

VA



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DATA MONITORING COMMITTEE GUIDANCE

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Acronyms

AE	Adverse Event
ACOS/R	Associate Chief of Staff for Research
CSPCC	Coordinating Studies Program Coordinating Center
CSR	Clinical Science Research and Development
COI	Conflicts of Interest
DMC	Data Monitoring Committee
PI	Principal Investigator
R&D	Research and Development
SAE	Serious Adverse Event
UPIRTSO	Unanticipated Problem in Human Subjects Research Involving Risk to Subjects or Others
VAMC	Veterans Affairs Medical Center
VHA	Veterans Health Administration

Data Monitoring Committee Guidance

1. Introduction

Under the auspices of the Department of Veteran Affairs Office of Research & Development and the Director of Clinical Science Research and Development (CSRD), this document defines the primary responsibilities of the CSRD Data Monitoring Committee (DMC) and guides the activities of the DMC, its relationship with other study components, membership, and the purpose and timing of meetings as managed by the DMC Team composed of the Team Lead from CSRD, and DMC Managers and Quality Assurance Nurses who are located at the Hines Coordinating Studies Program Coordinating Center (CSPCC). The DMC assesses the performance of CSRD-funded studies that include human subjects and may involve randomization. This guidance provides procedures for the DMC that include ensuring confidentiality, communication, proper reporting, statistical monitoring and other responsibilities as described below. Due to the breadth of subject areas supported by CSRD, multiple DMCs may be established. Although these DMCs are designated by different names, specific to the types of studies to be monitored, this guidance document applies to all and refers to them collectively as “DMC” or “Committee.”

2. Primary Responsibilities of the DMC

The DMC, under the leadership of the Chairperson, is primarily responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study interventions and monitoring the progress of assigned studies under review. The DMC conducts comprehensive reviews of each study. Recruitment will be monitored according to a schedule set by the DMC.

The DMC may also provide suggestions for action items relating to selection, recruitment and retention of research subjects; patient management; data management; and quality control. The DMC **will not evaluate the scientific merit, methodology or overall design, and budgetary constraints** of an Institutional Review Board (IRB) approved protocol under review, except where changes to the protocol may result in a change in safety level or monitoring.

The DMC functions as an independent advisory group to the Director of CSRD to ensure that projects proceed safely, with integrity and according to schedule. The DMC will report to the Director, CSRD, and make recommendations with regards to the performance of CSRD-funded studies.

A determination will be made by the Director, CSRD, with input from the CSRD DMC Team as needed, as to whether a study approved for CSRD funding warrants DMC oversight. Factors considered in determining the need for DMC involvement include but are not limited to whether the study is multi-site, whether it is a medication trial,

and whether it is greater than minimal risk. Once the determination for DMC oversight is made (prior to study initiation), the Director, CSRD, informs the PI's VA facility (ACOS/R) and the PI of the assignment. A DMC Manager from the DMC Team then communicates directly with the PI to provide DMC related information.

The DMC will:

- Familiarize itself with the research protocol, approved documentation, study data, and safety monitoring plans
- Review procedures and events that will maximize the safety of study participants and minimize risks
- Evaluate study progress and data, including participant recruitment, accrual and retention; performance of study site(s); and other factors that may affect study outcomes
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or ethics of the study
- Review adverse event (AE), serious adverse event (SAE) and unanticipated problem in human subjects research involving risks to subjects or others (UPIRTSO) documentation and safety reports and make recommendations regarding maximizing the safety of the study participants
- Report to the Director, CSRD, on the safety and progress of funded studies
- Evaluate and report to the Director, CSRD, on any perceived problems with study conduct, enrollment, sample size, and/or data collection
- Provide to the Director, CSRD, a recommendation regarding proceeding, continuing conditionally or unconditionally, probation, termination, or other modifications of the study.

