Health Services Research & Development (HSR&D)

Data and Safety Monitoring Board (DSMB) Charter

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1. Introduction

The requirement for data and safety monitoring of clinical trials is addressed in VHA Handbook 1200.05. The VA's policy on data and safety monitoring is consistent with that of the Department of Health and Human Services which states that: "The establishment of data and safety monitoring boards is required for multi-site clinical trials involving interventions that entail potential risk to the participants." (NIH Policy for Data and Safety Monitoring, June 10, 1998).

The purpose of this manual is to describe practices and procedures for the organization and function of the Data and Safety Monitoring Board (DSMB or Board) to review Health Services Research & Development (HSR&D) multi-site intervention trials which include human participants.

This charter will be reviewed periodically and updated. All versioning and updates to this document will be recorded in Appendix A – Versioning, accessible at the end of this document and this bookmark when accessed electronically.

2. Purpose and Responsibilities of the DSMB

The Data and Safety Monitoring Board provides ongoing evaluation of studies' progress including patient accrual and retention, monitoring of adverse events, and the adequacy and efficiency of the analysis plan to discern outcomes that might require study modifications, or result in early cessation of the study due its benefits or harms. The DSMB does not evaluate the scientific merit or methodology of the study, nor does it directly participate in the execution of a study's protocol, monitor the budget, or approve sub-protocols or other modifications to the study; these functions are performed by other committees within the HSR&D Service. The DSMB may review approved protocol modifications with substantive statistical and monitoring changes and request amended Data Analysis Plans (DAP) from the study principal investigator (PI) when necessary.

The major responsibilities of the Board are:

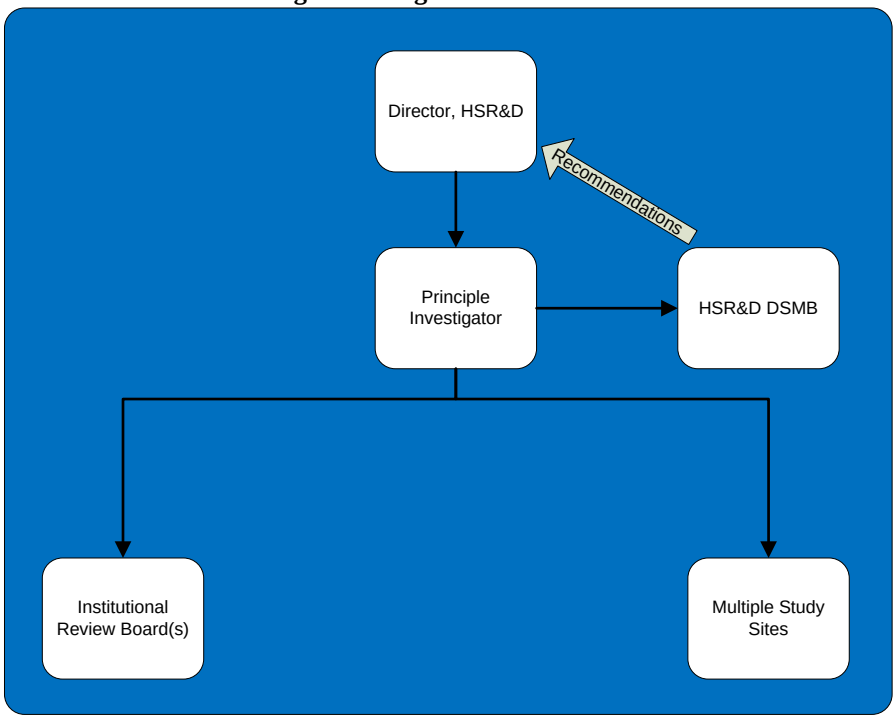
- To review the data analysis plan and make recommendations for additions or changes to the plan.
- To assess the performance of each participating center and make appropriate recommendations regarding continuation, probationary status, or termination.
- To consider patient accrual, overall study progress (timeline and follow-up participation), adverse effects and patient safety, treatment effectiveness/futility, and proper monitoring and reporting by the study team as these affect the ethical treatment of participants or the ethical conduct of research.
- Report to the HSR&D Director and PI on any perceived problems with study conduct, enrollment, sample size, and data collection.

