Health Services Research and Development Service

Data and Safety Monitoring Board

Reviews Multi-site Interventional Health Services Studies

GUIDELINES

Effective July 2006

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1. Introduction

The requirement for data and safety monitoring of clinical trials is addressed in VHA Handbook 1200.5, paragraph 7. A. (6). 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 to review Health Services Research & Development (HSR&D) multi-site intervention trials that include human subjects and involve randomization. The level of risk to study participants in these studies is also considered. Multi-site studies are those in which investigators from two or more VA (or non-VA, as appropriate) medical centers with separate IRBs agree to study collectively a selected problem in a uniform manner, using a common protocol with central coordination.

Although multi-site studies are generally not appropriate for the early development and refinement of new preventive or therapeutic techniques, they are particularly advantageous in the later stages of evaluation of safety, treatment effectiveness, and cost effectiveness of health care interventions that have already had the necessary preliminary trials in humans. Clinical trials and health services research studies of this type, as well as some epidemiological studies, can benefit from a multi-center approach that facilitates the accumulation of patient samples that are:

- Sufficiently large to provide a definitive answer to the research questions. For medical conditions that are relatively rare, multi-site studies may be the only feasible approach, but even in more common conditions, pooling the observations made in several facilities can accumulate knowledge more rapidly.

- Sufficiently diverse to permit broad generalizations of results.

The large number of medical centers within VA presents an ideal environment for conducting multi-center studies. VA has a large and relatively uniform patient base; this is especially appropriate for research that addresses medical problems and diseases prevalent in the veteran population. These characteristics facilitate the conduct of multi-center studies that require strict adherence to a common protocol. In this setting, it is more likely that the essential patient follow-up will be completed.

2. Purpose

The Data and Safety Monitoring Board (DSMB or Board) provides an ongoing evaluation of the study's progress including patient accrual and retention, monitoring of adverse events, and the analysis plan. The DSMB does not initially evaluate the scientific merit or methodology of the study, nor does it subsequently participate in the study's conduct, monitor the budget, or review and approve sub-protocols or other modifications to the study; these functions are performed by the HSR&D Service in VACO or by other committees.

The Board will perform many, but not all, of the functions of a classic clinical trials Data and Safety Monitoring Board. The major responsibilities of the Board are:

- To assess the performance of each participating center and make appropriate recommendations regarding continuation, probationary status, or termination.

- To consider whether the study should continue. Inherent in this question are considerations such as 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.

- To review the analysis plans and make recommendations for additions or changes to the plan.

The Board does not evaluate the "quality" of the data collected from the various sites.

After a study is approved and funded, the HSR&D Director's representative will notify the Palo Alto Cooperative Studies Program Coordinating Center (CSPCC) if the study is a multi-site intervention posing some potential risk to participants and should be reviewed on an annual basis by the Board. The CSPCC will then contact the Principal Investigator to provide information on the reviews.

3. Composition of Board

The HSR&D Director appoints members of the DSMB. DSMB members are highly qualified by background, training, experience, and knowledge in relevant disciplines.

- *Regular* Voting Members: *Regular voting members* will include, at a minimum, two HSR&D Researchers, two Biostatisticians, a Health Economist, an expert in human research protection issues who has served on an Institutional Review Board, a Physician, and an Epidemiologist. (The Board does not have specific subject experts for all studies reviewed.) These members will serve three-year terms, with not less than one year between terms. The terms will be staggered to provide partial change in membership on an annual basis.

- *Ex-officio* Non-voting Members: The HSR&D program representative(s) and the Palo Alto CSPCC representatives.

The HSR&D Director appoints the Chairperson of the DSMB. The responsibilities of the Chairperson are to conduct the meeting and to summarize the deliberations of the Committee.

Board members who participated in the planning of the study or who play a continuing key role in the study must recuse themselves when that study is under review.

The HSR&D Service will pay the travel expenses for DSMB members and, when in-person meetings are required, for the Principal Investigator from each study designated to attend the meeting. Non-VA DSMB consultants will be paid an honorarium. Meetings

of the DSMB are closed meetings so that additional attendees, such as pharmaceutical representatives, may not attend these meetings unless specifically invited by the DSMB for the purpose of clarifying specific issues.

4. Duration of Monitoring

DSMB review covers the period from study approval through completion of the final assessment (initial or follow-up, as appropriate) of the final study participant.

5. Overview of Reviews and PI Responsibilities

The DSMB reviews ongoing HSR&D multi-site, randomized intervention studies and makes recommendations to the HSR&D Director. Upon approval of a study, the PI will be asked to submit a description of the data analysis and adverse events monitoring plans for the study. Thereafter, each study will submit annually a progress report and a briefer mid-year report for DSMB review. Each of these documents and processes is described in greater detail below.

5.1. Briefing the DSMB about the Analysis Plan and Adverse Event Monitoring

To aid the Board to fulfill its responsibility of reviewing the data analysis plan and adverse event monitoring, the Principal Investigator will submit a 3 – 5 page description of the analysis plan and adverse event monitoring of the study to HSR&D within 30 days after being notified of study funding.

