UNIVERSITY OF KENTUCKY
Center for Clinical and Translational Science (CCTS)

DATA SAFETY MONITORING BOARD (DSMB)

CHARTER

Version:	Reviewed by:	Approved by:
4 07/17/15	Lisa Tannock, MD *DSMB Chair*	Ada Sue Selwitz, MA *Co-Director, Regulatory Support and Research Ethics, Center for Clinical and Translational Science*

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1. INTRODUCTION

This Charter is to establish the Data Safety Monitoring Board (DSMB) for the Center for Clinical and Translational Science (CCTS).
The Charter defines the primary responsibilities of the DSMB, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMB, and an outline of the content of the Open and Closed Reports that will be provided to the DSMB.
The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. PRIMARY RESPONSIBILITIES OF THE DSMB

The Data Safety Monitoring Board (DSMB) is established to conduct interim monitoring, oversight and analysis of study information and data. Its purpose is to assure the safety of research participants, efficacy and appropriateness of study interventions, relevance of the study questions, and integrity of the accumulating data throughout the life of a research project.

The direct responsibilities of the DSMB include:

- Initial review of the proposed research protocol, informed consent documents, data collection instruments and plans for data safety and monitoring;
- A discussion of regulatory issues, when appropriate;
- Evaluation of the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study site, and other factors that can affect study outcome;
- Review of reports from Quality Assurance audits;
- Review of study performance, making recommendations and assisting in the resolution of problems reported by the Principal Investigator;
- Protecting the safety of study participants;
- Reporting to the PI on the safety and progress of the study;
- Making recommendations to the Principal Investigator, concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;

- Ensuring the confidentiality of the study data and the results of monitoring;
- Assisting the Principal Investigator in the resolution of problems with study conduct, enrollment, sample size and/or data collection.
- For multi-site studies with the University of Kentucky identified as the lead study site, the DSMB will take the role of main DSMB for the study, providing a review of data for all sites (for multi-site studies where another institution is the lead site the DSMB will only review local site data)

The DSMB will be advisory to the Principal Investigator, hereafter referred to as the PI. The PI will be responsible to promptly review the DSMB recommendations, to decide whether to continue or terminate the study, and to determine whether amendments to the protocol or changes in study conduct are required.

The DSMB's role does not necessarily end when the opportunity for stopping enrollment passes. The DSMB should continue to review summaries of safety data by treatment group at least annually (local IRB will be notified of the results of these reviews) until either safety follow-up ends or another entity assumes this responsibility.

The DSMB will have neither a role in nor responsibilities for final analyses and preparation of manuscripts for publication.

3. MEMBERSHIP OF THE DSMB

3.1 Members

The DSMB is an independent multidisciplinary group with clinical research experience representing relevant specialties. This group will include a Research Subject Advocate (RSA) who is a Physician, a Pharmacist, an Internal Medicine Physician, Statistician, Safety Officer, CCTS Representative and Executive Secretary. There are 4 voting members including the Chair. The Safety Officer, CCTS Representative and Executive Secretary are non-voting members. Ad-hoc members may be added when experience in specific disease areas or procedures is required.
Alternate members are available as needed should a regular DSMB member be unable to attend a meeting. It is the responsibility of the DSMB member to notify the executive secretary if unable to attend a scheduled meeting so that an alternate can be scheduled to take their place.

3.2 Conflicts of Interest

Individuals invited to serve on the DSMB as either voting, ad-hoc or alternate members must disclose any potential conflicts of interest, whether real or perceived, to the PI and all DSMB members. Conflict of interest can include financial interest, professional interest, intellectual interests, proprietary interest, service on other DSMBs of the same, related or competing products, and miscellaneous interest. Potential conflicts that develop during a member's tenure on a DSMB must also be disclosed. Written documentation attesting to absence of conflict of interest is required. In the event that a DSMB members conflict of interest status changes they must notify the DSMB chair immediately and an alternate will be identified.

4 FREQUENCY AND TYPES OF DSMB REVIEW

4.1 Frequency of Review

The frequency of DSMB meetings is dependent upon the nature and risk of the studies to be monitored. DSMB meetings will be scheduled on an as-needed basis to address the needs of specific protocols. The DSMB Chair will determine the dates and time of the meetings, in conjunction with the members.
The Safety Officer will be the contact person for serious adverse event reporting.