- Provide the HSR&D Director and PI recommendations regarding continuation, termination or other modifications of the study based on evaluation of observed benefits or adverse effects of the intervention, as well as perceived likelihood of study efficacy based on patient accrual and retention.

3. Organizational Chart and Composition of Board

The Data and Safety Monitoring Board is an independent advisory group to the Director of HSR&D (Figure 1).

Figure 1: Organizational Chart



The HSR&D Director appoints members of the DSMB. The DSMB members are highly qualified by background, training, experience, and knowledge in relevant disciplines (see Appendix B for a current roster).

Regular Voting Members will include, at a minimum:

- two HSR&D Researchers
- two Biostatisticians
- a Health Economist
- a Physician
- an expert in human research protection issues who has served on an Institutional Review Board

Subject matter representation for studies monitored by the board is not required. Members will serve three-year terms and may fulfill multiple roles. The terms will be staggered to provide partial change in membership as necessary.

The HSR&D Director appoints the Chairperson of the DSMB. The responsibilities of the Chairperson include conducting meetings, assigning data analysis plans and reports to board members for review, conducting board deliberations associated with data analysis plans, mid-year and annual reports, and summarizing the deliberations of the Board. The Chairperson serves a three-year term with successive terms appointed at the discretion of the HSR&D Director. The first year of each term is a provisional period, at the end of which continuation to fulfillment or termination of term will be decided by the HSR&D Director.

Ex Officio Members: At the discretion of the HSR&D Director, *non-voting* participatory members may include the HSR&D DSMB Program Manager and Program Coordinator, selected HSR&D staff and investigators, and field-based administrative support.

The HSR&D service pays the travel expenses for DSMB members and, when in-person meetings are required, for Principal Investigators designated to attend the meeting. Non-VA DSMB consultants are paid an honorarium. Meetings of the DSMB are closed meetings so that additional attendees, such representatives for pharmaceutical companies and other vendors, may not attend meetings unless invited by the DSMB to clarify specific issues.

4. Conflicts of Interest

Any real or perceived conflicts of interest (COI) of board members will be identified at the outset of each annual meeting. Board members who participated in the planning of a study, have a key role in a study, or have a reasonably anticipated conflict of interest will recuse themselves when that study is under review. Members with identified conflicts of interest will sign a COI form identifying their conflicts (template available in Appendix C – COI Template, bookmark).

5. Monitoring

The DSMB has the authority to monitor HSR&D multi-site, intervention trials involving human participants. The level of risk to study participants is a consideration in the Board's decision to monitor the study. The decision to monitor a study is ultimately the responsibility of the DSMB Chair. The degree of monitoring will be commensurate with the nature, size and complexity of the study, the risks associated with participation, and the vulnerability of the particular population from which the sample is drawn. All HSR&D multi-site intervention studies that entail potential risk to participants are reviewed annually by the DSMB.

For the purpose of this charter, a multi-site intervention trial is defined as a study where an intervention occurs at two or more VA facilities covered by separate Federal Wide

Assurances (FWA; see VHA Handbook 1058.03). These types of studies use a common protocol with central coordination but may seek multiple Institutional Review Board (IRB) approvals or a single IRB approval through the VA Central IRB.

DSMB review covers the period from study approval through completion of the final assessment of the last study participant. The DSMB monitoring period concludes after the final contact with study participants or after the final record assessment to determine whether further contact is required.

6. Communications

Communications between the DSMB and a study PI will be conducted through the DSMB Program Manager and/or Coordinator. It is expected the study PI or team will not communicate about the study directly with the DSMB members or Chair unless solicited by the DSMB members, Chair, Program Manager or Coordinator, except when making presentations at scheduled meetings.

7. Overview of Reviews, DSMB and PI Responsibilities

Within 30 days of notification of intent to fund, the PI is to submit a description of the data analysis and adverse events monitoring plans for the study using the Just-In-Time (JIT) document manager. Thereafter, each study submits an annual progress report due December 1 each year. Notifications of reminders for submission of annual reports will be sent before the due date; however, it is ultimately the responsibility of the PI to submit annual reports by December 1 each year. At the request of the DSMB, each study may be asked to submit a briefer mid-year report for review. Notification of due date and review date will be sent to the PI in advance of mid-year reviews. Each of these documents and processes are described in detail below.

