

Data and Safety Monitoring Board Charter

<Insert title of trial>

<Insert date of document>

Version <insert #>

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Table of Contents

Data Safety Monitoring Board (DSMB) Overview	<insert page #>
Introduction	<insert page #>
Study Overview/Summary	<insert page #>
Roles and Responsibilities	<insert page #>
DSMB Membership	<insert page #>
DSMB Meetings	<insert page #>
Study Review Criteria/Stopping Rules and Guidelines	<insert page #>
DSMB Reports	<insert page #>
DSMB Closeout	<insert page #>
Confidentiality	<insert page #>
Amendments to the DSMB Charter	<insert page #>
Archiving of DSMB Activities and Related Documents	<insert page #>

Data Safety Monitoring Board (DSMB) Overview

Trial Description and Study Design

- Trial name: <insert title of trial / trial identifier>
- Trial sponsor: <insert name of sponsor (and funding agency if different from sponsor)>
- Trial design: <list characteristics; e.g., multi-center, randomized, placebo-controlled, parallel group comparison of xx versus yy>
- Phase: <insert appropriate phase for device trial (e.g., feasibility, first-in-man, pilot, pivotal) or drug phase I/II/III/IV>
- Number of patients: <insert # of patients>
- Number of sites: <insert # of sites>

DSMB Description

- This DSMB will be coordinated by <insert name of DSMB management organization or sponsor>.
- This DSMB will be independent of <sponsor> <trial coordination center>, <data coordination center(s)>, regulatory agencies, IRB/EC, and investigators.
- This charter will be approved by its DSMB members as attested to by signature of the chairperson.

DSMB Membership

- Members will disclose conflicts of interest and will be cleared of significant conflicts of interest and potential conflicts of interest in accordance with provisions in this charter.
- DSMB members will sign confidentiality agreements covering DSMB activities.
- Composition of membership will be <list minimum requirements; e.g., at least 2 physicians with expertise in the area pertaining to the study and at least 1 biostatistician>.
- Qualifications of membership will be <list various physician specialties, other qualifications if applicable, biostatistician>.
- Remuneration will be provided by the <study sponsor or funding agent> in accordance with standard procedures of the DSMB.

Reporting

- Data reviewed by the DSMB will be provided by <insert group or individual statistician(s) responsible for these functions>.
- Issues and recommendations identified by the DSMB will be provided to <list organizations and/or persons> by the DSMB chairperson in accordance with this charter.
- Details of closed session deliberations (e.g., minutes) will be considered privileged and not subject to disclosure except as required by law.

Introduction

The purpose of this charter is to define the roles and responsibilities of the Data Safety Monitoring Board (DSMB), delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.

The DSMB will function in accordance with the principles of the following documents: <give document title(s) and url(s); e.g., ICH GCP and/or ISO 14155 and/or FDA document "Guidance for Clinical Trial Sponsors: On the Establishment and Operation of Clinical Trial Data Monitoring Committees">.

Study Overview/Summary

<This section includes a brief summary of the study, including name, sponsor, study design, phase, number of patients, number of sites, a description of the device, biologic or drug under study, follow-up schedule, and hypothesis endpoints.> <The study protocol is attached.>

Roles and Responsibilities

DSMB Roles and Responsibilities

This DSMB will

- Meet periodically (see DSMB Meetings) to review aggregate and individual subject data related to safety, data integrity and overall conduct of the trial.
- <Review specific interim analyses for efficacy (see Study Review Criteria/Stopping Rules and Guidelines).>
- Provide recommendations to continue or terminate the trial depending upon these analyses.
- Communicate other recommendations or concerns as appropriate.
- Operate according to the procedures described in this charter and all procedures of the DSMB.
- Follow conflict of interest guidelines as detailed below (see DSMB Membership).
- Comply with confidentiality procedures as described below (see Confidentiality).
- Maintain documentation and records of all activities as described below (see DSMB Meetings, DSMB Reports).

Sponsor (or Designees) Roles and Responsibilities

The sponsor will directly or through delegation:

- Assure the proper conduct of the study.
- Assure collection of accurate and timely data (monitoring and data management).
- Compile and report SAEs to the DSMB.
- Promptly report potential safety concern(s) to the DSMB.
- Prepare summary reports of relevant data for the DSMB. (This may include analyses not otherwise outlined in this charter based upon findings.)
- Provide an independent facilitator for presentation of results during DSMB meetings if requested by the DSMB.

- Communicate with regulatory authorities, IRB/EC, and investigators, in a manner that maintains integrity (e.g., blinding) of the data, as necessary. (This communication is not the responsibility of the DSMB.)
- Provide funding for the study and DSMB.