4.2 DSMB Reviews

The types of DSMB review include the following:

Initial Review
Each study will be presented to the DSMB for an initial review at the time of its initiation, preferably before enrollment begins. The first meeting will take place before initiation of the study to discuss the protocol, the commencement of the study, and to establish guidelines to monitor the study. The PI will prepare a brief summary, including a review of operating procedures, reporting of adverse events, stopping rules, interim analysis plan, etc.
This review is generally conducted during a regularly scheduled DSMB meeting, but may be scheduled as a separate meeting if circumstances necessitate an expedited initial review.

This initial review does not constitute participation in trial design, which would compromise the independence of the DSMB. Rather it gives the DSMB an opportunity to communicate to the study PI that it cannot take responsibility for oversight unless major issues and concerns related to Data and Safety Monitoring are addressed. In this case, the DSMB will provide the PI with a comprehensive list of specific issues that need to be resolved before assuming oversight responsibilities.

Interim Monitoring Review

The Interim monitoring review is conducted during a regularly scheduled DSMB meeting, and reviews the study's progress from initiation through study close.

Once the study has closed to enrollment and any corresponding follow-up activities have been completed, PI's will be given the option to inactivate DSMB review.

A study can be inactivated by the PI provided that the following conditions have been met:

- Study is closed to enrollment
- Any corresponding follow-up activities are complete
- 30 days of more have passed since completion of follow-up activities

A written request for inactivation must be forwarded by the study PI confirming that the conditions for inactivation, as provided above, have been met.

If the review requires re-activation, the Principal Investigator must provide a written request to the DSMB including the circumstances for the re-activation.

Expedited Review

An Expedited review may be held to review minor changes in previously approved research. Expedited review is performed by the DSMB chair or designee.

Study Close Review

Documentation of study close with the IRB must be provided by the Principal Investigator to the DSMB upon receipt of the study closure documentation from the IRB.

Emergency Meetings

An emergency meeting of the DSMB may be called at any time by the Chair should questions of patient safety arise.

5 DSMB REVIEW FORMAT

5.1 Procedures to ensure confidentiality and proper communication

Procedures will be implemented to ensure proper communication is achieved between the DSMB and the PI. To provide a forum for exchange of information among various parties to ensure the successful conduct of the studies, a format for Open Sessions and Closed Sessions will be implemented. The intent of this format is to enable the DSMB to preserve

confidentiality of the studies being reviewed while at the same time providing opportunities for interaction between the DSMB and the PI who has valuable insight into study-related issues.

5.2 Meeting Format

Meetings will usually be face-to-face, occasionally by conference call (particularly for urgent reviews). The PI or designee will be present for those DSMB meetings that review his/her protocol.
Sessions will be of 3 types, not all of which would be needed at every meeting. The DSMB meetings will consist of open, closed (as needed) and executive sessions. The clinical study team, at the request of the DSMB, may attend the open sessions.

5.3 Open Session

Discussion during the **open session** will focus on the conduct and progress of the study including, but not limited to; compliance with protocol, participant accrual, drop-out rates, protocol violations, inclusion/exclusion requirements and problems encountered. Unblinded data are not presented in the open session.

5.4 Closed Session

If needed, the **closed session** will be held following the open session to present comparative outcome data and to identify and discuss the DSMB's recommendations to the PI. The study statistician may be present, at the request of the DSMB, during the closed session. Data presented in the closed session may include un-blinded information.

5.5 Executive Session

The **executive session** will be held following the open and closed sessions in order to discuss study issues independently. Only the DSMB members and support staff are present during the executive session.
If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions and to clarify the recommendations. The meeting is then adjourned.

5.6 Recommendations

Each DSMB meeting should include a recommendation regarding study continuation. One of the following actions, appropriate to study status, will be recommended upon completion of the DSMB review.