Principal Investigators (PIs) will be informed at study initiation and throughout the study life cycle of data or procedural factors that warrant conditional approvals or probationary status and the benchmarks that must be instituted to reverse them. The study PI will submit Progress Reports to the DMC Manager for distribution to DMC members, no later than 30 days prior to Committee meetings. Under the leadership of the DMC Chairperson, the DMC will make recommendations to the Director, CSRD, with regards to safety and efficacy of all study processes and overall study progress.

3. Membership of the DMC

3.1 Members

The DMC is an independent multidisciplinary group, whose members have collectively through education, training, experience, and expertise, the requisite knowledge pertinent to the subject areas to be reviewed. DMC membership is established through an approval process based on nomination. Following favorable background checks, Committee member nominations are submitted by the DMC Manager to the Director, CSRD, through the DMC Team Lead. The Director, CSRD, will determine approval or non-approval of a nominated individual. The Director, CSRD, may also suggest alternative nominations. Once a membership approval is in

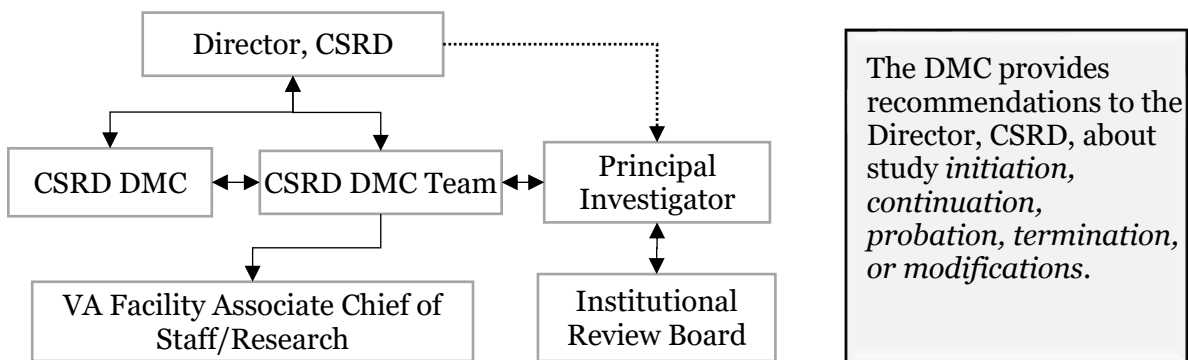
place, that member may be designated as Chairperson or Vice Chairperson without further approval from the Director, CSRD. A guidance document titled, “Qualifications/Requirements for Data Monitoring Committee Membership” is included (see Appendix).

DMC membership terms will be staggered, and no member, including the Chairperson, will serve for a period longer than 6 consecutive years. However, after a 1-year absence, an individual may return to the membership. If any Committee members leave the DMC, they will be promptly replaced. DMC members will be selected based on their expertise in the subject areas to be reviewed.

Other individuals who attend DMC meetings include the Director of CSRD, other Central Office representatives, Hines CSPCC leadership, and DMC Team members. Individuals who provide additional scientific expertise on a non-regular or ad hoc basis will not be considered as members and will not have any formal term of appointment.

The following diagram depicts the general relationships between the Director, CSRD; the DMC and other stakeholders involved in a study.

Organizational Diagram



DMC oversight will cover the period from Initial Review until final study completion and subject assessments. Once the final comprehensive progress review for a study is completed, Committee members, are forbidden to participate in any primary or secondary data analysis.

3.2 Authority of the DMC

The DMC is authorized by the Director, CSRD, to evaluate research projects funded through various research funding mechanisms. All studies will be reviewed at least every 12 months. The need for more frequent reviews will be determined on a case-by-case basis, according to the study charter developed upon assignment to the DMC. Reviews will involve the review of aggregate safety data. The DMC will

determine at a study's Initial Review whether subsequent reviews will also include aggregate efficacy data and or interim analytic assessments. This is to ensure that the CSRD project is not an exercise in futility. The DMC has the authority to make recommendations regarding the study proceeding initially (as previously approved by the R&D Committee and all applicable subcommittees or external committees), continuing the study at subsequent reviews (conditionally or with conditions to be addressed), probation or termination.

