusion criteria, frequency of safety monitoring, modifications of study procedures). For unexpected and SAEs, the expedited reporting should include the Safety Officer in addition to the IRB and other required recipients such as sponsors and the FDA. At predetermined intervals, expected adverse event reports will be reviewed by the Safety Officer. The adverse events may be reported in aggregate or by blinded treatment groups.

STUDY MONITORING

All parameters to be monitored should be **predetermined**. In addition to safety monitoring, the Safety Officer may review the general performance criteria for a clinical research study:

- Recruitment
- Enrollment data
- Accrual and retention status
- Demographic information
- Adherence to inclusion and exclusion criteria
- Protocol adherence
- Data quality and timeliness
- Other reports that describe study performance and progress

STUDY STOPPING CRITERIA

Stopping rules, if appropriate, should provide a set of guidelines under which a study may be stopped prematurely. Note that the stopping rules may be unbalanced with a lower threshold for stopping due to safety rather than stopping due to efficacy. The stopping rule criteria may include any or all of these parameters:

- Feasibility (based on accrual and/or retention)
- Safety and toxicity including: defined anticipated adverse events and expected rate; defined thresholds for stopping study for expected and unexpected events
- Efficacy, based on defined primary efficacy outcomes
- New information

INTERIM ANALYSIS

The Safety Officer may also review any interim analyses to ensure that the study concludes once the objectives of the study are met or stopping rule thresholds are reached.

MEETINGS AND REVIEWS

The Safety Officer will maintain confidentiality of any meetings, data, recommendations, and decisions throughout all phases of the trial. The frequency of meetings/data review with the investigator(s), the Sponsor, and/or the study statistician should be predetermined but a

frequency based on time, usually every 6 months, is recommended. There should, however, be flexibility to hold emergency meetings should safety issues arise. Other factors to consider in the meetings include these areas of interest to the integrity of the study:

- Rate of accrual
- Rate of safety outcomes
- Rate of efficacy outcomes
- Study complexity

STRUCTURE OF MEETINGS/REVIEWS

The meetings should have a climate of respectful communication and all information should be kept confidential. The routine attendees should be predetermined and whether meetings between the investigators and/or sponsors will occur.

REPORTS

The Safety Officer should have input on the following aspects concerning the study report(s) and/or meeting minutes:

- Content of reports to the Safety Officer
- Whether the data will be blinded, unblinded, or coded
- Who prepares the reports
- At what point prior to issuing reports or meetings will data be frozen
- How much time before a meeting should the data be sent (usually >1 week)
- The Safety Officer charter should specify how data are to be presented and triggers for presenting safety data in an unblinded manner
- Adverse events
- SAEs usually require detailed descriptions; other adverse events will likely need less detail
- The individual(s) who is(are) responsible for writing the reports should be defined
- Consider what should go into the reports and who should get them
- Recommendations to an IRB, investigator, sponsor, NIH, FDA without data
- If present, summaries of interim comparisons (unblinded data) are kept by the Safety Officer

Safety Officer recommendations

After review and evaluation of the specified periodic reports prepared by the research team, the Safety Officer will prepare a summary cover letter for submission to the investigator, the IRB, and any other regulatory entities previously identified. The letter should provide comments on the report, describe study safety, progress and performance, discuss any concerns or suggestions for modification, and provide recommendations as to the safe continuation or early termination of the study. If the study is blinded, the Safety Officer should be careful to maintain the blinding of the data in the reports.

SAFETY MONITORING COMMITTEE

A SMC is analogous to the Independent Safety Officer in that there may be one or more individuals with expertise in the study field plus a statistician. This committee is assembled to review data for a particular study with the purpose of assuring an independent and timely review of any safety issues associated with a clinical study. This type of oversight is also appropriate for moderate risk studies that due to size or complexity require the on-going assistance of the statistician in the review process. The independent reviewers may be recruited from within the institution or from an outside institution. If a biostatistician is part of the committee, ideally, they should also be independent to avoid unblinding of study data. Sometimes this is impractical and the study biostatistician will serve on the committee. The primary responsibility of the SMC is to monitor subject safety.

The SMC reviews all unexpected and SAEs and protocol deviations that have been reported to the IRB within mandated timeframes and copied to the designated Independent reviewer(s). The independent reviewer(s) will review the events and provide recommendations to the PI regarding any changes to the conduct of the protocol. The SMC will issue reports for review by the IRB on an annual basis at a minimum in conjunction with annual continuing review by the IRB, or more frequently, if required. This will include a statement regarding review of any serious and unexpected adverse events or protocol deviations and any recommendations regarding the continuing conduct of the protocol. This committee can operate under an umbrella charter or an ad hoc charter filed with IRB, but without the requirement for a detailed description of monitoring plans beyond listings members with qualifications, meeting schedule, and essential safety end points, such as stopping rules.

The SMC can be a reasonable alternative for studies that are not of sufficient size, complexity or risk to warrant a fully assembled DSMB, but by virtue of potentially increased risk compared to smaller or simpler trials should have an independent or more robust review.

Chapter 6 Key Points

- A Safety Officer is independent from the study staff and is responsible for data and safety monitoring for low to moderate risk studies.
- A Safety Officer has a charter guiding his/her role in monitoring a study.
- A Safety Officer prepares regular reports about the progress of a study which may include recommendations for improvement or alterations in the protocol.
- A SMC includes the independent Safety Officer as well as one or two more experts, generally including a biostatistician and an expert on the disease or patient population being studied.
- A SMC functions in the same manner as an independent Safety Officer.

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Definitions

Ad hoc Meetings – A meeting formed for or concerned with one specific purpose, case or situation at hand and for no other.

Ad hoc Members – Non-voting member of a group or board for a specific purpose. The appointment of ad hoc members may be temporary or long term. It is a way to get expertise or help for a specific goal without endowing other rights to the member.

Adverse Event – Any untoward medical occurrence associated with the use of a drug, therapy, or intervention in humans, whether or not considered related to the intervention. An adverse event (also referred to as an adverse experience) can also be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an intervention, without any judgment about causality. An adverse event can arise from any use of a drug (e.g., off label use, use in combination with another drug) and from any route of administration, formulation or dose, including overdose.

Adverse Reaction – An undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, but only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence to the adverse event.

Bias – A systematic as opposed to a random distortion of a statistic as a result of sampling procedure.

Bioethicist – One well versed in the study of the ethics surrounding medical research and health-care practices. Bioethicists are concerned with the ethical questions that arise in the relationships among life sciences, biotechnology, medicine, politics, law, philosophy, and theology.

Biostatistician – Individual who develops and uses the science of biostatistics.

Biostatistics – The application of statistics to a wide range of topics in biology. It encompasses the design of biological experiments, especially in medicine, pharmacy, agriculture

and fishery; the collection, summarization, and analysis of data from those experiments; and the interpretation of, and inference from, the results.

Blinded – Process by which the intervention is unknown to one or more people in a clinical trial. It is used to avoid introducing bias in a trial. Single blind is when the subject is blind to the treatment to reduce the potential for a placebo effect. Double-blind in which the subject, investigator, and study staff are blinded to avoid bias. The term “masked” is the same and is sometimes used.

Clinical Research – Patient-oriented research (human subjects, tissues, specimens, and cognitive phenomena), including epidemiologic and behavioral studies, outcomes research, and health services research in which a researcher directly interacts with human subjects.

Clinical Site – A facility at which clinical research is conducted.

Clinical Site Monitoring – Monitoring conducted at a specific trial site to assure that the data collected are accurate, the protocol is being conducted as approved, all regulatory obligations are being met and standards for assuring human subject safety are met.

Clinical Trial – A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Clinical Trial Monitoring – Clinical trial monitoring requires data collection and analysis throughout a project to ensure appropriateness of the research and project design, validity and integrity of the data, and protection of human subjects.

Clinical Trialist – Investigators who by their experience and training in research can provide a depth of understanding of the clinical trial process from inception through each progressive step of a clinical trial to publication of results. Their expertise in trial design, implementation and administration, risk/safety assessment, and analysis of efficacy or other endpoints, as well as knowledge of current clinical findings that would influence the trial may promote a comprehensive perspective for the DSMB that is often essential in monitoring larger or more complex trials.

Closed Session – A monitoring board session which involves discussion of grouped safety data and, if appropriate, efficacy data which are presented by the study statistician(s). Grouped data should be presented by coded treatment arm.

Co-Investigators (Co-I or Co-PI) – Individuals with whom the PI conducts research.

Confidential Information – Information one party discloses with restrictions to another party that is not generally known to the public and concerns scientific knowledge, processes, inventions, techniques, products, data, plans, software or similar information.

Conflict of Interest (COI) – A real, potential, perceived or apparent conflict of interest that arises when an individual’s commitments and obligations to a board, committee or other advisory body are likely to be compromised by a person’s other interests or commitments, particularly economic, especially if those interests or commitments are not disclosed. Such commitments or obligations may constitute a real, potential, or perceived conflict of interest from the viewpoint of some external observer, or some combination of these three categories.

Data Analysis Plan – The process of summarizing data, either to draw conclusions or simply to describe a process.

Data Coordinating Center (DCC) – Provides support for large studies and focuses on central training in research methods, statistical leadership, data collection and management. Also known as Coordinating Center or Biostatistical Center.

Data and Safety Monitoring Board (DSMB) – An independent committee that reviews clinical trial progress and safety, and advises the appointing body whether to continue, modify, or terminate a trial. This is sometimes called a Data Monitoring Committee (DMC) particularly by the FDA.

Data and Safety Monitoring Plan (DSM plan) – Designed by the investigator and approved by Program Staff to ensure safety of human subjects and integrity of data.

Data Monitoring Committee – Term used by the Food and Drug Administration (FDA) to refer to an independent committee that reviews clinical trial progress and safety, and advises the appointing body whether to continue, modify, or terminate a trial. This is more frequently referred to as a DSMB.

Double-blinded – Studies in which neither the participants nor the study team members know which medicine is being used, so data can be collected without bias.

DSMB Chair or Chairperson – Individual who is independent and knowledgeable in the clinical trial’s area of study. In collaboration with the PI and/or steering committee, he or she should be empowered to select an appropriately constituted, multidisciplinary group to monitor the trial’s progress.

DSMB charter – Study-specific written plan outlining the function of the DSMB 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.

Effect Size – Way of quantifying the difference between two groups that has many advan-

tages over the use of tests of statistical significance alone. Effect size emphasizes the size of the difference rather than confounding this with sample size.

Efficacy – The desirable effect of an intervention.

Enrollment – Generally means that a research participant has been consented and screened, with eligibility verified.

Epidemiologist – Public health professionals who investigate patterns and causes of disease and injury in humans. They seek to reduce the risk and occurrence of negative health outcomes through research, community education, and health policy.

Equipoise – Provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial. The term was first used by Benjamin Freedman in 1987. Clinical equipoise means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial. This applies also for off-label treatments performed before or during their required clinical trials.