- Initiate/Continue/Close the study as originally designed, in accordance with the protocol and any amendments.
- Initiate/Continue/Close the study with contingency - modifications to the study protocol (modifications may include, but are not limited to, changes in entry criteria, frequency of visits or monitoring, and alterations in study procedures) and/or additional information required. Please note that for sponsored studies, PI must notify sponsor of DSMB request and the sponsor's decision regarding their intentions to revise or not revise the protocol must be forwarded to the DSMB by the PI. *In the case of a vote for study continuation with modification or additional information required, the UK CCTS DSMB has given the individual chairing the meeting the authority to approve the minor revisions which do not involve substantive issues.*
  Action plan: If the DSMB's recommendations require significant changes or follow-up, DSMB staff in collaboration with the DSMB chair will prepare an action plan outlining the steps required to implement the recommendations.

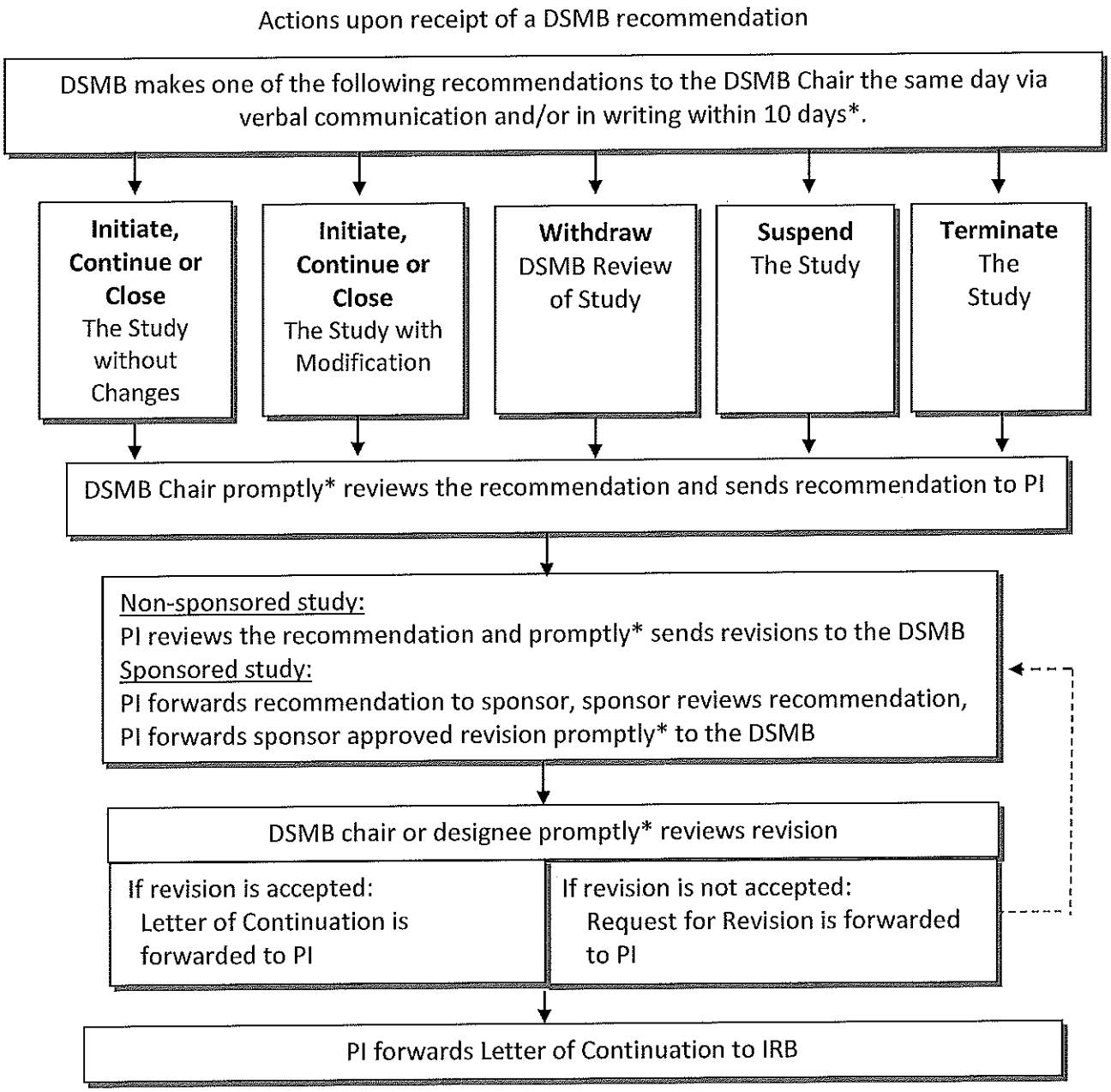
- Withdrawal of DSMB review – upon review, it may be determined that DSMB review is not needed, (ex.: another body will provide a DSMB to review the study, study is low risk and does not require DSMB review).