The sponsor has delegated the following responsibilities to the respective institutions:

- <Identify participatory organizations and their roles (e.g., monitoring, data management, Serious Adverse Event (SAE) management, data reporting, CEC adjudication, expedited adverse event reporting, funding through a funding agency, as applicable).>

DSMB Membership

The DSMB will consist of <insert # of members> members, of which <insert # of members> have had substantive previous DSMB experience as listed in Appendix <insert appendix #>. The chairperson has previously served on a DSMB for <insert # of studies> studies and has <insert number of years> cumulative years of service on DSMBs. The DSMB members have been selected by the <DSMB management organization or sponsor> in consultation with the <trial sponsor and investigators>.

As characteristic qualifications, members will:

- Work professionally and meet qualifications for their respective professions as <list membership composition (e.g., specialty physicians, statistician, ethicist, epidemiologist, toxicologist)>.
- Comply with accepted practices of their respective professions.
- Comply with the conflict of interest policies specified by the standard operating procedures (SOPs) of the < DSMB management organization or sponsor> to ensure that members do not have serious scientific, financial, personal, or other conflicts of interest related to the conduct, outcome, or impact of the study according to the guidelines specified below (e.g., engaged in any simultaneously occurring competitive trials in any role that could pose a conflict of interest for this study). See conflict of interest statement below.
- Be independent from the sponsor, IRB/EC, regulatory agencies, principal investigator, co-principal or sub-principal investigator, site investigator, site sub-investigator, steering committee membership, advisory board membership, CEC membership, clinical care of the study subjects, or any other capacity related to trial operations.
- Not be on the list of Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) (<http://www.fda.gov/foi/nidpoe/default.html>) and/or debarred list of investigators (http://www.fda.gov/ora/compliance_ref/debar).

Although each DSMB member will be expected to serve for the duration of the trial, in the unlikely event that a member is unable to continue participation, the reason will be documented and a replacement will be selected by <the DSMB management organization or sponsor>.

The DSMB will follow conflict of interest guidelines referenced by <insert document name, e.g., Department of Health and Human Services, Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject

Protection (<http://www.hhs.gov/ohrp/humansubjects/finreltnn/fguid.pdf>)>¹. DSMB members will sign a non-conflict of interest statement in regard to this study which will be on file with <list DSMB management organization or sponsor>. As determined by <list DSMB management organization or sponsor>, conflicts of interest and/or potential conflicts of interest (as determined by SOPs) will be reduced to the greatest extent that is consistent with assembling a highly competent DSMB. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DSMB chairperson with input from other DSMB members <and DSMB management organization or sponsor> as necessary.

DSMB Meetings

Projected Schedule of Meetings

An initial meeting of the DSMB will be held prior to any subject enrollment in the study in order for the members to review the charter, to form an understanding of the protocol and definitions being used, to establish a meeting schedule, and to review the study modification and/or termination guidelines. Subsequent interim and final review meetings will be held to review and discuss interim and final study data according to the schedule as described in the table below.

<i>Timeline</i>	<i>Data Review by</i>	<i>Type of Data</i>
<list monthly, quarterly, etc.>	<list DSMB chairperson, statistician, and/or physician expert>	<insert adverse events listing, protocol deviations listing, enrollment summary and tables for overall primary and secondary endpoints available>.
When enrollment is completed on first <insert #> patients	Entire DSMB	Same as above, coded by treatment arm
When follow-up is completed on first <insert #> patients	Entire DSMB	Same as above, coded by treatment arm
Upon completion or termination of study	Entire DSMB	Same as above, coded by treatment arm

Meeting Format

DSMB meetings will generally be conducted by <indicate format (e.g., teleconference, face-to-face meeting)> and coordinated by the <DSMB management organization or sponsor>. A quorum, defined as <enter definition of quorum, including whether or not chairperson must be present and whether or not statistician must be present> will be required to hold a DSMB meeting. Critical decisions of the DSMB should be made by unanimous vote. However, if this is not possible, majority vote will decide.

¹ Other reference documents include EMEA Procedure on the Handling of Conflicts of Interests for EMEA Scientific Committees Members and EMEA Experts (<http://www.emea.eu.int/pdfs/general/direct/conflicts/ProcedureHandlingofConflictsOfInterests.pdf>)

A facilitator (e.g., statistician responsible for the report preparation) will attend the DSMB meetings as a non-voting member in order to facilitate data presentation and follow-up reporting, unless deemed not necessary by the DSMB. The meetings will include both open and closed sessions.

Open and Closed Sessions

The open session may be attended by representatives of the sponsor and study investigators. Data presented in the open session may include enrollment data, individual adverse event data, baseline characteristics, overall data accuracy and compliance data or issues, and other administrative data. Minutes of the open session will be recorded by <insert example of responsible individual or group providing>. Minutes will be finalized upon signature of the chairperson and maintained by the <DSMB management organization or sponsor> in accordance with applicable statutory regulation.