Executive Committee – An Executive Committee (EC) is a formal group to whom a DSMB reports. NIH specific institutes often have ECs for their internal DSMBs. After unblinding for cause, the DSMB may report their findings or recommendations to the EC but the EC remains blinded to the data. The EC can communicate with the Steering Committee.

Executive Secretary – The person assigned to a DSMB, Observational and Safety Monitoring Boards or Protocol Review Committee, who is responsible for writing and transmitting minutes and recommendations to leadership and to the study team.

Executive Session – A monitoring board session which involves discussion of general trial conduct, and all outcome results, including toxicities and adverse events. DSMB members also make decisions, and formulate recommendations regarding the study.

Food and Drug Administration (FDA) – U.S. agency responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

Frequency – Refers to how often the Board plans to formally meet. All boards must meet on a regular basis and at least formally once a year. They may meet more often depending on the rate of enrollment, safety issues or unanticipated adverse events, availability of data, and, where relevant, scheduled interim analyses.

Futility – A determination made by the oversight committee based on the results of an interim analysis that no significant difference between treatment arms will occur

or are unlikely to change after accruing more patients or that a trial cannot accrue adequate enrollment to make a determination.

Human Subject – Legally defined term for living persons about whom an investigator obtains specimens or data through direct interaction or intervention or through identifiable, private information. Regulations include but are not limited to human organs, tissues, body fluids, and recorded information. Term is defined differently by the FDA.

Indemnification – Indemnification is the part of an agreement that provides for one party to bear the monetary costs, either directly or by reimbursement, for losses incurred by a second party.

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

Informed Consent – A person's voluntary agreement, based upon adequate knowledge and understanding, to participate in human subjects research.

Institutional DSMB – A board originating from an academic institution usually consisting of local members who have no conflict of interest with the study or PI.

Institutional Review Board (IRB) – A board or committee designated by an institution to ensure the protection of rights and welfare of human research subjects and reporting to the Office for Human Research Protection (OHRP). IRBs make ongoing independent determinations to approve, require modifications in, or disapprove research protocols based on whether human subjects are adequately protected. Also known as Research Ethics Boards (REB) or Ethics Committee (EC).

Interim Analysis – An analysis of data that is conducted before data collection has been completed. Clinical trials are unusual in that enrollment of patients is a continual process staggered in time. This means that if a treatment is particularly beneficial or harmful compared to the concurrent placebo group while the study is on-going, the investigators are ethically obliged to assess that difference using the data at hand and to make a deliberate consideration of terminating the study earlier than planned.

Investigational Device Exemption (IDE) – Similar to an IND, this allows an unapproved medical device to be used for investigational purposes.

Investigational New Drug (IND) – An application, filed by a drug sponsor with FDA to conduct clinical trials. It includes detailed descriptions of all trial phases, protocols, IRB members, and investigators.

Investigator – Person involved in human subjects research, excluding one who provides only coded private information or specimens, e.g., through a tissue repository, unless also a consultant or collaborator. Investigators who do not have access to identifiers are exempt from human subjects requirements.

Kaplan-Meier Plot – A graph showing survival of a cohort on the y-axis over time on the x-axis. A plot of the Kaplan–Meier estimator, a series of declining horizontal steps which, with a large enough sample size, approaches the true survival function for that population. The value of the survival function between successive distinct sampled observations (“clicks”) is assumed to be constant.

Lan-DeMets – Lan-DeMets alpha spending function provides a common and well accepted approach for controlling the Type I error rate when one or more interim analyses are conducted.

Life-threatening (Adverse Event) – An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk or death. It does not include an adverse or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Manual of Procedures (MOP) – Detailed, written instructions to achieve uniformity of the performance of a specific function. MOPs are necessary to achieve maximum safety and efficiency in clinical research. (Also: “Manual of Operating Procedures (MOOP)” or “Manual of Operations (MOO)”).

Medical Monitor – Individual, who is not a member of the study team, responsible for real-time monitoring of reports of serious adverse events submitted by the clinical centers to identify safety concerns quickly and to provide regulatory bodies with case-by-case reports of the SAEs.

Minimal Risk – The probability and magnitude of harm or discomfort anticipated in the research is not greater than that ordinarily encountered by the research population in daily life or during the performance of routine physical or psychological examinations or tests.

Null Hypothesis – Opposite of the research hypothesis and is what the investigator hopes to disprove.

O'Brien-Fleming Boundary – Statistical rules used in monitoring a clinical trial are called *group sequential* methods, distinguished from purely sequential methods by the fact that each interim analysis follows accrual of a *group* of subjects. This procedure has the advantage that the final test is carried out almost at the fixed trial alpha level, but early stoppage of the trial is much more difficult than the Pocock procedure.

Observational and Safety Monitoring Boards (OSMB) – Independent monitoring group whose principal role is to regularly monitor data from large or complex observational studies and to review and assess the performance of its operations.

Open Session – A monitoring board session which involves discussion of issues relating to the general conduct and progress of the study, 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 to preserve the masking of all subjects. Outcome results must not be discussed during this session.

P-value – The initial 'result' from a statistical significance test. It is the probability of getting a result at least as extreme as that observed if the null hypothesis is true. It is often misinterpreted as the probability that the null hypothesis is true and for many practical purposes, this may be sufficient. However, that is not the correct interpretation.

Phase I Clinical Trial – Testing in a small group of people (e.g., 20-80) to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).

Phase II Clinical Trial – Study in a larger group of people (several hundred) to determine efficacy and further evaluate safety.

Phase III Clinical Trial – Study to determine efficacy in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions, to monitor adverse effects, and to collect information to allow safe use.

Phase III (as defined by NIH) – A broad-based, prospective study, including community and other population-based trials, usually involving several hundred or more people, to compare an experimental intervention with a standard or control or compare existing treatments. It often aims to provide evidence for changing policy or standard of care. It includes pharmacologic, non-pharmacologic, and behavioral interventions for disease prevention,

prophylaxis, diagnosis, or therapy and includes community and other population-based intervention trials.

Phase IV Clinical Trial – Studies done after an intervention has been marketed to monitor its effectiveness in the general population and to collect information about any adverse effects associated with widespread use.

Placebo – A pill or liquid that looks like the new treatment but does not have any treatment value from active ingredients.

Pocock Boundary – A method for determining whether to stop a clinical trial prematurely. The concept was introduced by the medical statistician Stuart Pocock in 1977.

Primary Endpoint – A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

Primary Outcome – The measurable characteristic (clinical outcome assessment, biomarker) that is influenced or affected by an individuals' baseline state or an intervention as in a clinical trial or other exposure.

Protocol Review Committee (PRC) – An independent group which reviews multicenter protocols and makes recommendations to the Institute regarding the scientific review and possible modifications to protocols.

Quorum – The minimum number of (voting) members of an assembly that must be present at any of its meetings to make the proceedings of that meeting valid.

Randomized – Random allocation of subjects to different interventions to ensure that confounding factors are evenly distributed between treatment groups.

Randomized Controlled Trial (RCT) – A type of scientific experiment to test interventions or technologies involving the random allocation of subjects to different interventions to ensure that confounding factors are evenly distributed between treatment groups.

Risk/Benefit Ratio – Ratio of the risk of an action to its potential benefits. For research that involves more than minimal risk of harm to the subjects, the investigator must assure that the amount of benefit clearly outweighs the amount of risk. Only if there is a favorable risk–benefit ratio may a study be considered ethical.

Safety (or Medical) Monitor – An individual independent from the study who is responsi-

ble for data and safety monitoring activities and advises the Principal Investigator and the IRB regarding participant safety, scientific integrity and ethical conduct of a study.

Safety Monitoring Boards – Another term for a Safety Monitoring Committee.

Safety Monitoring Committee – An independent group of experts that advises the study investigators for Phase I and some Phase II trials. The primary responsibility of the SMC is to monitor human subject safety. SMCs are usually used for studies with a short duration and/or a small number of participants. SMCs often meet in real time or meetings are triggered by study-related adverse events.

Scientific Integrity – Results from adherence to professional values and practices, when conducting and applying the results of science and scholarship. It ensures objectivity, clarity, reproducibility, and utility. Scientific Integrity is important because it provides insulation from bias, fabrication, falsification, plagiarism, outside interference, censorship, inadequate procedural and information security.

Secondary Endpoint – Endpoints additional to the primary endpoint.

Secondary Outcome – Outcomes in addition to the primary outcome.

Serious Adverse Event (SAE) – An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Standard Operating Procedures (SOP) – Detailed, written instructions to achieve uniformity of the performance of a specific function. SOPs are necessary to achieve maximum safety and efficiency in clinical research.

Steering Committee – A group, in a network or multicenter study, composed of the PIs, sponsor representatives, the study statistician(s), and others who oversee the design, execution, analysis, and dissemination of results of a study.

Stopping Rules – Rule which is generally established before or shortly after the trial begins recruiting patients. It involves setting out the circumstances under which the trial will end and the action that will then be taken. Stopping rules can also be developed to apply to individual participants.

Unanticipated Problem (UP) – Any incident, experience, or outcome that meets all of the following criteria: (1) unexpected; (2) related or possibly related to participation in the research; and (3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Unblinded – Treatment assignment is made known.

Unexpected (Adverse) Event – An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, of an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. “Unexpected” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Z-score – A statistical measurement of a score’s relationship to the mean in a group of scores. A Z-score of 0 means the score is the same as the mean. A Z-score can also be positive or negative, indicating whether it is above or below the mean and by how many standard deviations.

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Appendix A: List of Documents for a DSMB

GENERAL

- Data and Safety Monitoring plan
- DSMB charter
- Protocol
- Manual of Operating Procedures
- Investigators' brochure
- Pharmacy brochure, if applicable

REGULATORY

- Updated list of regulatory documents
- IRB Letter of Approval (with expiration date)
- Approved Informed Consent Form(s)
- IND/IDE information (name of holder, date)
- ClinicalTrials.gov (number, documentation, date)

DSMB MEMBERS

- Curriculum vitae
- Confidentiality agreement (signed)
- Conflict of Interest statement (signed)
- Consultant agreement (if applicable)

DSMB MEETINGS

- Agenda
- Minutes
- Correspondence from the DSMB to the PI and from the PI to the DSMB
- Data reports
- Adverse event reports
- Committee reports to PI (and if applicable, to the Sponsor, IRB)

Appendix B: Data and Safety Monitoring Plan

DESCRIPTION OF THE MONITORING PLAN

All prospective studies involving human subjects that are designed to answer questions about the effects or impact of specific biomedical or behavioral interventions must include a data monitoring plan as a component of the research protocol. This includes all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III); etc.

- Monitoring methods and intensity should be commensurate with risks
- Monitoring should be commensurate with size and complexity
- Monitoring may be conducted in various ways or by various individuals or groups

ELEMENTS OF THE MONITORING PLAN

DESCRIPTION OF MONITORING ENTITIES

State the person or persons who have monitoring responsibility. Depending upon the size, complexity or inherent risk of the protocol a plan may include the Principal Investigator, experts in the field of study, consultants (such as biostatisticians) and other specialists as needed. The Principal Investigator is responsible for oversight of all aspects of the trial including safety and the inclusion of other reviewers does not relieve the investigator's responsibility. In smaller trials, the Principal Investigator may take on the monitoring responsibility. Other monitoring entities can include an Independent Safety Officer, a Safety Monitoring Committee (SMC), or a Data and Safety Monitoring Board (DSMB).