7.1. Briefing the DSMB about the Data Analysis Plan and Adverse Event Monitoring

To aid the Board in fulfilling its responsibility of reviewing the data analysis plan and adverse event monitoring before initiating data collection, the Principal Investigator must submit a 3-7 page description of the data analysis plan (with appendices, if extensive detail is required for description), which also includes the plan to monitor adverse and serious adverse events during the study to HSR&D within 30 days after being notified of HSR&D's intent to fund the study. The Principal Investigator uploads the DAP to the JIT Document Manager as **a single paginated PDF (include page number, PI, and date on the footer of each page) with table of contents**.

The description of the data analysis plan should summarize all of the statistical analyses for the primary, and important secondary, hypotheses or research questions specified in the original proposal. While there may have been a data analysis plan included with the original proposal, the Principal Investigator should assure that the description includes a discussion of each of the following points applicable to the study:

DAP (Document should be named Doe_IIR00-000_DAP.pdf)

1. The rationale for the study sample size
2. A specific description of how the data will be collected
3. The method of randomization (describing any stratification and blocking techniques)
4. Plans for and specification of the purpose of any interim looks at the data (with regard to stopping rules for superiority, futility, or sample size re-estimation)
5. Methods for handling missing data points and subject dropouts
6. Definitions of covariates to be included in adjustment models
7. Methods for dealing with data transformations
8. Definitions of the analytical sets (i.e. intent-to-treat, per-protocol, and any other analytical subsets)
9. A list of adverse and serious adverse events to be monitored, how they will be defined, and a plan for prospectively tracking them

Items to include in a single file (pdf preferred) when submitting the DAP to the JIT (Document Manager, the document should be named Doe_IIR00-000_DAP_docs.pdf)

1. Table of Contents
2. Abstract
3. Project narrative*
4. Response to conditions, if applicable
5. Gantt chart
6. Draft consent forms

*Project narrative is the body of the proposal submitted to SMRB, excluding all 1313s (budget, personnel, etc). Please contact HSR&D if you have questions.

Board members, and especially the biostatisticians on the Board, will review and comment on the character and definition of response variables, sample size, and plans for measurement, data collection, frequency of observations, data processing and analysis, as well as any other relevant study issues that may affect research integrity, the safe conduct of the study, or the welfare of participants.

7.2 Annual Progress Report and Meeting

Overview and Procedures

The DSMB meets during the second quarter each fiscal year, either face-to-face or by teleconference. The initial progress review will take place as scheduled by HSR&D staff. The Principal Investigator may be requested to participate in the review meeting by teleconference. However, at the discretion of the DSMB and in consultation with HSR&D Central Office, a Principal Investigator may be asked to attend the meeting in person. Annual reviews will be based on a progress report prepared by the Principal Investigator. The deadline for this report is December 1 each year of monitoring. Principal Investigators will be reminded in advance of the due date; however, it is the

responsibility of the PI to ensure annual reports are submitted by December 1 each year of monitoring.

At the meeting, the PI will be asked to make an opening statement not to exceed fifteen minutes. The statement should include the background of the study, a brief summary of the study design, the participant recruitment and retention record, patient safety issues, and any interim monitoring. In making the opening statement, the PI may make reference to material in the study's progress report, but there will be no access to audio-visual equipment. Handouts should be kept to a minimum. If the PI is not attending the meeting and has not selected an alternate study team member for representation, a Board member assigned to review the report will give a brief overview. Board members with declared conflicts of interest will recuse themselves from discussions and voting during reviews of identified studies.

After the overview, the project will be discussed among the DSMB members and the PI (if present) to focus on questions based on the written progress report that the DSMB has been able to review prior to the meeting. Board reviewers are asked to comment on the recruitment and retention strategies and performance, study progress, the data analysis plan, and any other pertinent features of the report. The biostatistician reviewer is asked to comment also on the character and definition of response variables, measurement, data collection, frequency of observations, sample size, progress on data processing and analysis, and any other relevant features that affect the protection of participants across all study sites or challenge the potential validity or merit of the study. It would be unethical to continue enrolling participants in a study that could not generate knowledge.