3.3 Conflicts of Interest

DMC members will have no major apparent financial, personal, institutional, or intellectual conflict of interest that could prevent them from objectively reviewing a study under their assignment. Members who aided in study planning or have concrete or perceived personal and or institutional conflicts of interest with a study which is under review, must recuse themselves when that study is under consideration for a recommendation. At the discretion of the DMC Chairperson and/or CSRD DMC Team, such members may participate in the discussion of the protocol but must recuse themselves prior to any Committee actions. Prior to each convened meeting, all Committee members and any ad hoc reviewers must declare any conflicts of interest to the Chairperson and/or CSRD DMC Team by filling out the appropriate forms. Subsequently, a revised statement of disclosure must be made when any apparent financial, personal, intellectual, or institutional conflict of interest occurs as any study progresses.

4. Authority of the Sponsor

CSRD, as sponsor, may grant certain special approvals to funded projects monitored by the DMC. The Director, CSRD, or designee, is the only authority with the purview to grant special approvals such as cost extensions, no-cost extensions, early study terminations, or other special actions. The Director, CSRD, may, however, take into account the DMC's recommendations. The PI must submit all requests for special approval to the Director, CSRD, through the facility Research Office, to the shared mailbox, VHABRD-CSRD@va.gov. The DMC will direct PI's who wish to obtain any special approvals to submit their requests as described above, to the Director, CSRD; a copy of the request must be sent to the CSRD DMC Team simultaneously.

5. Quorum Establishment, Organization and Format of DMC Meetings

5.1 Quorum Establishment

A quorum of more than 50 percent of the DMC voting membership must be established and maintained throughout a DMC meeting in order for recommendations to be made. Although the number of DMC members may vary, the quorum must always consist of more than 50 percent of the membership being present including at least two clinicians and one biostatistician. While formal votes

may be taken, recommendations routinely are made via consensus of the quorum of members present. In the event of a DMC recommendation for termination, a formal vote is required.

Attendance at DMC meetings must include the DMC Manager or other individual who is responsible for writing meeting minutes and the CSR DMC Team Lead who is responsible for writing, processing and maintaining the Committee minutes and the CSR DMC Team Lead or representative. Employees of the Hines CSPCC who may be involved in studies being reviewed may attend open and closed sessions of the DMC meeting to present reports but should not be present when consensus is reached or when recommendations are made.

5.2 General Format of Meetings

The format of the initial DMC meeting for a **newly convened** DMC may be face-to-face or via teleconference. This meeting will focus on explaining the role and responsibilities, scope of authority, and conventions of the DMC, as well as identification of the member who will serve as Chairperson. A newly assigned protocol may also be reviewed at an initial meeting of a newly convened DMC with the PI and study team, as applicable, participating via teleconference.

In situations other than that of a newly convened DMC, initial review of each newly assigned protocol will be reviewed via a study-specific teleconference as described in Section 5.3 below. The teleconference will be attended by designated reviewers (primary, secondary, and biostatistical) and Chairperson from the DMC membership, the PI and applicable study staff, CSR DMC Team Staff and other potential representatives from Central Office.

Subsequent meetings will be held either face-to-face or via teleconference as described in Section 5.4 below. These meetings are generally scheduled every 12 months.

Each subsequent meeting will include the following:

- General business, including but not limited to items such as introductions of new members, review of DMC member roles and responsibilities, changes in VA policies that may impact DMC function, and any global or other concerns of the Committee members
- Comprehensive progress reviews of ongoing studies, including enrollment/retention, AE's/SAE's/UPIRTSO's, safety issues, and statistical considerations
- Updates of studies (new or recently completed) assigned to the DMC but not scheduled for review at a particular meeting
- Recommendation to the CSR Director including action items to be addressed by the PI.