- Suspend the study, in order to gather additional information etc. prior to making a recommendation.

- The study should be terminated (with provisions for orderly discontinuation in accordance with good medical practice). Please note that for sponsored studies, PI must notify sponsor of the DSMB recommendation to terminate and the sponsor's reply must be forwarded to the DSMB, by the PI, prior to proceeding with study termination activities.

5.7 DSMB Action and Recommendation Diagram

The following diagram shows the action to be taken upon PI receipt of a DSMB review recommendation.



** Taking into consideration recommendations and circumstances. Critical information is expected to be communicated as timely as possible.*

5.8 Voting

The above recommendations are made by a formal DSMB majority vote. In order to vote on a recommendation during a meeting a quorum of 3 voting members must be present.
It is expected that all meetings will be face-to-face. However, if not possible, e-mail voting will be acceptable ***except*** for termination recommendations. Should the DSMB decide to issue a termination recommendation, the full vote, in person, of the DSMB is required. In the event of a split vote in favor of, majority vote will rule and a minority report should be appended. In the event of a 50-50 split vote, the DSMB Chair provides the tie breaker.
A recommendation for immediate suspension of a study in order to prepare for a potential study termination may be made by the DSMB at any time by majority vote. The Chair should transmit such a recommendation to the Executive Secretary (ES) and PI immediately.

5.9 Meeting Materials

A packet of information that describes the status of the study should be prepared by Study staff and forwarded to the ES at least one week prior to the meeting for immediate distribution to the DSMB. The ES will distribute the reports to the DSMB members via SharePoint. Materials may be presented in two parts.

- Part 1 contains reports for the open session of the meeting and
- Part 2 contains materials for the closed session.

Reports for both the open and closed session and plans for interim analyses should be established at the initial DSMB meeting, although changes throughout the study may be requested by the DSMB.

It is important that access to outcome data be limited to the statistician and DSMB, when necessary, to protect the study from bias in patient entry and/or evaluation.

5.10 Meeting Minutes

The ES will prepare meeting minutes for review and approval by the Chair within ten calendar days of the meeting. DSMB meeting minutes will be divided into two parts, according to whether they include discussion of confidential data (usually unblinded comparative data). The second part of the minutes will typically summarize discussion of the comparative unblinded outcome data and provide the rationale or the recommendations made to the PI. Generally, this portion of the minutes is not circulated outside the DSMB membership until the study is

terminated. Once approved by the Chair, the ES will send the minutes to the full DSMB. Comments from DSMB members will be obtained within 15 calendar days and meeting minutes finalized no later than 30 days after the meeting. Once approved by the DSMB, the ES will forward a letter with the DSMB's recommendations to the Principal Investigator. Each report will conclude with a recommendation to continue or to terminate the study.

6 STATISTICAL MONITORING GUIDELINES

A formal review meeting will occur 3 times per year. The purpose of each review meeting is to safeguard subjects against excess harm related to treatment. Although the complete body of safety information will be considered during each review, the DSMB may recommend stopping the study. The total number and percentage of primary composite events will be presented to the DSMB by the study group. If interim stopping rules are part of the protocol, the statistical monitoring will include a review of the primary endpoint for early stopping due to efficacy and/or futility provided the monitoring occurs at agreed upon time intervals in the study.

7 CONTENT OF THE DSMB'S OPEN AND CLOSED REPORTS

The information provided for interim DSMB review will be established during the initial review meeting and provided by the PI/designee at every review, and any additional meetings as requested by the DSMB. The DSMB may direct additions and other modifications to the reports on a one-time or continuing basis as the study progresses.

7.1 Open Session DSMB Report: An Outline

DSMB reports for the open session of the meeting include but are not limited to, those items listed below.
For multi-site studies where UK is the lead site, the reports must include data for all study sites, with activity at each site clearly specified.