The closed session will be restricted to the DSMB members, a facilitator, and a recorder. Data which may compromise the integrity of the study (e.g., comparative data) will be analyzed and discussed only in the closed session. The minutes of the closed session will be recorded by <DSMB designee>. Minutes from the closed session will be recorded separately from the minutes of the open session and stored securely by the <DSMB management organization or sponsor>. Closed session minutes, finalized by signature of the chairperson, will be maintained in confidence and retained until discarded in accordance with applicable statutory regulation.

Following each meeting, a report separate from the minutes of the open and closed sessions will be sent to the sponsor describing the DSMB recommendations and rationale for such (see DSMB Communication of Findings and Recommendations).

Study Review Criteria/Stopping Rules and Guidelines

Guidance for the conduct of safety <and effectiveness> analyses, and guidelines / stopping rules <and adaptive protocol modification> will be established prior to the DSMB's first evaluation of data.

Safety Analyses

The primary safety endpoint is <insert safety endpoint>. <In addition to the primary safety endpoint, the DSMB will monitor the following adverse events:<list events here or specify types of adverse events or serious adverse events>.

Stopping Guidelines / Stopping Rules: Safety

The DSMB may recommend termination or modification of the study if any of the following predefined conditions are met: <describe basis for early termination for

safety, including applicable statistical methodology>. In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the primary endpoint, device failures resulting in adverse events, or unexpected SAEs.

Effectiveness Analyses

The primary effectiveness endpoint is <insert effectiveness endpoint>. <If applicable, include a comment such as "There is no plan <to perform interim effectiveness analyses> <to terminate the study for early evidence of effectiveness>."> <The DSMB will monitor effectiveness outcomes to determine relative risk/benefit, futility, or for early termination due to overwhelming effectiveness.> <<As defined in the study protocol,> the DSMB will review the interim analyses of effectiveness measures after enrollment and follow-up of approximately <X, Y, and Z> patients. Statistical assessment will be based on <insert method to control alpha risk and details necessary to perform assessment>. <(see table below) suggest a table and/or figure showing stopping boundaries for proposed statistical method>

Adaptive Protocol Modification

<Describe any prospectively determined accommodation for protocol modification or indicate no modifications are planned.> <If no modifications are planned, include a comment such as: "There is no planned sample size re-estimation; however if the DSMB reveals a need, the sample size calculation can be re-evaluated."> <If modifications are planned, include a comment such as: "The DSMB will review the primary safety and effectiveness hypotheses in order to assess the need for a modification to the trial design. The planned modification is <sample size re-estimation, a change in endpoints, a change in hypothesis (from superiority to non-inferiority, for example) or modifications to inclusion/exclusion criteria> utilizing <insert details of planned method>".>

Consideration of External Data

The DSMB will also consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the patients and design of the current study.

DSMB Reports

Monitoring for Safety

The primary charge of the DSMB is to monitor the study for patient safety. Formal DSMB safety reviews will occur as specified above (see Study Review Criteria/Stopping Rules and Guidelines). <It is useful to refer here to table shells or a listing of tables and figures to indicate specific data tables or figures that will be presented.>

Monitoring for Effectiveness

The DSMB <will or will not> monitor effectiveness outcomes to determine relative risk/benefit, futility, or for early termination due to overwhelming effectiveness. DSMB effectiveness reports will occur as specified above (see Study Review

Criteria/Stopping Rules and Guidelines <and sample tables # x, y and z>).<If there is no proposed plan to terminate the study for early evidence of effectiveness it should be stated here.>

Monitoring for Study Conduct

The DSMB <will or will not> review data related to study conduct. Data to be reviewed and listed in the DSMB reports includes: <enrollment rates over time, time from last patient enrolled to date of report (indication of delay between treatment or follow-up and reporting), summary of protocol violations, completeness of treatment and follow-up visit data, and follow-up duration for the population included in the report>.

Data Flow for Adverse Events

The DSMB will carefully monitor adverse events periodically throughout the duration of the study. This process will be dynamic to include <list specified time (e.g., monthly, quarterly)> reviews of all reported SAEs by <specify DSMB chairperson or statistician or entire DSMB>. The investigators will be expected to report Serious Adverse Events (SAEs) to sponsor <or designee> within <24 hours> of knowledge of the event. <Sponsor or designee> will then report it to the DSMB within <insert #> day(s).

Clinical Events Committee

<All clinical endpoints in this trial will be referred to the Clinical Events Committee (CEC) for adjudication. The DSMB reports will include adjudicated data whenever possible. If time does not allow for CEC review prior to a DSMB meeting, unadjudicated data will be presented, noting such to the Board. Should the DSMB need additional information or rationale for CEC decisions, the chairperson will notify the {DSMB management group or sponsor}>.