After the discussion, the PI will be excused for the DSMB Executive Session. The HSR&D and program representatives will remain as non-voting members. This Executive Session will include consideration of a formal motion to continue the study, the language of the DSMB report to IRBs when applicable, and any recommendations for changes in the conduct of the study.

Content of the Annual Progress Report

For the annual review of multi-site HSR&D studies, whether in-person or by teleconference, the PI will be responsible for uploading the progress report to http://art.puget-sound.med.va.gov/ChooseProject.cfm as **a single paginated PDF (include page number, PI, and date on each page) with table of contents** in the following format:

1. Table of Contents.

2. Principal Investigator's **Summary of Progress Cover Letter**. The Principal Investigator shall prepare a short letter (maximum 5 pages) addressed to the DSMB covering study progress and performance. This letter should include a history of the study to date, including current study stage (pre-initiation of recruitment, recruitment and follow-up, follow-up only, post-data collection

analysis only) and a statement of the current status. The latter includes the number of participants (usually patients but could also include caregivers or providers) entered into the study and a comparison with the projected number; losses to the study and a statement of when and why these occurred; comparison of recruitment results to date with study objectives; and estimates of the prospects of success.

3. Executive Summary or Abstract of the Study.

4. A **GANTT** chart (by specific calendar year or specific fiscal year).

5. A **chronology** of major events that have occurred (e.g. start of funding, start of patient recruitment, study meetings, changes in participating sites, important protocol changes, scheduled end of funding).

6. Consolidated Standards for Reporting of Trials (*CONSORT*) diagram (http://www.consort-statement.org/consort-statement/flow-diagram0/).

7. Tabular material: Each table or set of tables should be interspersed with narrative sections. ***All tables should be submitted as described***. These narrative summaries should point out salient features and emphasize areas of special interest. They should serve the reader as a 'road map' guide to the tables. The tables should present data on the following areas:

    a. **Enrollment** – number of patients entered into the study (by time and site) in comparison with the projected number. Graphs comparing actual recruitment with projected recruitment over time, overall and by site, are suggested.
    b. **Baseline comparison** with control versus intervention of relevant characteristics of study groups
    c. **Recruitment and retention flow diagram** (http://jama.jamanetwork.com/public/InstructionsForAuthors.aspx#CONSORTFlowDiagramandChecklist)
    d. **Patient Retention**– deaths, losses to follow-up, withdrawals, etc., by site and blinded study group
    e. **Patient Safety** – The report should elaborate adverse and serious adverse events including tables of adverse events and serious adverse events by group, with the groups identified solely as Group A, Group B, etc. The report should include a 2 X 2 table for each site with intervention and control groups and with adverse events and serious adverse events. The report should also include a listing of all deaths and hospitalizations.

        i. ***Adverse Event (AE)***–Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a ***medical product, procedure or other therapy, or in***

conjunction with a research study whether or not considered related to the ***product, procedure, or other therapy, or study .***

ii. ***Serious Adverse Event (SAE)***–An assessment based on subject/event outcome, or required intervention, of whether one or more adverse event occurrences pose a threat to a study participant's life or functioning. This includes:

- Death - Any life-threatening experience
- Any event which requires or prolongs a hospital stay
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient, or may require intervention to prevent one of the other outcomes.

iii. ***Categorization of AEs and SAEs–***Each AE and SAE should be evaluated as to whether it was expected or unexpected, and the likelihood that the AE or SAE was related to participation in the study.

iv. ***Expected/Unexpected***—an assessment of whether the adverse **event** commonly occurs as part of the clinical condition and is consistent with the applicable study documentation (e.g., investigator's brochure, protocol document, or consent document) or product labeling (package insert).

v. ***Relationship to Participation in the Study***—an assessment of the degree to which it is reasonable to make a causal connection between the AE or SAE and participation in the study.

Patient safety includes safeguarding the rights and welfare of subjects of research, and reporting unanticipated problems involving risk to subjects or others. The risks include events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the study places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized. Unanticipated problems that involve risk to study subjects or others may be physical, mental, emotional, economic, or involve privacy. When appropriate, unanticipated problems should be included in the report.

f. **Effectiveness**–When appropriate, the DSMB may request a comparison of the overall outcome and event rates with the rates predicted in the original proposal in order to determine if a study warrants early cessation due to its benefits or harms.