DESCRIPTION OF PLAN FOR INTERIM ANALYSIS AND REPORTING

Describe plans for examining safety and efficacy data on an explicitly defined schedule, e.g.,

by whom and how often. Include a statement of Protocol Stopping Guidelines for overall trial conduct, safety concerns, interim boundaries, and futility. This statement should include data reviewed, e.g., enrollment and dropout rates, protocol deviations, subject interview and conduct, review of subject symptoms and performance status, review of clinical test results, physical examinations, vital signs, diagnostic tests and evaluations (e.g., in compliance with IRB required review plus any study-specific considerations). In many cases, such a summary will be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

DESCRIPTION OF PLAN FOR ASSURING DATA ACCURACY, DATA SECURITY, AND PROTOCOL COMPLIANCE

The plan should include procedures for ensuring that data are collected and analyzed per protocol and that confidentiality of study subjects is maintained.

DESCRIPTION OF MECHANISM FOR REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

The Plan should include a statement of reporting problems such as serious adverse events, including required reporting entities (e.g., the IRB, FDA, sponsor, and NIH, if applicable). The urgency of reporting depends upon the issues that have led to an early termination or significant change to a study. Note that protocol deviations that affect safety are considered an adverse event.

Box B.1 Generic Data and Safety Monitoring Plan

Study Information	Title	
	Principal Investigator	
	Study sites	
Study Description	Intervention arms	
	Phase	
	Duration of intervention	
	Duration of follow-up	
	Endpoints	
	<i>Primary endpoints</i>	
	<i>Secondary endpoints</i>	
Study Participants	Planned enrollment	
	Description of population	
	Summarized inclusion criteria	
	Summarized exclusion criteria	
Study Protocol	Procedures for standard of care (control)	
	Procedures and interventions for treatment group	
Monitoring Entity	Any monitoring Entity in addition to PI	
Risk of Study	Risk category	<input type="checkbox"/> Minimal risk <input type="checkbox"/> Low risk <input type="checkbox"/> Moderate risk <input type="checkbox"/> High risk
	Rational for designation of risk category (explanation of categorization of risk based on the study protocol for both standard of care and the interventions)	

Appendix C: DSMB Charters

OUTLINE OF A TYPICAL DSMB CHARTER

Box C.1 Outline of a Typical DSMB Charter

1. Title page
 - a. Includes version, version date, study title, PI
 - b. Page footers should include: DSMB charter version and date, study title or abbreviation, and page number (x of y pages)
 - c. A table of contents is helpful for longer documents
2. Introduction
 - a. The purpose of the DSMB
 - b. Optional protocol summary
3. DSMB functions and responsibilities
 - a. Safety monitoring
 - b. Monitor performance of the trial
 - c. Stopping rules for safety, efficacy, and/or futility (if applicable)
4. Principal Investigator responsibilities
5. Sponsor responsibilities (if applicable)
6. DSMB membership and role-specific responsibilities
 - a. All members: Conflict of interest, confidentiality, communications
 - b. Responsibilities of the chairperson
7. Structure and conduct of DSMB meetings
 - a. DSMB meetings
 - b. Quorum and voting
 - c. DSMB recommendations
 - d. Ad hoc meetings
8. DSMB operations
 - a. Data to be reviewed
 - b. Disbanding the DSMB and destruction of documents
 - c. Procedures for replacing a member

9. Reports
 - a. Minutes
 - b. DSMB recommendations
 - c. Reports to PI for IRB review
10. Signature page
11. Appendices
 - a. DSMB membership, affiliations and contact information
 - b. Template for recommendations from the closed (executive) DSMB session
 - c. Stopping rules

SIMPLE DSMB CHARTER TEMPLATE

This is a template for a simple DSMB charter for a single study. The document should be paginated with the page, version number and date.

DATA AND SAFETY MONITORING BOARD CHARTER

[Study Title]

Version:

Version Date:

Introduction

A Data and Safety Monitoring Board (DSMB) has been commissioned to evaluate safety data of the clinical trial: *[Study Title]* sponsored by *[Sponsoring Organization or Company]*. The DSMB will act in an advisory capacity to *[Principal Investigator Name]*, the Principal Investigator of the study.

The primary purpose of this DSMB is to ensure the safety of the subjects in the trial by monitoring safety data and serious adverse events (SAEs), evaluate risk/benefit where possible, monitor the performance of the trial and data, and identify any clinically relevant trends. Any data related to the safety or well-being of the patients in this study may be considered.

DSMB Functions and Responsibilities

1. To monitor the trial for the safety of the participants
2. To examine adverse events and serious adverse events (SAEs) for relationship to study participation.
3. To make independent recommendations to the PI to continue, amend, or terminate the study based on interim analysis of the safety data following the stopping principles defined in the Data and Safety Monitoring Plan. The study statistician will provide the unblinded adverse event data for DSMB review. All attempts will be made to maintain the blind of the PI and clinical staff, unless DSMB makes a study-wide decision to unblind the study.
4. *[If interim analyses are planned, the timing of these should be stated here. If not, state: There is no planned interim unblinded analysis for efficacy due to (e.g., the long-term follow-up requirements of the trial design)].*
5. To monitor performance of the trial and data quality including protocol violations, improper entry criteria, slow accrual rate, low participation rate, failure of randomization, inadequate treatment adherence, inadequate follow-up rate, poor data quality, and severely compromised validity.
6. To make independent recommendations for improvement or termination if the trial would be unable to prove anything meaningful, regardless of modifications (futility).
7. *[If specific early stopping principles have been developed, state this here (e.g., for efficacy or safety). Refer to the appendix of the charter for the details of these plans.]*

Principal Investigator Responsibilities

The PI is responsible for providing all relevant data to the DSMB in a timely manner.

The PI will notify the DSMB of any safety events including detailed reports of any adverse events, unexpected problems, or deaths. The PI will notify the DSMB within [24-72 hours] of any deaths that are reportable to the Institutional Review Board (IRB). In addition, the PI is expected to report any serious adverse events, unexpected problems, or protocol violations to the IRB, and to the Sponsors.

The PI will provide regulatory information, protocols, informed consent forms, any amendments, correspondence with the IRB as well as study data to the DSMB. The study data should be sent at least 14 days before a DSMB meeting to allow time for review.

The PI is expected to convey relevant recommendations from the DSMB to the IRB and the Sponsor in a timely fashion.

Sponsor Responsibilities

If applicable, complete as negotiated with sponsor. [*These may include adverse events monitoring, monitoring responsibilities, data preparation for the DSMB, statistical and study support personnel responsibilities in regard to the DSMB, etc.*]

DSMB Membership and Responsibilities

1. **Membership:** The DSMB will consist of members completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. The board will include experts in the fields of [*study related*] and biostatistics. The names of the DSMB members and contact information are listed in Attachment 1. If a DSMB member is no longer able to serve on the DSMB due to other time obligations or to a new conflict of interest, the Chairperson, in consultation with [*Name of PI*], will appoint a replacement member to the DSMB. If, in the opinion of the Chairperson, a DSMB member is unable to fulfill their duty, the Chairperson will discuss the reason for dismissal from the board with the Principal Investigator. If both the Chair and Principal Investigator are in agreement, the individual member will be removed from the board with prorated compensation and the [*Sponsor*] will be notified.
2. **Conflict of Interest:** The DSMB members will have no financial, scientific, or other conflict of interest with the trial. All members of the DSMB will be asked to disclose any potential conflicts of interest before the initiation of the study. Annually, members will be asked to update their conflict of interest. The conflict of interest forms will be kept in the study regulatory binder maintained by the PI.
3. **Protection of Confidentiality:** All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. The DSMB will be provided with anonymized subject data. If data is to be provided in electronic format, files must be password protected and stored on secure computers of DSMB members or on secured websites. If paper files are to be used, attention must be paid to the proper destruction of files.

Structure and Conduct of DSMB Meetings

1. **Frequency of Meetings:** The DSMB will meet at least [*insert time frame*] a year. The first meeting should occur before recruitment of subjects begins, primarily to approve the protocol (particularly the monitoring plan). The meetings will occur in person and with the use of video or teleconferencing, as needed.
2. **Pre-meeting Materials:** The Principal Investigator will be responsible for

providing DSMB committee members with a summary of the study data at least 14 days before the scheduled meeting.

3. Structure of the Meetings

- a. The **open** session is by invitation only and may be attended by the Principal Investigator, Research Coordinator, Epidemiologist and/or Biostatistician, and other study staff determined by the PI. The PI will provide a comprehensive assessment of enrollment rates and current adverse events. The assessment will indicate the significance of any adverse events, and whether these toxicities have affected the conduct of the trial. The DSMB chair will lead a discussion on general conduct of the trial, a review of outcome results and factors external to the study (such as scientific or therapeutic developments). Issues discussed at open sessions may include all aspects of the research related to safety and conduct of the study.
- b. The **closed** session will be attended only by DSMB members for determination of any recommendations. The discussion at the closed session is completely confidential. At the end of the closed session, the DSMB will vote to either:
 - i. Continue the trial
 - ii. Continue the trial with suggestions
 - iii. Continue the trial with mandatory changes
 - iv. Suspend further enrollment in the trial pending analysis of events and/or data, *or*
 - v. Terminate the trial

4. **Quorum and Voting:** A quorum is [*define the minimum number of committee members that must be present at a meeting in order to conduct a valid meeting; e.g., a number which is at least half the voting committee plus one*]. Should a member need to resign from the committee, the remaining members can fulfill board functions until a replacement member can be identified. Should there be more than two vacancies, the Chairperson and the Principal Investigator will confer with the [*Sponsoring Organization or Company*] for guidance. Recommendations are made with majority vote [*or consensus vote*]. If a member is unable to attend, but has reviewed the data, their input can be considered in the deliberations of the meeting. However, only those board members present for the majority of the meeting and present for critical deliberations can vote. In some circumstances

(such as lack of a quorum) it may be acceptable to conduct a vote by email after a transcript of the meeting has been circulated to all DSMB members.

Most charters should outline a process for this contingency, if deemed an acceptable alternative. There will be an attempt to maintain consensus in all decisions. Should the Chairperson of the DSMB not be available, the chair will nominate a deputy chair during his/her absence.

5. **Ad Hoc Meetings:** Either the Principal Investigator or the DSMB Chairperson can call an ad hoc meeting. In the event of an serious adverse event or an emergent safety concern, the Principal Investigator or his designee will report the event to the IRB, [*Sponsoring Organization or Company*], and DSMB Chairperson. Depending on the nature of the SAE, the DSMB Chairperson may decide to meet within 7 days (via conference call or email discussion) following the notification of an serious adverse event and decide if enrollment should be altered. The structure of the ad hoc meetings will follow that of regular meetings. The DSMB members will vote on recommendations for continuing, modifying, stopping enrollment in or terminating the trial. The Chairperson will provide the Principal Investigator with a written report summarizing the recommendations.