5.3 Initial Reviews of New Protocols

When a protocol is newly assigned to the DMC, primary and secondary clinical reviewers and a biostatistical reviewer will be assigned to conduct the review. The review of a newly assigned protocol will include:

- Open Reports *do not*
- include efficacy data
 - report safety data by treatment group

DMC Review, Newly Assigned Protocol

<p>The DMC will discuss</p> <ul style="list-style-type: none"> • Roles and responsibilities of the DMC • Study protocol presentation by the PI
<ul style="list-style-type: none"> • Biostatistical considerations: Sample size, interim monitoring rule, safety monitoring rule, frequency and type of reporting to DMC
<ul style="list-style-type: none"> • Issues by the DMC
<p>The review process will include</p> <ul style="list-style-type: none"> • Initial draft and review of study charter • Review of the study safety plan • Review of proposed recruitment methods • Determination of meeting type and frequency • Determination of frequency of reviews (at minimum every 12 months, DMC has the authority to decide more frequent reviews are necessary) • Discussion of whether the study can proceed as approved by the R&D Committee and all applicable subcommittees or external committees (DMC Recommendation) • Determination of whether review will include open and closed sessions or only open sessions* • Establishment of study progress benchmarks and development of a recommendation and action items for the investigator • If closed reports are requested, there will be a decision as to whether data summaries will be masked to hide the identity of randomizing groups (e.g., Group A, Group B rather than identifying the specific treatments) • If interim monitoring of the primary outcome measure is to be provided, review of the statistical monitoring plan

**The DMC may elect to request only open reports based on the level of risk in the study and whether interim monitoring for the primary outcome measure is deemed necessary. The DMC may elect at any time to additionally request a closed safety report, if the open safety data indicate a closer examination is warranted.*

The PI will submit the following to the DMC for review (although the list may be amended for special situations) and will be informed of the deadline for submission:

Documents to Submit, *Initial Review*

<ul style="list-style-type: none"> • Abstract
<i>Study protocol</i>
<ul style="list-style-type: none"> • Most current version • Version sent to IRB for approval • Changes to study protocol since original submission for scientific review • Flow diagram depicting all arms of study • Study Safety Plan
<i>IRB</i>
<ul style="list-style-type: none"> • Submission packet • Reviews and related correspondence • Approved consent forms • List of Serious Adverse Events the Investigator will be looking for, should they occur, and that are unique to the study • Data Analysis Plan

5.4 Progress Reviews of Ongoing Studies

The comprehensive progress review of an ongoing study will be scheduled at least every 12 months. The DMC can decide at any time to increase the frequency of such reviews for a particular study. The DMC may meet face-to-face or by teleconference to conduct comprehensive progress reviews. When necessary, the PI and study biostatistician may participate in the review meeting via teleconference.

The PI will submit to the DMC Manager, a progress report 30 days before the scheduled review meeting, using the standard progress report template issued by the DMC. If the DMC has also requested a closed report, the study biostatistician will separately provide this report to the DMC through the DMC Manager 30 days before the scheduled review meeting.

When possible, the original primary and secondary clinical reviewers and the biostatistical reviewer will lead the progress review. The DMC may meet in closed session to review the progress report and other information provided by the PI and the study biostatistician. If appropriate, the PI may subsequently join the open session of the progress review. The PI will present highlights of the open report and answer questions posed by the DMC. The study biostatistician may also participate in the open session. If the DMC has requested a closed report, the PI will then leave the call and the closed progress review will proceed. The study biostatistician, if available, will present the highlights of the closed report and answer questions posed by the DMC. Then the study biostatistician will leave the call prior to the DMC summarizing action items and making a recommendation.

5.5 Protocol Modifications

At each convened meeting the DMC will consider modifications that have been approved by the IRB and Central Office or are pending with respect to feasibility, justification, and relation to DMC recommendations made for each study.

5.6 Overview of Safety Reviews

Individual SAEs and UPIRTSOs will be reviewed by the CSRD DMC Team (i.e., Quality Assurance Nurse) and directed to the Chairperson and/or assigned reviewers for the particular study as needed. Aggregate AE and SAE safety data and UPIRTSOs will be reviewed at comprehensive progress reviews.