Reports should include only aggregated data; however, the DSMB may request blinded or unblinded data. To prevent the Principal Investigator from being influenced by the interim results, if requested, these sections should be completed by the Study Biostatistician and mailed to Administrative Officer Liza.Catucci@va.gov separately, utilizing PKI when sending identifiable data.

g. Reconsideration of the power/sample size issues may be necessary. In the case of a request to VACO for extension of patient intake or follow-up duration, the report to DSMB should also contain a summary of the justification for the request. When investigators request an extension or if there is any problem with the conduct of the trial, the calculation of conditional power must be provided to the DSMB.

8. Appendices

a. Previous DSMB feedback reports, if any. The DSMB feedback report is generated to reflect the DSMB review and approval of the study to continue, and it is signed by the DSMB Chairperson.
b. (Possibly updated) 25 page narrative section from the approved proposal together with any post-approval updates. (Do not include entire proposal.)
c. Approved current versions of Informed Consent Form(s)
d. Other supplemental material and additional information not included in cover letter. (optional)

Once HSR&D ART (http://art.puget-sound.med.va.gov/ChooseProject.cfm) receives the report, it is reviewed to ensure that all the required information is included.

DSMB Recommendations

Generally one of four actions is taken:

- Unconditional approval. The study is approved to continue.
- Conditional approval. The Board approves the study to continue, but approval is contingent on specific recommended modifications.
- Close the study. The Board recommends that the study be terminated.
- Exempt from monitoring.

Principal Investigators who attend the meeting in-person will be informed of the DSMB recommendation(s) immediately after the Executive Session; those attending by teleconference will have an opportunity to be informed of the DSMB recommendation(s)

within 10 working days of the close of the DSMB meeting. The recommendation is forwarded to the HSR&D Director, who will issue a formal report to each PI.

In addition to chairing each meeting, the Chairperson of the DSMB will be responsible to finalize a brief feedback report of each study review session. The feedback report states those actions that the Board believes are necessary or highly desirable. These are phrased as recommendations to the HSR&D Director. The DSMB may also make suggestions that are not intended to be binding but are to be considered and discussed by the Principal Investigator. In the case of conditional approval, after the HSR&D Director issues the report, the Principal Investigator will be asked to submit a response within 30 days to indicate how the recommendations will be implemented.

When requested by the study PI or at the discretion of the DSMB Chair, the DSMB Chair will finalize a short report (a draft of which is prepared by staff at the meeting) that the PI may distribute to the Human Subject Subcommittees/Institutional Review Boards (IRBs) of the participating sites, informing them of any safety issues in the study. Since the Human Subject Subcommittees/IRBs will not have access to blinded data results, the report will provide them some assurance that the DSMB is monitoring the safety of study patients and will make them aware of any safety issues. The report needs to be worded such that blinded study results are not revealed unless absolutely necessary.

The DSMB reports are provided to the HSR&D, Director who determines the action needed for each report, transmits the report with a cover letter of the action to the appropriate PI with a copy to the Associate Chief for Research, Center Director, and Hospital Director.

7.3. Midyear Review

At mid-year between annual reviews, Principal Investigators who are required to submit a mid-year report should upload a (4-6 page) mid-year progress report to http://art.puget-sound.med.va.gov/ChooseProject.cfm as **a single paginated PDF (include page number, PI, and date on each page) with table of contents** in the following format:

- Table of contents.
- Principal Investigator's **Summary of Progress Cover Letter (**at most 1 page). The Principal Investigator should prepare a letter covering study progress, performance, and important protocol modifications since the last review of the study.
- Recruitment table or graph showing actual vs. expected recruitment rates over time for the entire study and by site
- Completeness of follow-up
- Status of data collection and data entry and cleaning
- Safety: AEs and SAEs classified by group (A vs. B, i.e., blinded), cumulative and for the period since the last DSMB review. The report should include a 2 X 2 table for each site with intervention and control groups and with adverse events and serious adverse events.

- Appendices
    - Previous DSMB feedback reports, if any. The DSMB feedback report is generated to reflect the DSMB review and approval of the study to continue, and it is signed by the DSMB Chairperson.