Reports

The following reports will be made available for each DSMB meeting:

1. **Meeting Data:** Relevant meeting data will be collected by the PI and his staff and distributed to DSMB members at least 14 days prior to the DSMB meeting. Data will consist of total enrollment data, follow-up data, adverse events (adverse events, SAEs, reported events), and information on the performance of the trial and data quality and any additional data requested by the DSMB.
2. **Meeting Minutes:** Minutes will describe key points of discussion and any recommendations with rationale. These will be read and approved by all DSMB members. The minutes of the open meeting will be sent to the PI. The minutes of the closed meeting are confidential and are kept for the DSMB members only. These will be released to the PI at the termination of the study.
3. **Recommendations:** Following each DSMB meeting, the DSMB will provide the Principal Investigator with a written report, as shown in Attachment 2 summarizing recommendations, suggestions for the performance of the study, or requests for specific data or clarification. The PI is expected to convey relevant recommendations to the IRB and the Sponsor in a timely fashion. [*State if institutional policy is for the DSMB to send a copy of the recommendations directly to*

the IRB.] Copies of all correspondence will be maintained in the study regulatory binder.

4. **Correspondence to the PI and IRB:** DSMB will send a letter to the PI for the IRB review at the time of annual recertification. This letter will state the dates that the study has been reviewed and the number of subjects enrolled but will not specify issues unless a recommendation is made to close or amend the study. The PI is responsible for forwarding a copy of this letter to the IRB. [*Insert any institution specific requirements.*]

Signature Page

The Chairperson may sign and date this on behalf of the DSMB committee. The charter should be voted on in the initial meeting. Any changes should be specified in a different version, e.g., ‘Version 1.1 on Date’. The minutes of the DSMB meeting should reflect the acceptance of the charter by the DSMB.

SIMPLE CHARTER ATTACHMENT 1

DSMB Members

[Study Title]

Member Type	Member Information	Expertise
Chairperson	Name Titles, Positions Mailing address Email Telephone	
Member		
Member		
Member		

SIMPLE CHARTER ATTACHMENT 2

DSMB Meeting Report

[Study Title]

To: *[Name]* Principal Investigator

Meeting Date:

Meeting Attendees: Names of attendees

Recommendation:

- Continue the trial
- Continue the trial with suggestions
- Continue the trial with mandatory changes
- Suspend further enrollment in the trial
- Terminate the trial

Comments:**Chairperson (initials and date):****SIMPLE CHARTER ATTACHMENT 3**

Include if applicable.

DSMB Early Stopping Principles

[Study Title]

Early Stopping Principles [*These should include statistical monitoring guidelines*]

1. For safety
2. For efficacy
3. For futility

COMPLEX DSMB CHARTER TEMPLATE

This is useful for multisite studies or complex study designs.

DATA AND SAFETY MONITORING BOARD CHARTER

[Study Title]

Version:

Version Date:

IRB Number:**Table of Contents**

[insert page numbers]

1. Introduction
2. Trial Overview and Study Design
3. Organization of the DSMB
4. Responsibilities and Functions of the DSMB
5. Responsibilities and Functions of the Investigators, Coordinating Center, Sponsor, Etc.
6. Conduct of DSMB Meetings
7. DSMB Reports
8. Amendments to the DSMB charter
9. Attachments

Introduction

The purpose of this charter is to *[define the responsibilities of the DSMB, delineate qualifications of the members, describe purpose and frequency of meetings, provide the procedures for ensuring confidentiality and proper communication, outline the content of the DSMB reports, etc.]*.

The DSMB will function in accordance with the principles of the following documents: *[list document titles, e.g. ICH GCP, FDA Guidance's, etc.]*.

The *[insert name of trial]* trial is a *[list characteristics; e.g., randomized, multicenter, placebo-controlled, insert appropriate drug phase or device trial]*. The trial is sponsored by the *[insert name of sponsor and funding agency if different from sponsor]* through a grant to *[insert name of PI or consortium]*. The Principal Investigators *[and Coordinating Center (if applicable)]* for the trial are located at the *[list location(s)]*. A Steering Committee comprised of leadership in the *[list funding agencies]* oversees the general scientific direction of the trial. The Data and Safety and Monitoring board (DSMB) provides independent safety review and trial guidance during the course of the ongoing trial. This document outlines the formal operating procedures for the *[insert name of trial]* DSMB.

The DSMB periodically reviews *[insert data reviewed by DSMB, e.g., safety data, results across treatment groups]* and judges whether the overall safety and feasibility of the trial remains

acceptable. The DSMB has access to *[insert description of data]*; however *[insert any exceptions; e.g., no formal analyses of efficacy data are planned]*. Any recommendations to alter study conduct will be based on safety not efficacy, so monitoring of the study will not affect the statistical operating characteristics of the final efficacy analysis. The criteria for assessing the safety data are outlined in the *[insert name of trial]* DSMB Monitoring Plan attached to this document (Attachment 2).

The DSMB will specifically review adverse event data as well as summary reports of all serious adverse events and available lab data, and may review individual cases if deemed appropriate or necessary to determine if a safety concern is emerging. The *[insert sponsor, steering committee, or investigators]* may also make recommendations to the DSMB for additional data review should a concern arise. The DSMB may recommend a new course of action for a specific treatment group or may suggest other appropriate courses of action to address general study safety issues which may arise. If warranted, the DSMB may recommend at any time that the entire protocol be suspended temporarily or terminated permanently. These recommendations, containing fully blinded information, will be directed to the *[insert name of DSMB management organization, sponsor, steering committee, or other overseeing entity]* which has the responsibility to accept, reject or modify DSMB recommendations.

Trial Overview and Study Design

This section includes a brief summary of the study, including name, sponsor, study design, hypotheses, specific aims, phase, number of patients, number of sites, description of the drug or device under study, study treatments and allocation, follow-up schedule, primary outcomes, sample size.

Organization of the DSMB

1. **Composition of the DSMB:** The DSMB membership includes *[insert number]* clinical investigators and *[insert number]* statistician, all with prior experience and expertise in clinical trials. Committee members may not participate in the study as principal or co-investigators, or as study physicians.
2. **Selection of DSMB Members:** The DSMB Chairperson and members will be initially selected by the *[insert responsible party, e.g., Principal Investigator]*. In the event that a member is unable to continue participation on the DSMB, the *[insert title]* will recommend a replacement to the Principal Investigator *[and steering committee]*.
3. **DSMB Membership:** DSMB members will follow conflict of interest guidelines as detailed in the *[list relevant COI policies]* and be cleared of any real or potential conflicts of interest in accordance with the provisions in this charter.

4. Remuneration will be provided by the *[list study sponsor or funding agency]*.

Responsibilities and Functions of the DSMB

This DSMB will be coordinated by *[list name of sponsor, DSMB management organization]*.

This DSMB is responsible to the *[insert group or individuals responsible]* for oversight of study safety considerations.

Initially, the DSMB is responsible for:

1. *[List initial responsibilities including finalizing DSMB charter; insert the names of groups or individuals whose additional approvals will be needed.]*
2. Defining, with input from the Principal Investigator and *[insert names of any other groups or individuals]*, safety and related parameters to be monitored, frequency of committee monitoring reviews and interim safety analyses, methods for review, statistical methodologies, quorum of Committee members, and establishing criteria for making recommendations to *[insert name of group or individuals]*.
3. Documenting and approving the procedures defined above.

The DSMB reviews data generated by the study and study safety events on a periodic basis. The DSMB biostatistician will provide interpretation of interim safety analyses per the attached DSMB Monitoring Plan (Attachment 2).

The DSMB recommends one of the following actions to the *[insert group or individual responsible]*:

1. Continue the study according to the protocol and any related amendments.
2. Modify the study protocol. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency of visits of safety monitoring, alterations in study procedures, changes in duration of observation, and follow up.
3. Discontinue the study (with provisions for orderly discontinuation in accord with good medical practice).

After each meeting, the DSMB will issue their findings via a letter signed by the DSMB Chair to the *[insert PI, sponsor, Study Monitoring Committee, others to whom findings are reported]* in writing within 7 working days of the meeting. These findings will also be included in the open minutes and distributed by email to the DSMB members and the *[list any others to whom findings will be distributed by email]*. The DSMB chair will take minutes during the closed sessions and report to the *[sponsor, others]*. These findings will also be distributed to *[all sites and/or IRBs]*, following approval by the *[name of DSMB management organization or sponsor]*.

Responsibilities and Functions of the [Investigators, Coordinating Center, Sponsor, Etc.]

The [list Principal Investigator, trial Statistician, trial coordinating center, others responsible for these functions] are responsible for the coordination of the DSMB activities and materials including the following items. [List name of individual, organization, trial coordination center] will oversee the preparation of the data to be reviewed by the DSMB:

1. Identifying an administrative assistant for the DSMB and an independent statistician to provide any unblinded safety data and related interim analyses.
2. Recommending DSMB members and providing the initial draft of the DSMB charter.
3. Managing any transfer of the clinical safety data [and randomization codes]. As determined by the DSMB, the [list those responsible for coordinating the DSMB activities] will provide:
 - a. [The randomization codes]
 - b. [Blinded] summaries of any adverse events (serious adverse events and adverse events)
 - c. [Blinded] safety data as outlined in the attached open and closed report templates
4. Preparing periodic reports containing summaries of the safety data pertinent to DSMB review as outlined in the attached [specify if necessary, e.g., open and closed] DSMB report templates. These reports will be prepared [and validated] for each DSMB meeting. Reports will be generated by the Investigators [list any others generating reports, e.g., project statistician (open report) and the independent statistician (closed report)]. The [specify if needed, e.g., open and closed] reports will be distributed to the DSMB at least two weeks before the DSMB meeting via [specify method, e.g., email, express mail]. The reports will be finalized at the DSMB meeting, and the open report along with the DSMB recommendations will be distributed to the [list responsible group or individuals, e.g., Steering Committee and Principal Investigators]. Copies of the closed DSMB report will be collected and destroyed by the administrative assistant following the DSMB meeting. For record-keeping purposes, copies of the closed reports will be maintained by the independent statistician.
5. Ad hoc data summaries may be prepared upon written request by the DSMB to address a specific safety concern (email is an acceptable method of communication). Ad hoc reports will be prepared by the PI and study statistician.

The [*list those responsible, e.g., Trial Statistician*] will oversee the preparation of ad hoc reports as directed by the DSMB. The [*responsible party, e.g., independent statistician*] will prepare any unblinded ad hoc reports.