The CSRD DMC Team may schedule an emergency meeting of the DMC if it receives information, either external or internal to the study, indicating significant new risks to study participants may be present. Such information could include new safety information from sources such as the Food and Drug Administration, one or more concerning SAE reports within the study, or other changes in the study that may represent a significant new risk to study participants. In these instances, the DMC may recommend to the CSRD Director temporary suspension until the DMC has met to review the new information, decide whether the study can resume, and decide whether protocol modifications are needed.

6. Procedures to Ensure Confidentiality & Proper Communication

Reporting procedures must be established to ensure confidentiality for all parties and to enhance the integrity and credibility of the study. DMC reporting and procedural and communication plans outlined in the study charter will ensure appropriate communication without unduly restricting transfer of information and decision making by the DMC. These plans will also facilitate exchange of information without compromising the blinding, statistical integrity and conduct of the study. The following principles guide the functions and communication of the DMC:

- The DMC is independent of the PI and study team, but supportive of the aims and methods of the study
- The DMC serves in an advisory role to the Director, CSRD
- The DMC, PI and CSRD work collaboratively to ensure rigorous and timely conduct of the study
- The Director, CSRD, receives the DMC recommendation under advisement. The recommendation is final once approved by the Director, CSRD
- The DMC Manager is the conduit of information for communications between the PI and DMC members (outside of formal teleconference exchanges or convened meetings).

6.1 Open and Closed Reports

Progress reports are provided to the DMC by the PI for each meeting. Open reports are available to all who attend the open session of the DMC. Contents of open statistical reports are described in Section 7 of this guidance.

Closed reports, if needed, will be made available only to those attending closed sessions of the DMC. Closed reports are prepared by the primary study biostatistician, or a suitable surrogate. A basic principle of research integrity is that anyone directly involved in the collection of the research data should not have knowledge of treatment comparisons until data collection is complete. This reduces the likelihood of bias. Thus, the study PI and others directly involved in collection of study data and evaluation of study participants should not have access to closed reports or any other treatment comparison summaries. Contents of closed statistical reports are described in Section 7 of this guidance.

6.2 Recommendations to the Director, CSRD

At each meeting the DMC will make recommendations to the Director, CSRD. Recommendation will be made for a study to proceed initially or continue with unconditional or conditional approval, probation, or termination. This recommendation will be based primarily on safety and efficacy considerations as stated in the study charter. Any recommendation to pause or suspend enrollment may be permanent or temporary until the DMC has completed additional review of new safety information, or protocol modification.

6.3 Minutes of the DMC Meeting

The DMC Manager will prepare minutes of meetings in consultation with the DMC Team Lead. The DMC Chairperson or designee will review and approve the draft minutes before they are forwarded to the CSRD Director for approval. Draft minutes should be made available to the DMC Team Lead no later than 10 working days after each DMC review. Once finalized and signed by the DMC Chairperson, the Director, CSRD, will be responsible for promptly reviewing the minutes that will include review assessments in terms of study progress, participant accrual and retention, adverse events monitoring, and validity of statistical assessment plans; and DMC recommendations plus any action items. After the Director, CSRD, endorses the minutes they become official documentation. Upon receipt of approved/endorsed minutes from the CSRD Director, the DMC Manager will provide them to the study PI and the PI's Associate Chief of Staff for Research (ACOS/R). The CSRD DMC Team may elect to append documents providing additional explanatory information that may be helpful to the PI in responding to DMC's recommendation. The PI will have up to 30 days to respond in writing to the DMC Manager to the DMC recommendation and any action items. These responses will then be forwarded to Committee members for their review and acceptance.

Open minutes will describe the proceedings of the open session of the DMC meeting and present all recommendations by the DMC. If the DMC also conducts closed reviews of the study, it is critical that the open minutes do not un-blind the efficacy and safety data if the DMC is not recommending early termination.

If the DMC also conducts closed reviews, closed minutes will describe the proceedings from all sessions of the DMC meeting including a list of all recommendations by the Committee. These minutes are available only to the members of the DMC; Director, CSRD; CSRD DMC Team; and the primary study biostatistician during the course of conduct of the study. Copies of the closed minutes will be archived by the DMC Team and should be archived by the primary study biostatistician as well.