The mid-year report will be due mid-year. A reminder will be sent to the Principal Investigators four weeks in advance of the due date. Possible actions include acceptance without comment, sharing the document with the entire DSMB for an email vote, or requesting the Principal Investigator to present the report at a teleconference of the entire DSMB.

Data and Safety Monitoring Board Signature Page

As Director of HSR&D, I approve this charter as the governing policy document of the HSR&D DSMB committee. Any non-editorial changes to the terms outlined in this Charter will be communicated by the DSMB Program Coordinator to the Chair and members.

David Atkins 105921

Digitally signed by David Atkins 105921
DN: dc=gov, dc=va, o=internal, ou=people, 0.9.2342.19200300.100.1.1=david.atkins@va.gov, cn=David Atkins 105921
Date: 2015.11.18 13:51:08 -05'00'

Signature, Director HSR&D

David Atkins, MD, MPH
Printed Name

Appendix A - Versioning

Version	Details of Change	Approval Date
1.0	Establishment of Charter	6/15/2012
1.1	Membership Update	7/3/2012
2.0	Personnel, Membership Update, Email	11/17/2015

HSR&D Data Safety and Monitoring Board 2011 Board					
Name	Role	Term	Background	Location	Contact
Lisa Dixon, MD, MPH	Chair	2012-2015	IRB, Physician, Researcher	Columbia	Dixonli@nyspi.columbia.edu
Joe Collins, ScD	Member	2014-2015	Biostatistician/Researcher	Perry Point	Joseph.Collins2@va.gov
Ying Lu, PhD, MS	Member	2015-2018	Statistician	Palo Alto	Ying.Lu@va.gov
Paul Shekelle, MD, MPH	Member	2013-2016	Physician, Researcher	Greater LA	Paul.Shekelle@va.gov
Martin Laurence Lee, PhD, Cstat	Member	2015-2018	Biostatistician/Researcher	West LA	Martin.Lee@va.gov
Dave Oslin, MD	Member	2015-2018	Physician, Researcher	Philadelphia	Dave.Oslin@va.gov
Todd Wagner, PhD	Member	2015-2018	Health Economist	Menlo-Park	Todd.Wagner@va.gov

Staff				
Name	DSMB Role	HSR&D Role	Location	Contact
David Atkins, MD, MPH	Program Manager	HSR&D Director	VACO	David.Atkins@va.gov
Liza Catucci, BA	Interim Program Coordinator	Administrative Officer	VACO	Liza.Catucci@va.gov

Appendix C – COI Template

CONFLICT OF INTEREST DECLARATION (HSR&D DSMB MEMBERS)

This form is to be used by HSR&D DSMB members to declare any conflict of interest with projects to be reviewed at a convened meeting of the HSR&D DSMB.

Instructions:

1. The Conflict of Interest Declaration must be signed after you review the mid-year or annual meeting agenda.

2. At the meeting, all DSMB members must turn-in these forms prior to the start of the meeting. Members attending via video or teleconference (or meetings held by teleconference) should fax or scan and email the form to the HSR&D DSMB Program Coordinator.

3. Members having a conflict of interest with a particular project must declare it prior to the discussion of the project and leave the room during the discussion and voting. Members participating via video or teleconferencing must disconnect. Members will be summoned to return upon completion of the voting.

4. Members may remain in the room or on the call if requested by the Chair to provide information but must leave or disconnect after the information has been presented.

CONFLICT OF INTEREST DECLARATION

I have reviewed the agenda for the HSR&D meeting to be held on_____.

Please check one of the boxes below and identify which project(s) for which you have a COI.

☐	I have reviewed the agenda for the above meeting and am not involved in and have no other conflict of interest regarding any of the projects to be reviewed at the above meeting. I will promptly update this declaration should I discover such a conflict during the meeting.
☐	I am involved or I have another type of conflict of interest in the projects listed below. I will leave the room during any discussion and vote on these projects. I have no other conflicts of interest regarding any of the other projects to be reviewed. I will promptly update this declaration should I discover such a conflict during the meeting.

List of projects in which a conflict of interest is being declared:

_____

_____

Printed name:_____

Signature: _____ Date: _____