6. Performing planned analyses as described in the DSMB Monitoring Plan and report templates (Attachments).
7. Scheduling DSMB meetings and conference calls and preparing and distributing agendas under the direction of the DSMB Chairperson.
8. Distributing serious adverse event reports to the DSMB in a timely manner.
9. Preparing summary minutes for the open portion of each DSMB meeting, and maintaining all open meeting records.
10. Maintaining the DSMB files and archives of electronic data sets and programs used to generate each summary report.
11. Making resources available in a timely fashion to the DSMB as required to carry out its designated functions including:
 - a. Study documents (e.g., protocols, investigator brochures, protocol amendments)
 - b. Study [*Clinical*] data
 - c. Serious adverse event reports
 - d. Additional medical records and supporting documentation as requested to address specific safety concerns
 - e. Other data as requested in writing by the DSMB

Conduct of DSMB Meetings

1. **Scheduled Meetings:** An initial meeting of the DSMB will be held before any subject enrollment in the study occurs in order for the members to finalize the DSMB charter, establish a meeting schedule, review the study protocol, and study/participant termination guidelines. The DSMB will meet twice per year, or when [*list parameter, e.g., enrollment, study procedures*] is completed on the first [*insert number*] of subjects, whichever is sooner. DSMB meetings will generally be conducted by [*indicate format, e.g., face-to-face, teleconference*]. The actual frequency of convened DSMB meetings and conference calls may vary depending on actual subject enrollment and safety event rates.

2. **Voting:** DSMB members vote on all recommendations to be submitted to the [*list responsible individual or group, e.g., PI, Steering Committee*]. To vote, a DSMB member must be present at convened scheduled meetings or participate through conference calls. A simple majority of members present passes a proposal, motion, or recommendation to the [*list responsible individual or group*].
3. **Quorum:** A minimum of [*enter definition of quorum, including whether or not chairperson must be present, whether or not statistician must be present*] committee members constitutes a quorum for the purposes of voting on recommendations to the [*list responsible individual or group*].
4. **Procedures for Communicating DSMB Recommendations** [*List responsible individual or group*]: Duly voted and passed DSMB recommendations to the [*list responsible individual or group*] are transmitted in writing within seven working days of the meeting at which the recommendation was formulated and passed. The [*list responsible individual or group*] has the responsibility to communicate final recommendations to the [*list individuals or groups notified, e.g., individual Investigators at all study sites, IRBs and the FDA*] if required.
5. **Minutes:** Meeting minutes will be kept for each meeting of the DSMB, by the PI for the open session by the DSMB chair for the closed session. The PI and DSMB chair will keep these meeting minutes on file for the duration of the study. Two separate versions of the minutes will be generated. The Open Minutes will be completely blinded to study groups. The Closed Minutes may contain partially unblinded information (treatment groups), and will be distributed to DSMB members and the independent statistician who will have the code to fully unblind the treatment groups.
6. **Meeting Format:** Meetings will consist of open and closed sessions. During the initial open portion of a meeting, the investigators will briefly review the study data and progress as outlined in the open DSMB report and the investigators will be available for questions from DSMB members. The remaining closed portion of the meeting will take place with only the DSMB members in attendance. The final open portion of the meeting will occur during which time the DSMB members will summarize for the investigators the recommendations they plan to submit to the [*list responsible individuals or groups involved in safety monitoring of study*].

DSMB Reports

DSMB reports containing enrollment data, patient safety data and adverse event summaries will be reviewed at the DSMB meetings. Two versions of the DSMB report will be generated:

1. **Open DSMB Report:** The Open DSMB Report will be prepared by the [*list*

responsible individual or group, e.g., PI, trial statistician]. It will contain [*specify blinded or unblinded*] safety information and will be distributed to [*list any individuals or groups as needed*]. An Open DSMB Report template is provided with this charter to provide an example of the report organization and examples of table formats. The contents of the report and data tables may evolve with the study and information requirements of the DSMB.

2. **Closed DSMB Report:** The Closed DSMB Report will be prepared by the [*list responsible individual or group, e.g., statistician, independent statistician*] if deemed necessary by the DSMB. It will contain [*may specify blinded or unblinded*] safety information and will be distributed to DSMB members. For record-keeping purposes, copies of the closed reports will be maintained by the [*list responsible individual, e.g., DSMB Chair, the statistician, independent statistician*]. All other copies of the closed reports should be destroyed. The contents of the report and data tables may evolve with the study and information requirements of the DSMB.
3. **Response to DSMB Findings and Recommendations:** [*List individuals or groups specified above*] will review and respond to the DSMB recommendations. If the DSMB recommends continuations of the study without modification, no formal response will be required. However, if the recommendations request action, such as modification of the protocol or study termination, the DSMB will request that [*list individuals or groups specified above*] provide a formal written response indicating whether the recommendations will be followed, and the plan for carrying out the recommendations or addressing the issues. [*Describe procedure in the unlikely event of irreconcilable differences*].

Confidentiality

All committee members will treat as confidential the reports, meeting discussions, and minutes. Master copies of the DSMB reports and recommendations will be kept in a limited access, locked file cabinet.

Amendments to the DSMB Charter

This DSMB charter can be amended as needed during the course of this study. Information to be included as amendments will be any [*insert description of types of modifications*]. All amendments will be documents with [*insert version numbers, dates, etc.*] and will be recorded in the minutes of the DSMB meeting. Each revision will be reviewed and agreed upon by the [*sponsor, investigator, etc.*] and the DSMB. All versions of the charter will be stored in [*insert*].

Attachment 1: DSMB Members

Attachment 2: Data and Safety Monitoring Plan

Attachment 3: DSMB Open Report Template

Attachment 4: Early Stopping Rules

Appendix D: Sample Meeting Agendas

SAMPLE AGENDA FOR REVIEW OF A SINGLE STUDY

[Institution] Data and Safety Monitoring Board (DSMB) Committee

Date:

Time:

Location:

[Study Title]

Principal Investigator:

Attendees

Voting Members: *[List]*

Non-Voting Members: *[List]*

Prior to beginning of the meeting:

1. State whether the meeting will be audio recorded
2. Ask everyone to state their name and title for the record
3. Ask Board Members to verbally confirm that they do NOT have a financial or scientific conflict of interest which would affect their participation on the DSMB

Agenda for Open Meeting

1. Review of minutes and recommendations from *[last meeting date]*
2. DSMB administrative issues and education
3. Summary of study progress:

- a. Updates from the PI: this may include general statements about the progress of the study (e.g., new sites, protocol changes), study challenges, and scientific or therapeutic developments in the field that affect the research.
 - b. Subject recruitment, accrual and retention rates
 - c. Adherence to eligibility and exclusion criteria
 - d. Study protocol deviations
 - e. Subject missed appointments, withdrawals, complaints
 - f. Protection of data confidentiality and patient privacy
4. Study outcome data
 5. Adverse events
 6. Review of data quality, missing data, and data monitoring

Agenda for Closed Meeting

1. Review of minutes of previous closed meeting [*last meeting date*]
2. Re-review of Open Meeting content by treatment group
3. Risk/Benefit ratio
4. DSMB Recommendations
5. Timing of the next DSMB meetings

Documents

[*List of all documents provided for review*]

SAMPLE AGENDA FOR REVIEW OF MULTIPLE STUDIES

[Institution] Data and Safety Monitoring Board (DSMB) Committee

Date:

Time:

Location:

[Study Title]**Attendees****Voting Members:** *[List]***Non-Voting Members:** *[List]*

Prior to beginning of the meeting:

1. State whether the meeting will be audio recorded
2. Ask everyone to state their name and title for the record
3. Ask Board Members to verbally confirm that they do NOT have a financial or scientific conflict of interest which would affect their participation on the DSMB
4. Identify Board Members who have a conflict of interest and review the necessity for their recusal from discussion of the relevant studies

Agenda

1. Review of minutes and recommendations from *[last meeting date]*
2. DSMB administrative issues and education
3. **Closed studies:** review needs for monitoring
 - a. *[Study name], [Name of Principal Investigator], [Name of Reviewer]*
 - i. Study status
 - ii. Discuss need for continued monitoring
 - b. *[Study name], [Name of Principal Investigator], [Name of Reviewer]*
 - i. Study status
 - ii. Discuss need for continued monitoring
4. **Active studies**
 - a. *[Study name], [Name of Principal Investigator], [Name of Reviewer]*
 - i. Summary of study progress
 - i. Subject recruitment, accrual and retention rates; enrollment period and data cutoff date

- ii. Adherence to eligibility and exclusion criteria
- iii. Study protocol deviations
- iv. Subject missed appointments, withdrawals, complaints
- v. Protection of data confidentiality and patient privacy
- ii. Study outcome data
- iii. Adverse events
 - i. List serious adverse event number and date
- iv. Review of data quality, missing data and data monitoring
- v. Update on relevant information, such as scientific or therapeutic developments
 - i. Risk/benefit ratio
- vi. DSMB recommendations
- vii. Timing of next follow-up meeting
- b. [*Study name*], [*Name of Principal Investigator*], [*Name of Reviewer*]
 - i. Repeat above format for all additional studies to be reviewed

5. New studies

- a. [*Study name*], [*Name of Principal Investigator*], [*Reviewer: not assigned*]
 - i. Study status information
 - ii. Review of protocol and safety monitoring plan
 - iii. DSMB recommendations

6. Date of next DSMB meeting [*proposed date*]

Enrollment for Studies Reviewed by the DSMB

Study	Principal Investigator	Total on Study	Active	Reviewer
Study Name	PI Name	Initial: # New: #	Y/N	Name
Study Name	PI Name	Initial: # New: #	Y/N	Name

Documents

Location where documents posted electronically (if applicable)

General documents:

1. Agenda for this meeting [*date*]
2. Minutes of last meeting [*date*]
3. Tracking sheets

Study documents for meeting:

1. [*Study Name*]
 - a. Document name
2. [*Study Name*]
 - a. Document name

Appendix E: Sample Request for Study Information

REQUEST FOR STUDY INFORMATION PRIOR TO DSMB MEETING

INVESTIGATOR STUDY REPORT

[DSMB Name]

Please respond to each of the following requests for information and add additional pages, if needed. Please send all correspondence to *[Name, email]*

Study Information	
Today's date	
PI	
Study title	
Funding source	
Co-investigators	
DSMB Information	
DSMB #	
Frequency of DSMB	
Last DSMB meeting date	
IRB Information	
IRB #	
Current IRB approval date	
Study risk level per IRB	<input type="checkbox"/> Minimal Risk <input type="checkbox"/> Greater than Minimal Risk <input type="checkbox"/> Low Risk <input type="checkbox"/> Moderate Risk <input type="checkbox"/> High Risk
Status of study	<input type="checkbox"/> Pending <input type="checkbox"/> Open to accrual <input type="checkbox"/> Clinical hold <input type="checkbox"/> Closed to accrual <input type="checkbox"/> Completed
Target accrual #	
Estimated duration of study (enrollment through follow-up)	
Have there been any changes to the protocol and/or consent since the last DSMB review?	<input type="checkbox"/> No* (*Please attach the most recent protocol and consent) <input type="checkbox"/> Yes** (**If yes, please attach all revised study documents and IRB approval letter)
Detailed list of modifications since last DSMB review	<input type="checkbox"/> Attached
General Study Conduct Information	