All copies of the closed DMC minutes will be made available to the PI and study team upon request after closure of data collection in the study.

7. Content of Open and Closed Statistical Reports

7.1 Open Statistical Report: An Outline

Open statistical reports should contain the following:

- An outline of the study design
- Statistical commentary explaining issues presented in Open Report figures, tables and accrual target graphs
- DMC monitoring plan and summary of Open Report data presented at prior DMC meetings
- Major protocol changes
- Information on participant screening
- Study accrual by month by institution
- Eligibility violations
- Quality control variables as developed by the Study Team
- Length of follow-up
- Protocol deviations, especially deviations from the assigned treatment plan
- AE data summaries
- SAE reports and aggregate SAE data summaries
- UPIRTSO reports and summaries
- Withdrawals from treatment and withdrawals from study.

Data tables in open reports do not report data by treatment group.

7.2 Closed Statistical Report

Closed statistical reports, if requested, should contain the following:

- Detailed statistical commentary explaining issues raised by Closed Report figures and tables (by treatment group)
- DMC monitoring plan and summary of Closed Report data presented at prior DMC meetings

- Repeat of the Open Report information, in greater detail by treatment group
- Analysis of primary and secondary efficacy endpoints by treatment group.

If the DMC has elected to receive closed reports where treatment group identification is masked, the primary study biostatistician will unmask the treatment groups upon request by the DMC.

Appendix: Guidance on the Qualifications/Requirements for Data Monitoring Committee Membership

CLINICAL SCIENCE RESEARCH & DEVELOPMENT OFFICE OF RESEARCH AND DEVELOPMENT VETERANS HEALTH ADMINISTRATION

The Clinical Science Research & Development (CSR&D) Data Monitoring Committee (DMC) is an independent multidisciplinary group, whose members have collectively – through research, education, training, experience, and expertise – the requisite knowledge pertinent to the subject areas to be reviewed and the experience to serve as advisors on clinical trials. The DMC establishes membership through an approval process based on nomination by the DMC Manager, following a favorable background check. Upon completion of a favorable background check, the DMC Manager submits the nomination to the DMC Team Lead. The Director of CSR&D may approve, disapprove, or suggest alternative nominations.

This document outlines expected qualifications/requirements for an individual's nomination to the DMC. DMC members must have demonstrated experience in the subject matter of the projects to be reviewed by the DMC. The following are qualifications to be considered:

Funding History: A nominated individual must have at least four years of independent peer-reviewed clinical trial funding (current or previous) at the national level such as:

- VA Merit Review Award funding as Principal Investigator for a clinical trial
 - Nominee must have completed at least one VA Merit Review Award
 - Note that completion of a Career Development Award does not qualify an individual for DMC membership
- National Institutes of Health funding
- Other funding (e.g., National American Heart Association grant)

Academic Position: Individuals should be nominated in the following order of preference: Professor→Associate Professor→Assistant Professor. Please note:

- Level of Associate Professor or above is typically the minimum requirement
- Level of Assistant Professor or below is not typically approved
- Exceptions to the above include:
 - Nominee is at an institution where promotions are known to be delayed
 - Nominee has a pending promotion at his institution, documented in a letter from the Department Chair
 - Nominee has expertise in specialty area, such as biostatistics, pertinent to projects reviewed by the DMC.

Publications: A solid publication record commensurate with academic rank and clinical trial experience is expected. Publications should be in the subject matter area(s) appropriate to the projects under review by the DMC with clinical trials publications highlighted.

Review Experience: It is advantageous for nominated individuals to have current or previous experience on national peer-review panels such as:

- Service on VA Scientific Review Group(s), NIH Study Section(s), or on other review panel(s) (i.e., American Heart Association, American Cancer Society, Paralyzed Veterans of America, etc.)
- Membership on Institutional Review Boards, Research & Development Committees, and editorial boards of scientific journals