<If a Clinical Events Committee will not be utilized for endpoint adjudication or a delay is expected to limit the inclusion in DSMB reports, include a comment such as: "A Clinical Events Committee will not be utilized for this clinical study or will not be included in DSMB reports.">

Preparation of Reports to the DSMB

Formal DSMB reviews will include data as specified in Appendix <insert appendix # (this may include table shells or tables and figures listing)>. The <data management organization, independent statistician, or sponsor> will prepare and distribute reports to the DSMB. <Add wording here if there are separate safety and effectiveness reports, and/or pooled analyses.> The reports will be delivered by <list express mail service, electronically> approximately <insert #> days prior to the date of each DSMB meeting.

In order to provide the maximum amount of information to the DSMB, the analyses will employ the most recent data (recognizing limitations thereof) available at the time of the analysis. Requests for additional data by the DSMB members will be made to the DSMB chairperson or his or her designee, who will be responsible for communicating the request with the <data management organization or sponsor>.

The DSMB will review the data <coded by treatment arm> and discuss the analyses during the closed portion of the scheduled meeting. Should the committee find it necessary to unblind the study, this will be noted in the DSMB minutes and the procedure outlined below will be followed.

<Describe criteria and mechanism for unblinding.>

DSMB Communication of Findings and Recommendations

Following each meeting and within <insert # days> of the meeting, the chairperson will send findings and recommendations of the DSMB in writing to <list recipient(s) (e.g., sponsor, principal investigator, steering committee)> identified by the sponsor in the Table below.

<insert name>	<insert title and organization>	<insert contact information>

These findings and recommendations can result from both the open and closed sessions of the DSMB. If these findings include serious and potentially consequential recommendations that require immediate action, the chairperson will also promptly notify <list recipient(s)> by phone.

Sponsor’s Response to DSMB Findings and Recommendations

<List individuals specified in the table above> will review and respond to the DSMB recommendations. The recommendations of the DSMB will not be legally binding but require professional consideration by the recipients. If the DSMB recommends continuation of the study without modification, no formal response will be required. However, if the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the DSMB will request that the sponsor provide a formal written response stating whether the recommendations will be followed and the plan for addressing the issues.

It is recognized that the sponsor may need to consult with regulatory agencies or other consultants before finalizing the response to the DSMB. Upon receipt, the DSMB will consider the sponsor response and will attempt to resolve relevant issues, resulting in a final decision. Appropriate caution will be necessary during this process to avoid compromising study integrity or the ability of the sponsor to manage the study, should the study continue. The sponsor will agree to disseminate the final decision to the appropriate regulatory agencies, IRB/EC, and investigators within an appropriate time.

In the unlikely event of irreconcilable differences, especially regarding study termination or other substantial study modifications, the DSMB may decide to discontinue monitoring the current study and disband. This decision will be communicated to the <sponsor and other parties identified here>.

Public disclosure of the sponsor’s final decision or DSMB recommendations will be at the discretion of the sponsor or their designee. The DSMB will not make any public announcements either as a group or individually.

DSMB Closeout

This study may be terminated under a variety of circumstances including, but not limited to, termination for overwhelming effectiveness, futility, or safety issues per protocol or DSMB monitoring guidelines. Responsibilities of the DSMB with regard to

closeout will be to review the final study report to ensure study integrity. The DSMB may recommend continuing action items to <sponsor> based upon the final review.

Confidentiality

All data provided to the DSMB and all deliberations of the DSMB will be privileged and confidential. The DSMB will agree to use this information to accomplish the responsibilities of the DSMB and will not use it for other purposes without written consent from the <DSMB management organization or others as specified in this charter (e.g., study sponsor, steering committee)>. No communication of the deliberations or recommendations of the DSMB, either written or oral, will occur except as required for the DSMB to fulfill its responsibilities. Individual DSMB members must not have direct communication regarding the study outside the DSMB (including, but not limited to the investigators, IRB/EC, regulatory agencies, or sponsor) except as authorized by the DSMB.

Amendments to the DSMB Charter

This DSMB charter can be amended as needed during the course of the study. Information to be included as amendments will be any modifications or supplements to the reports prepared for the DSMB, as well as amendments to other information addressed in this charter. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the minutes of the DSMB meetings. Each revision will be reviewed and agreed upon by both the <study sponsor, DSMB management organization> and the DSMB. All versions of the charter will be archived in accordance with this document (see Archiving of DSMB Activities and Related Documents).

Archiving of DSMB Activities and Related Documents

All DSMB documentation and records will be retained in <list location> by <group (e.g., DSMB management organization, sponsor) or individual responsible for archiving > until discarded in accordance with <insert statutory guideline> or for a time period of <state time period> after completion of the study, whichever is longer. Access to archived data will be controlled by the <DSMB management organization or sponsor> which will release the information only as specified in this charter or as required by law.