Date first subject enrolled	
Number of subjects enrolled <i>since last Investigator Study Report</i> (Date of last report:)	
Total number of subjects enrolled to date (including those above)	
Are subjects screened before enrollment?	<input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please explain) Comments:
Overall, study subject enrollment has been:	<input type="checkbox"/> As projected <input type="checkbox"/> Higher <input type="checkbox"/> Lower/Acceptable <input type="checkbox"/> Lower/Not Acceptable* (*If enrollment is slower than projected, please provide a rationale for it and justification for why the study should be continued) Comments:
Study Conduct for this Review Period (or Not Previously Reported)	
1. Have all enrolled subjects been determined to be eligible subjects during this review period, as specified in the Study Protocol?	<input type="checkbox"/> No*(*If no, please explain) <input type="checkbox"/> Yes Comments:
2. Have any subjects been withdrawn from the study during this review period?	<input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please attach a summary of subject dropout data without patient identifiers) Comments:
3. Have any subjects missed any study follow-up contacts during this review period?	<input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please explain) Comments:
4. Have there been any subject complaints during this review period?	<input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please explain) Comments:

<p>5. Have there been any breaches of subject privacy and/or study data confidentiality during this review period?</p>	<p><input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please attach a summary or describe below these breaches and action taken) Comments:</p>
<p>6. Have there been any Adverse Events during this review period:</p>	<p><input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please attach a completed cumulative Adverse Event Table)</p>
<p>7. Have there been any Unanticipated Problems during this review period (e.g., study protocol deviations, unexpected new risks)?</p>	<p><input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please attach cumulative report and explain the unanticipated problems, the action taken, including date the IRB was notified) Comments:</p>
<p>8. Study Outcome Data Available during this review period?</p>	<p><input type="checkbox"/> No* (*If no, please provide projected date or timeframe) <input type="checkbox"/> Yes** (**If yes, please explain) Comments:</p>
<p>9. Has there been any external relevant information, including scientific or therapeutic developments that would change the administration or design of the protocol during this review period?</p>	<p><input type="checkbox"/> No <input type="checkbox"/> Yes* (*If yes, please explain) Comments:</p>
<p>I certify that the above information is correct <i>[PI must type in name if in agreement]</i>:</p>	
<p>Principal Investigator Name (above)</p>	<p>Date (above)</p>

Appendix F: Sample Minutes for DSMB Meetings

SAMPLE MINUTES FOR INITIAL MEETING

Data and Safety Monitoring Board (DSMB) Committee Initial Meeting Minutes

Date:

Study: *[Study Title]*

IRB Number:

Principal Investigator:

Co-Investigators:

Attendees

DSMB Voting Members: *[Include remote attendees]*

DSMB Chairperson:

DSMB Voting Members (Absent):

DSMB Coordinators & Others (Non-voting):

Others Present: *[All other attendees' names and titles]*

Open Session of the Initial Meeting

Dr. XX, MD has agreed to be Chair of the DSMB. Members of the DSMB are introduced.

The DSMB Board members have signed the Confidentiality and Conflict of Interest statements *[Initial meeting only]*. All board members verbally stated that they do not have a conflict of interest with the study. *[Ask at the beginning of every meeting]*

Review of the DSMB charter

The DSMB charter is reviewed in detail with the responsibilities of the PI and the DSMB, structure of the meetings, and DSMB reports. If early stopping principles are included, these are reviewed in detail.

Study Protocol

1. Recruitment [*At initial meeting: describe the recruitment plan*]
2. Screening [*At initial meeting: describe the method for screening, and the inclusion and exclusion criteria.*]
3. Enrollment [*At initial meeting: describe enrollment plan including the total projected enrollment and the expected enrollment timeline.*]

Data and Safety Monitoring

1. Data and Safety Monitoring Plan [*At initial meeting: the DSMB should carefully review the DSM plan*]
2. Adverse Events [*At initial meeting: the expected adverse events should be reviewed based on the literature and DSMB expert members experience. The definitions of adverse events and serious adverse events should be agreed on by all members. The board should review how safety data will be captured and reported and whether these methods are adequate. Finally, the frequency and method of communicating adverse events should be discussed.*]
3. Unanticipated Problem Report [*At initial meeting: describe plan*]
4. Reports [*At initial meeting describe the type of reports that the DSMB will want to review. These include reported adverse events, SAEs, unanticipated problems, and the types of data reports required for the next meeting.*]

Questions from the Board

[*Insert any other Board questions/ PI answers that do not fit in the categories above*]

Closed Session of the Meeting

[*Reported separately*]

Requests and Questions from the Board [*This may also be called “Action Items”*]

The DSMB has requested the following:

Recommendations from the Board

The DSMB has recommended the following:

1. The DSMB voted for the study to [begin] or [continue without modification]
2. The DSMB agreed to meet every [xx] months
3. Report templates with data for the next meeting

These recommendations are also sent separately to the PI in a letter. [*See Appendix G, “Correspondence, Sample Letter to the Principal Investigator with DSMB Recommendations”*]

Follow-up Meeting

The DSMB will meet again in [xx] months. If there is a Serious Adverse Event, or Unanticipated Problem, the Chair may call an emergency meeting if warranted.

Respectfully submitted by [Name]

Circulated to DSMB

Audio on file:

Documents Reviewed

SAMPLE MINUTES FOR SUBSEQUENT MEETINGS

These minutes are for DSMB meetings after the initial meeting.

Data and Safety Monitoring Board (DSMB) Committee Open Meeting Minutes

Date:

Study: [Study Title]

IRB Number:

Principal Investigator:

Co-Investigators:

Attendees

DSMB Voting Members: [Include remote attendees]

DSMB Chairperson:

DSMB Voting Members (Absent):

DSMB Coordinators & Others (Non-voting):

Others Present: *[All other attendees' names and titles]*

Review of Minutes and Recommendations from the Last Meeting *[Date]*

[State that the board has voted to accept the minutes of the last meeting with or w/o changes]

Administrative Issues

All board members verbally stated that they do not have a conflict of interest with the study.
[Ask at the beginning of every meeting]

Introduction of any new participants in the meeting.

Study Updates

[By the PI]

Study Data

[Review of recruitment, enrollment, withdrawals, protocol violations, and follow-up data]

Safety Data

1. Review of individual adverse events, SAEs, and unanticipated problems *[Since the last meeting]*
2. Review of cumulative adverse events, SAEs, and unanticipated problems

Data Quality

[Missing data, data quality checks, etc.]

Questions from the Board

[Insert any other Board questions/ PI answers that do not fit in the categories above]

Closed Session of the Meeting

[Reported separately]

Requests and Questions from the Board *[This may also be called "Action Items"]*

The DSMB has requested the following:

Recommendations from the Board

The DSMB has recommended the following:

1. The DSMB voted for the study to [*begin*] or [*continue without modification*]
2. The DSMB agreed to meet next in [*xx*] months
3. Report templates with data for the next meeting. [*Any changes*]

These recommendations are developed in the open and closed meetings of the board. This section summarizes the recommendations. These recommendations are also sent separately to the PI in a letter. [*See Appendix G, “Correspondence, Sample Letter to the Principal Investigator with DSMB Recommendations”*]

Follow-up Meeting

The DSMB will meet again in [*xx*] months. If there is a Serious Adverse Event, or Unanticipated Problem, the Chair may call an emergency meeting if warranted.

Respectfully submitted by [*Name*]

Circulated to DSMB

Audio on file:

Documents Reviewed

SAMPLE MINUTES FOR CLOSED SESSION OF MEETING

Data and Safety Monitoring Board (DSMB) Committee Closed Meeting Minutes

Date:

Study: [*Study Title*]

IRB Number:

Principal Investigator:

Co-Investigators:

Attendees

DSMB Voting Members: *[Include remote attendees]*

DSMB Chairperson:

DSMB Voting Members (Absent):

DSMB Coordinators & Others (Non-voting):

Others Present: *[All other attendees' names and titles]*

Review of Minutes and Recommendations from the Last CLOSED Meeting *[Date]*

Study Data

[Review of recruitment, enrollment, withdrawals, protocol violations, and follow-up data]

Safety Data

[Review of adverse events, SAEs, unanticipated problems, study response to problems presented at the open meeting for comments]

Data Quality

[Discussion of oversight of data quality]

Questions from the Board

[Insert any other Board questions/ PI answers that do not fit in the categories above]

Requests and Questions from the Board *[This may also be called "Action Items"]*

These appear in the Open Minutes and in the Letter to the PI with DSMB Recommendations. The DSMB should state the reasons for these requests.]

The DSMB has requested the following:

Recommendations from the Board

The DSMB has recommended the following:

1. The DSMB voted for the study to *[begin]* or *[continue without modification]*
2. The DSMB agreed to meet next in *[xx]* months
3. Report templates with data for the next meeting. *[Any changes]*

These recommendations are also sent separately to the PI in a letter. [*See Appendix G, “Correspondence, Sample Letter to the Principal Investigator with DSMB Recommendations”*]

Follow-up Meeting

The DSMB will meet again in [xx] months. If there is a Serious Adverse Event, or Unanticipated Problem, the Chair may call an emergency meeting if warranted.

[At the final DSMB meeting, the board votes to close the DSMB. This is stated in the minutes along with the reason for closing the DSMB.]

[At the final DSMB meeting, the Chairperson documents that all DSMB members are requested to destroy all data and correspondence from the study and DSMB meetings. The Chairperson will keep a copy and send one to the PI which should be retained based on institutional and sponsor guidelines.]

Respectfully submitted by [Name]

Circulated to DSMB

Audio on file:

Documents Reviewed

Appendix G: Correspondence

SAMPLE LETTER TO THE PRINCIPAL INVESTIGATOR WITH DSMB RECOMMENDATIONS

This letter is sent to the PI from the DSMB Chair after each meeting outlining the determinations of the DSMB and giving reasons for any suggestions and/or modifications to the study plan or enrollment.

DSMB Report and Recommendations

Study: [*Study Title*]

To: [*Principal Investigator*]

CC: [*If any*]

Meeting Date:

Attendees: [*List DSMB committee voting members present*]

Recommendations:

- Continue the trial as planned
- Continue the trial with suggestions
- Continue the trial with mandatory changes
- Suspend further enrollment in the trial pending analysis of events and/or data
- Terminate the trial
- Other (see Comments)

Comments:

[Specific comments from the meeting. Rationale for making suggestions and modifications.]

Name and Signature of Chair:

Date:

SAMPLE LETTER TO THE INSTITUTIONAL REVIEW BOARD

This letter is required annually by the IRB when the study comes up for recertification. It documents for the IRB that the DSMB has met to review the study.

[Letterhead]

[Date]

[Principal Investigator]

[PI Address]

RE: IRB identifier (login) number

Study: *[Study Title]*

Dear *[PI Name]*:

The *[DSMB Name]* met on the following occasions during the last year to discuss the *[Study Name]*: *[dates]*. The study opened to enrollment on *[date]*.

The DSMB reviewed enrollment, follow-up, and safety data. The DSMB discussed the reported serious adverse events to participants: *[ID-1, ID-2, etc.]*.