The description of the analytic 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:

- The rationale for the study sample size
- A specific description of how the data will be collected
- The method of randomization (describing any stratification and blocking techniques)
- 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)
- Methods for handling missing data points and subject dropouts
- Definitions of covariates to be included in adjustment models
- Methods for dealing with data transformations
- Definitions of the analytical sets (i.e. intent-to-treat, per-protocol, and any other analytical subsets)
- A list of adverse and serious adverse events to be monitored and a plan for prospectively tracking them

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 features.

5.2 Annual Progress Report

Overview and Procedures

The DSMB meets face-to-face once a year in January/February in the San Francisco area.

All HSR&D multi-site intervention studies that entail potential risk to participants are reviewed annually by the DSMB. The initial progress review will take place as scheduled by HSR&D staff in VACO. In general, the Principal Investigator will participate in the review meeting by teleconference. However, at the discretion of the DSMB, in consultation with VACO, a Principal Investigator may be asked to physically attend the meeting. Annual reviews will be based on a progress report prepared by the Principal Investigator. The deadline for this report is *six-eight* weeks prior to the scheduled meeting; Principal Investigators will be reminded by CSPCC *six to eight* weeks in advance of the due date.

At the meeting, the Principal Investigator (whether attending in-person or by teleconference) 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, safety issues, and any interim monitoring. In making the opening statement, the Principal Investigator may make reference to material in the study's progress report, but there will be no access to audio-visual equipment, e.g., slide projector, overhead projector, PowerPoint presentation, etc. Handouts should be kept to a minimum.

After the formal statement, 45 minutes will be allotted for a discussion between the DSMB members and the Principal Investigator, to focus on questions based on the written progress report that the DSMB has been able to review prior to the meeting. Committee reviewers are asked to comment on the plan of investigation, the participant recruitment and retention performance, study progress, the analysis plan, and any other pertinent features of the report. The biostatistical 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.

After the discussion, the Principal Investigator will be excused for the DSMB Executive Session of about 30 minutes. The HSR&D and the CSPCC program representatives will remain as non-voting members. The Executive Session will include consideration of a formal motion to continue the study, the language of the DSMB report to IRBs, 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 Principal Investigator will be responsible for submitting the progress report to the CSPCC in the following format:

1. 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 & 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.

2. Table of Contents.

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. Tabular material: Each table or set of tables should be interspersed with narrative sections. 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** of relevant characteristics of study groups
   c. **Recruitment and retention flow diagram (http://jama.ama-assn.org/misc/ifora.dtl#CONSORTFlowDiagramandChecklist)**
   d. **Patient Retention**– deaths, losses to follow-up, withdrawals, etc., by site and blinded study group
   e. **Patient Safety** – The report should include tables of adverse events and serious adverse events by group, with the groups identified solely as Group A, Group B, etc.

      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 research 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.

Unanticipated problem involving risk to subjects or others: Events that (1) are not expected given the nature of the research procedures and the subject population being studied; and (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

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 .***

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:

1) Death - Any life-threatening experience
2) Any event which requires or prolongs a hospital stay
3) A persistent or significant disability/incapacity
4) A congenital anomaly/birth defect
5) 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.

Expectedness—an assessment of whether the *specificity* (nature), *frequency,* or severity of an adverse **event** is consistent with the applicable study documentation (e.g., investigator's brochure, protocol document, or consent document) or product labeling (package insert). The expectedness of an event should be collected as part of the Adverse Event reporting.

Reporting requirement: The AE and SAE tables should be presented by group, i.e., identified solely as Group A, Group B, etc.

f. **Effectiveness** - Aggregated outcome data, including a comparison of the overall outcome-event rates with the rate predicted in the original protocol. The DSMB prefers the presentation of aggregate data, but at their discretion, the DSMB, after reviewing the aggregated results, may request outcome data by blinded treatment assignment (group A vs. group B), or, in unusual circumstances, unblinded outcome data. To keep the Principal Investigator from being influenced by the interim results, if requested, these sections should be completed by the Study Biostatistician and mailed to the CSPCC separately.

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.

h. Appendices
   (1) 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.
   (2) (Possibly updated) 25 page narrative section from the approved proposal together with any post-approval updates. (Do not include entire proposal.)
   (3) Approved current versions of Informed Consent Form(s)
   (4) Other supplemental material (optional)

Once the CSPCC receives the report, it is reviewed to ensure that all the required information is included. Copies of the report are then sent to the DSMB members.

DSMB Recommendations

Generally one of three 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.

Principal Investigators who attend the meeting 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.

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, a draft of which is prepared by staff at the meeting. 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 to indicate how the recommendations will be implemented.

Along with the DSMB feedback report, the DSMB Chairperson will finalize a short report (a draft of which is prepared by staff at the meeting) that the Principal Investigator 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 Hospital Director with a copy to the Associate Chief for Research and the Principal Investigator of the study.

5.3. Midyear Review

At mid-year between annual reviews, all Principal Investigators should submit a (4-6 page) Six Month progress report which includes:

- 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: SAEs and AEs classified by group (A vs B, i.e., blinded), cumulative and for the period since the last DSMB review.

The mid-year report will be due in July/August of each year. A reminder will be sent by the CSPCC to the Principal Investigators four weeks in advance of the due date. . The document will be sent to the CSPCC to be reviewed by the DSMB Chair and HSR&D Representative. 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.