- Study Overview
- Enrollment reports, including study accrual by month
- Consort Diagram
- Protocol violations, deviations and exceptions
- Adverse Events

- When the University of Kentucky study site is listed as the lead study site, all study sites will follow UK IRB AE/SAE reporting requirements

Note: Listings of adverse events and serious adverse events as well as any other information requested by the DSMB should not be presented in an unblinded manner.

- Copies of safety letters (i.e. SAEs) provided to sites and regulatory agencies on an ongoing basis throughout the course of the study
- Other pertinent study updates from the study team

7.2 Closed Session DSMB Report: An Outline

DSMB reports for the closed session contain at a minimum the following, and may include any additional items/data requested by the DSMB.

- Repeat of the Open Report information, in greater detail , as appropriate
- Audit results
- Other pertinent updates

The closed session reports are confidential and copies distributed prior to and during a meeting are collected by the executive secretary at the conclusion of the meeting.

8 RECORDS

One set of paper copies of a documentation reviewed during each meeting (review reports, meeting minutes, and follow-up documentation, etc.) is maintained in the CCTS regulatory office, C304 Chandler Medical Center. Electronic datasets used for each set of interim analyses as well as an electronic copy of meeting minutes is maintained in a secure CCTS directory. Records are maintained for a minimum of 7 years after the study has been closed, or until as determined by the CCTS Director.

9 REFERENCES

- University of Kentucky Office of Research Integrity and Institutional Review Board Standard Operating Procedures SOP #: 3-7 Revision#: 5 Data and Safety Monitoring Plan
- FDA Guidance for Clinical Trial Sponsors

  Establishment and Operation of Clinical Trial Data Monitoring Committees- March 2006
- NIDA (National Institute for Drug Abuse):
  Guidelines for Developing a Data and Safety Monitoring Plan
  http://www.nida.nih.gov/funding/DSMBSOP.html
- NIH Policy for data and Safety Monitoring, release date June 10, 1998

  http://grants.nih.gov/grants/guide/notice-files/not98-084.html
- Further guidance on a data and safety monitoring for phase I and Phase II trials, release date June 5, 2000
  http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

Attachment A

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Attachment B

DSMB Member Charter Agreement

I have read the CCTS Data Safety Monitoring Board (DSMB) Charter. I agree to conduct the data monitoring process for all trials that I review as stipulated in the CCTS Data Safety Monitoring Board (DSMB) Charter.

I understand that individuals invited to serve on the DSMB as either voting or non-voting members must disclose any potential conflicts of interest, whether real or perceived, to the Principal Investigator and UK CCTS. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest. Potential conflicts that develop during a member's tenure on a DSMB must also be disclosed and may require a DSMB member to recuse themselves as determined by the CCTS in consultation with the remaining uninvolved members of the DSMB.

I do not have any potential conflicts of interest, either real or perceived to disclose at this time.

I will notify the UK CCTS DSMB Chair promptly if a change occurs in any of the above that may affect my objectivity. In such an event, I will abstain from participation in the Board until instructed otherwise by the UK CCTS DSMB Chair. When in doubt, I will seek a determination from the UK CCTS DSMB Chair.

DSMB Member Name (Printed)

DSMB Member Signature

Date

Attachment C

DSMB Charter Revision History

Version	Revised From:	By:
	Revised To:	_____ _____ *Initial* *Date*
Version	**Revised From:**	**By:**
4	Pharmacist: Wermeling, Carrico,	
	Revised To: Pharmacist: Davis Alternates for all positions added Rice position changed to CCTS representative	RB 07/17/15 *Initial* *Date*
	General revisions	
Version	**Revised From:**	**By:**
3	Delete R. Means	
	Revised To:	RB 01/15/14 *Initial* *Date*
	Add L. Tannock and J. Carrico, Add Initial Expedited review, Update address for V. Adams	
Version	**Revised From:**	**By:**
2	Chair: Kramen	
	Revised To:	RB 06/08/12 *Initial* *Date*
	Chair: Means, added Expedited Review, PI to forward final DSMB report to IRB	
Version	**Revised From:**	**By:**
1	N/A – initial release	
	Revised To:	RB 10/14/10 *Initial* *Date*
	N/A	