While the *[DSMB Name]* had no concerns about the safety of subjects enrolled in this study, the committee made several recommendations which were conveyed to you in letters on *[Dates of correspondence]*

Sincerely,

[Chairperson Name]

Chairperson, *[DSMB Name]*

Appendix H: Sample Safety Officer Documents

SAMPLE SAFETY OFFICER CHARTER

The templates for Safety Officers are similar to those for a DSMB but may include specifics of the study protocol and how periodic review will be structured.

TITLE PAGE

Safety Officer Charter

[Study Title]

[Date of Document]

Version *[x.x]*

[IRB number]

TABLE OF CONTENTS

[Insert page numbers for all sections]

Table of Contents

1. Introduction
2. Trial Overview and Study Design
3. Responsibilities and Functions of the Safety Officer
4. Conduct of Safety Officer Meetings

5. Safety Officer Reports
6. Amendments to the Safety Officer Charter

SAFETY OFFICER CHARTER

[*Study Title*]

[*PI Name*], Principal Investigator

Study Sponsored by [*Name of sponsor*]

[*IRB number*]

[*Date of Document*]

Version [*x.x*]

Introduction

The purpose of this charter is to define the responsibilities of the Safety Officer, describe the purpose, frequency, and structure of meetings, define the data to be reviewed, and outline the content of the Safety Officer reports.

The [*insert name of trial*] study is a [*list characteristics; e.g., randomized, multicenter, placebo-controlled*] [*insert appropriate drug phase or device trial*]. The study is sponsored by the [*insert name of sponsor (and funding agency if different from sponsor)*] through a grant to the [*name of PI or consortium*]. The Principal Investigators for the trial are located at the [*list location*]. The Safety Officer provides independent safety review and trial guidance during the course of the ongoing trial.

The Safety Officer periodically reviews [*insert data reviewed by Safety Officer, e.g., safety data, results across treatment groups*] and judges whether the overall safety and feasibility of the trial remains acceptable. The Safety Officer has access to [*insert description of data*]; however, no formal analyses of efficacy data are planned. Any recommendations to alter study conduct will be based on safety not efficacy, so monitoring of the study will not affect the statistical operating characteristics of the final efficacy analysis. The criteria for assessing the safety data are outlined in the [*insert name of trial*] Data and Safety Monitoring Plan attached to this document (Attachment 2).

The Safety Officer will specifically review adverse event data as well as summary reports of all serious adverse events (SAEs) and available lab data, and may review individual cases if deemed appropriate or necessary to determine if a safety concern is emerging. The [*insert sponsor, steering committee, or investigators*] may also make recommendations to the Safety

Officer for additional data review should a concern arise. The Safety Officer may suggest appropriate courses of action to address general study safety issues which may arise. If warranted, the Safety Officer may recommend at any time that the entire protocol be suspended temporarily or terminated permanently. These recommendations, containing fully blinded information, will be directed to the investigator, the Institutional Review Board(s), and [*insert, management organization, sponsor, steering committee, or other overseeing entity*] which has the responsibility to accept, reject or modify the Safety Officer's recommendations.

Trial Overview and Study Design

[*This section should be a brief summary of the study, including name, sponsor, study design, hypotheses, specific aims, phase, number of participants, number of sites, description of the drug or device under study, study treatments and allocation, follow-up schedule, primary outcomes, sample size.*]

Responsibilities and Functions of the Safety Officer

Initially, the Safety Officer is responsible for:

1. Reviewing the initial protocol and recommending one of the following actions to the investigator:
 - a. The Safety Officer is in agreement with and supports the initial protocol.
 - b. The Safety Officer requests the following alterations to the protocol:
[*insert any requested modifications*].
2. Defining, with input from the Principal Investigator and [*insert names of any other groups or individuals*], safety and related parameters to be monitored, frequency of monitoring reviews and interim safety analyses, methods for review, statistical methodologies, and establishing criteria for making recommendations to [*insert name of group or individual, e.g., Principal investigator*].
3. Finalizing this Safety Officer charter with approval of the [*insert name of group or individuals*].

At periodic intervals (to be determined), the Safety Officer:

1. Reviews data generated by the study and study safety events on a periodic basis. The study biostatistician will provide interpretation of interim safety analyses per the attached Data and Safety Monitoring Plan (Attachment 2).

2. Evaluates the progress of the trial, including periodic assessments of [*insert assessments e.g., recruitment, screen failures, dropouts etc.*].
3. Reports on the safety and progress of the study.
4. Determines whether the overall integrity and conduct of the study remain acceptable.
5. Reviews any protocol amendments and makes recommendations with regard to changes.
6. Considers the impact of new or relevant information such as scientific or therapeutic developments that may have an impact on the safety or scientific integrity of the study.
7. Recommends one of the following actions to the [*insert group or individual responsible*]:
 - a. Continue the study according to the protocol and any related amendments.
 - b. Modify the study protocol. Modifications may include, but are not limited to [*changes in inclusion/exclusion criteria, frequency of visits of safety monitoring, alterations in study procedures, changes in duration of observation, and follow up*].
 - c. Discontinue the study (with provisions for orderly discontinuation in accord with good medical practice).

Conduct of Safety Officer Meetings

1. **Scheduled meetings:** An initial meeting with the Safety Officer and the investigator will be held before any subject enrollment in the study occurs in order for the Safety Officer to establish a meeting schedule, review the study protocol, and study/participant termination guidelines. The Safety Officer will meet every [*insert number*] months to review the study progress OR after the first [*xx*] number of participants have been enrolled, and then after the enrollment of every [*insert number*] additional participants.
2. **Meeting format:** The Safety Officer meetings will generally be conducted [*insert format, e.g., the Safety Officer alone will review the study progress and prepare all reports; an open meeting will be held to review the study with Investigators, Sponsor, only the Safety Officer, others; a closed session with possible discussion of blinded data will be held with the Sponsor, only the Safety Officer, others*]

3. Data to be Reviewed by the Safety Officer:

- a. Adverse events
- b. Recruitment strategy
- c. Recruitment and enrollment statistics
- d. Gender and ethnicity enrollment (if required by sponsor)
- e. Disqualified and excluded individuals
- f. Study progress timeline
- g. Procedures for data quality control and adherence monitoring
- h. Study progress by participant
 - i. The data will be *[insert whether the data is blinded, coded i.e. data sorted by Arm but without identifying the specific arms, unblinded, or both, e.g., blinded to all but coded to the Safety Officer only]*
- i. Summary Statistics
 - i. The data will be *[insert whether the data is blinded, coded i.e. data sorted by Arm but without identifying the specific arms, unblinded, or both, e.g., blinded to all but coded to the Safety Officer only]*
- j. Safety data
 - i. *[List tests, procedures, etc.]*
 - ii. The data will be *[insert whether the data is blinded, coded i.e. data sorted by Arm but without identifying the specific arms, unblinded, or both, e.g., blinded to all but coded to the Safety Officer only]*
- k. Efficacy data
 - i. *[List tests, procedures, etc.]*
 - ii. The data will be *[insert whether the data is blinded, coded i.e. data sorted by Arm but without identifying the specific arms, unblinded, or both, e.g., blinded to all but coded to the Safety Officer only]*
- l. Newly published relevant data *[describe who is responsible]*
- m. *[Other information]*

- i. The data will be *[insert whether the data is blinded, coded i.e. data sorted by Arm but without identifying the specific arms, unblinded, or both, e.g., blinded to all but coded to the Safety Officer only]*
- ii. The data to be reviewed will be “frozen” approximately [xx] weeks before the Safety Officer review. The data will be sent to the Safety Officer approximately *[insert number]*days before the Safety Officer review.

4. Study stopping criteria defined by the Safety Officer and Investigators

- a. Feasibility (accrual and retention) *[describe criteria]*
- b. Safety and toxicity
 - i. *[List anticipated adverse events and estimated frequency]*
 - ii. *[Threshold for stopping study based on above anticipated adverse events]*
 - iii. *[Threshold for stopping based on unanticipated adverse events]*
- c. Efficacy *[This is rarely included in the role of the Safety Officer due to the size and structure of trials reviewed]*
 - i. *[List primary outcome and anticipated treatment effect]*
 - ii. *[Threshold for stopping study based on above efficacy outcome]*

Reports

The meeting minutes will be prepared by *[Safety Officer only; the Safety Officer for data review, other, for open session and other discussions]*.

The minutes from the open sessions will be sent to *[list all entities, e.g., the IRB, etc.]*.

The minutes from the closed session will be sent to *[list all entities, e.g., the IRB, etc.]*.

The Safety Officer report will include a brief evaluation, including recommendations, by the Safety Officer. A Safety Officer Report template is provided with this charter to provide an example of the report organization and examples of table formats. The contents of the report and data tables may evolve with the study.

Amendments to the Safety Officer Charter

This Safety Officer charter can be amended as needed during the course of this study. Infor-

mation to be included as amendments will be any [*insert description of types of modifications*]. All amendments will be documents with [*insert version numbers, dates, etc.*] and will be recorded in the minutes of the Safety Officer meeting. Each revision will be reviewed and agreed upon by the [*sponsor, investigator, etc.*] and the Safety Officer. All amended Safety Officer charters will also be sent to the IRB for review. All versions of the charter will be stored in [*insert where files will be stored*].

Attachments

Attachment 1: Safety Officer, Investigators, Key Personnel Contact Information

Attachment 2: Data and Safety Monitoring Plan

Attachment 3: Safety Officer Report Template

ATTACHMENT 1: CONTACT INFORMATION TEMPLATE

Safety Officer

Name, Degree

Title

Institution

Address

Phone:

Fax:

Email:

Past research and/or Safety Officer experience:

Other relevant background:

Potential Conflicts of Interest:

Principal Investigators and Key Personnel

Name, Degree

Principal Investigator

Title

Institution

Address

Phone:

Fax:

Email:

Name, Degree

Co-investigator

Title

Institution

Address

Phone:

Fax:

Email:

Name, Degree

Co-investigator (Biostatistician)

Title

Institution

Address

Phone:

Fax:

Email:

Name, Degree

Trial Coordinator

Institution

Address

Phone:

Fax:

Email:

ATTACHMENT 2: SAMPLE DATA AND SAFETY MONITORING PLAN

Safety Officer Responsibilities

The Safety Officer will be responsible for the following: (1) monitor recruitment, enrollment, and retention of study participants; (2) formulate criteria for modifying or discontinuing drug treatment of individual subjects; (3) formulate trigger criteria for possible discontinuation of the study; and (4) review serious adverse events (SAEs). The Safety Officer was selected to provide expertise in [*list disciplines*] (with clinical trials experience).

The Safety Officer is charged with assessing the progress and safety of the study to assure continued feasibility and the safety of study participants. The Safety Officer will: (1) review

the protocol as funded and make suggestions for any changes (especially safety related); (2) assess the agreed upon interim data reports; (3) review study progress and data quality; (4) determine formatting for data reports; (5) review endpoints for safety and efficacy; (6) submit written reports and recommendations to the *[insert responsible individual or group]*; and (7) add to or modify this list of objectives. Apart from these responsibilities the Safety Officer will have no other involvement with the study.

Because of the relatively small number of subjects (N=), and short duration of the intervention, the Safety Officer will monitor for safety, but usually does not monitor for efficacy or futility. In the event the Safety Officer determines that the study or an arm of a study should be stopped for reasons of safety, this will be communicated to *[insert name of responsible individual or group]*; the PI will then inform *[list responsible individual or group, e.g., IRB, NIH, FDA]* as appropriate.

Meetings of the Safety Officer will be held *[insert frequency of meetings, e.g., every 6 months, after 25, 50, 75% of patients have been recruited etc.]*. The following people will attend meetings: *[list of people and affiliation, e.g., PI's, sponsors, biostatisticians, etc.]*. The Safety Officer will present the safety report to the meeting attendees after which there will be discussion to clarify any questions/concerns. All data will be presented in a blinded fashion using codes for the different treatment groups. After the meeting, the Safety Officer will prepare a summary cover letter for submission to the investigator, the Institutional Review Board, and any other regulatory entities previously identified. The letter will provide comments on the report, describe study safety, progress and performance, discuss any concerns or suggestions for modification, and provide recommendations as to the safe continuation or early termination of the study.

Defining and Reporting of SAEs

The Safety Officer will follow the *[insert appropriate guidelines]* guidelines that require investigators to promptly notify *[insert groups notified]* (within *[insert #]* days of the occurrence) when unexpected adverse events occur. These are events that are not listed in the consent form, and are possibly related to the intervention, or are listed but occur more frequently or are more severe than anticipated. Serious adverse events are defined to include death, life threatening illness, hospitalization or prolongation of hospitalization, congenital anomaly/birth defects, and persistent/significant disability. *[Insert responsible group]* requires that any adverse event that is unexpected and related or possibly related to the drug, biologic device or other research intervention be reported. Risks that are described in the protocol and consent form do not have to be reported as SAEs, unless the expected serious adverse event occurs more frequently or is more serious than expected. One exception to this rule is in the case of a death. All deaths must be reported, whether or not the death was related to the research.

[The following criteria need to be defined by the Safety Officer]

In addition to following the requirements above, we will define study-specific serious adverse events as:

1. Reportable Adverse Events
2. Serious Adverse events

Stopping Criteria

The Safety Officer will review data related to individual stopping criteria as detailed in the study protocol. The Safety Officer may recommend modifications to individual stopping rules if additional safety concerns arise during from their continuing reviews of the study data.

The Safety Officer may recommend stopping the study for the following reasons [*keep all that apply*]:

1. The data show a significantly increased risk of serious adverse effects in one of the treatment groups.
2. If it becomes clear that successful completion of the study is not feasible (e.g., there is an excess of patient dropout, missing data, lack of recruitment etc).

Safety Monitoring Plan

The monitoring of safety outcomes will utilize several approaches.

Verification of Study Eligibility

An enrollment checklist will be used to verify that volunteers meet study criteria. Values for some of these parameters will be used to evaluate changes during the study intervention.

Safety Monitoring Form

Participants will have safety evaluations in months of the intervention. The results of these evaluations will be recorded on the safety monitoring form. If any of the triggers for serious adverse event is reached, a repeat test will be performed. If the trigger is confirmed, an serious adverse event report will be generated.

Complaint/Adverse Event Form

This form will be completed for any complaints/adverse events that: (1) occur during a study procedure; (2) are found at a follow-up visit; or (3) are participant-initiated. An serious adverse event report will be generated if the criteria are met (i.e. serious, unexpected, and possibly study-related).

ATTACHMENT 3: ADDITIONAL REPORT TEMPLATES

The following templates are available from NIH Institutes. They are meant as a guide and do not constitute a set of requirements.

National Institute on Aging (NIA). Data and safety monitoring. Bethesda, MD: National Institutes of Health. Available from: <https://www.nia.nih.gov/research/dgcg/clinical-research-study-investigators-toolbox/data-and-safety-monitoring>.

National Institute of Allergy and Infectious Diseases (NIAID). Study progress, data, and safety monitoring plans. Bethesda, MD: National Institute of Allergy and Infectious Diseases; 2016 Dec 21. 13 p. Report No.: DRAFT v 3.17. Available from: <https://www.niaid.nih.gov/sites/default/files/SPDSMPPolicy.pdf>.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Clinical study tools and templates. Bethesda, MD: National Institutes of Health; [updated Mar 7, 2018]. Available from: <https://www.niams.nih.gov/grants-funding/conducting-clinical-research/trial-policies-guidelines-templates/data-safety-monitoring-guidelines-policies/clinical-study-templates-forms>.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Data & safety monitoring plans. Bethesda, MD: National Institutes of Health; [cited 2017 Sep 15]. Available from: <https://www.niddk.nih.gov/research-funding/human-subjects-research/policies-clinical-researchers/data-safety-monitoring-plans>.

SAMPLE CONFLICT OF INTEREST AND CONFIDENTIALITY FORMS

These agreements come from the contract a DSMB member signs with the sponsor or academic entity on joining a DSMB. They can be used for a Safety Officer.

SAMPLE CONFLICT OF INTEREST FORM

[Add any institutionally required COI declaration]

The role of a Safety Officer is restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DSMB.

The Safety Officer should not own stock in the companies having products being evaluated by the clinical trial. The DSMB members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organization for the trial (if any), or with other sponsors having products that are being evaluated in the trial. The DSMB will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The Safety Officer will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any Safety Officer who develops significant conflicts of interest during the course of the trial should resign from the role.

The role of a Safety Officer is intended to be for the duration of the clinical trial. If an individual resigns the role during the course of the trial, the sponsor, in consultation with the steering committee and/or investigators will promptly appoint a replacement.

SAMPLE CONFIDENTIAL INFORMATION FORM

[Add any institutionally required COI declaration]

During the conduct of the services, it will be for the study sponsor to disclose proprietary, trade secret, drug and trial information, and/or other confidential information (hereinafter, "Confidential Information") to the DSMB consultant/Safety Officer. All such Confidential Information shall remain the property of the sponsor disclosing same. The consultant agrees that any such Confidential Information disclosed to him or her, shall be used only in connection with the legitimate purposes of this Agreement, shall be disclosed only to those who have a need to know it and are obligated to keep same in confidence, and shall be safeguarded with reasonable care. The consultant acknowledges that all service materials including Protocol amendments, Investigator's Brochure and other FDA submissions are the sponsor's Confidential Information. The consultant acknowledges that all trial data and data summaries are the Confidential Information of the sponsor.

With the exception of the aforementioned Confidential Information, the foregoing confidentiality obligation shall not apply to Confidential Information which:

1. Has been in or subsequently enters the public domain through no fault of the consultant
2. Prior to disclosure hereunder is within the legitimate possession of the consultant without obligation of confidentiality, as documented by written evidence
3. Subsequent to disclosure hereunder is lawfully received from a third party having rights therein without restriction of the third party's right to disseminate the information and without notice of any restriction against its further disclosure
4. Is disclosed with the prior written consent of the other party
5. Is obligated to be produced under order of a court or governmental authority of competent jurisdiction. In such case, however, the party legally compelled to disclose Confidential Information of the other party shall provide prompt notice thereof to such other party so that it may seek, in its sole discretion, a protective order or other appropriate remedy. In the event that such protective order or other remedy is not obtained, or such other party waives compliance with the provisions hereof, the party legally compelled to disclose shall furnish only that portion of the Confidential Information which is legally required

The terms of this Agreement shall not be disclosed to any third party, except as required by law or with the permission of the other party. The obligations hereunder shall remain in effect for a period of seven (7) years after the termination of this Agreement and indefinitely with respect to any individually identifiable health information.

Additional Resources

NATIONAL INSTITUTES OF HEALTH

GENERAL NIH GUIDELINES AND POLICIES

National Institutes of Health (NIH). NIH policy for data and safety monitoring. Bethesda, MD: National Institutes of Health; 1998 Jun 10. Report No.: NOT-98-084. Available from: <https://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

NIH. Guidance on reporting adverse events to Institutional Review Boards for NIH-supported multicenter clinical trials. Bethesda, MD: National Institutes of Health; 1999 Jun 11. Report No.: NOT-99-107. Available from: <https://grants.nih.gov/grants/guide/notice-files/not99-107.html>.

NIH. Further guidance on a data and safety monitoring for phase I and phase II trials. Bethesda, MD: National Institutes of Health; 2000 Jun 5. Report No.: NOT-OD-00-038. Available from: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.

Office of Inspector General. Data and Safety Monitoring Boards in NIH clinical trials: meeting guidance, but facing some issues. Washington DC: Department of Health and Human Services; Jun 2013. Report No.: OEI-12-11-00070. Available from: <https://oig.hhs.gov/oei/reports/oei-12-11-00070.pdf>.

INSTITUTE-SPECIFIC GUIDELINES AND POLICIES

The following NIH Institutes have specific DSM guidelines:

National Cancer Institute (NCI): <http://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf>

National Center for Complementary and Integrative Health (NCCIH): <http://nccih.nih.gov/research/policies/datasafety>

National Eye Institute (NEI): <https://nei.nih.gov/funding/policy/policy6>

National Heart, Lung, and Blood Institute (NHLBI): <http://www.nhlbi.nih.gov/funding/policies/dsmpolicy.htm>

National Institute on Aging (NIA): <http://www.nia.nih.gov/research/dea/implementation-policies-human-intervention-studies>

National Institute on Alcohol Abuse and Alcoholism (NIAAA): <http://www.niaaa.nih.gov/ResearchInformation/ExtramuralResearch/ResourcesAppGrantees/guidelines.htm>

National Institute on Allergy and Infectious Diseases (NIAID): <https://www.niaid.nih.gov/grants-contracts/human-subjects>

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): <https://www.niams.nih.gov/grants-funding/conducting-clinical-research/data-safety-guidelines-policies>

National Institute of Child Health and Human Development (NICHD): <http://www.nidcd.nih.gov/research/clinicalstudies/Information-for-Researchers-and-Health-Professionals/Pages/NIDCD-Guidelines-for-Data-and-Safety-Monitoring-of-Clinical-Trials.aspx>

National Institute on Deafness and Other Communication Disorders (NIDCD): <https://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DataandSafetyMonitoring.htm>

National Institute of Dental and Craniofacial Research (NIDCR): <http://www.nidcr.nih.gov/GrantsAndFunding/PoliciesandGuidance/ClinicalResearch/DataandSafetyMonitoring.htm>

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): <http://www.niddk.nih.gov/research-funding/process/human-subjects-research/policies-for-clinical-researchers/data-safety-monitoring-plans/Pages/data-and-safety-monitoring-plans.aspx>

National Institute on Drug Abuse (NIDA): <http://www.drugabuse.gov/Funding/DSMB-SOP.html>

National Institute of Environmental Health Sciences (NIEHS): <https://www.niehs.nih.gov/research/clinical/patientprotections/dsmb/index.cfm>

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