

Clinical Science Research & Development (CSR&D)

Data Monitoring Committee Guidance

Version 1.2
Date: 01/02/2012

Version 1.3
Date: 09/02/2015

1. Introduction

Under the auspices of the Department of Veteran Affairs (VA), Office of Research and Development (ORD), and the Director of Clinical Science Research and Development (CSR&D), this document defines the primary responsibilities of the CSR&D Data Monitoring Committee (CSR&D DMC) and guides the activities of the CSR&D DMC, its relationship with other trial components, membership, and the purpose and timing of meetings as managed by the Hines Cooperative Studies Program Coordinating Center (CSPCC). The CSR&D DMC is composed of multiple panels that are convened to assess the performance of funded CSR&D clinical protocols that include human subjects and may involve randomization. This guidance also provides the procedures for ensuring confidentiality, communication, statistical monitoring, and proper reporting of the activities of convened CSR&D DMC panels. Due to the breadth of subject areas supported by CSR&D, multiple DMCs may be established. This guidance applies to each CSR&D DMC.

2. Primary Responsibilities of the CSR&D DMC

The CSR&D DMC is primarily responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of trial interventions and monitoring the progress of assigned clinical trials under review. The DMC conducts comprehensive reviews of each study at each meeting, unless otherwise specified by the DMC. Recruitment is monitored according to a schedule set by the DMC.

Additionally, the DMC may also make recommendations 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 CSR&D DMC is advisory to the Director of CSR&D. The DMC will report to the Director, CSR&D, and make recommendations with regards to the performance of CSR&D funded studies. The Principal Investigator (PI) will also be advised of review assessments in terms of study progress, participant accrual and retention, adverse events monitoring and the validity of statistical assessment plans. The Director, CSR&D, will be responsible for promptly reviewing the DMC recommendations. The Director, CSR&D, will then decide to approve CSR&D DMC minutes and recommendations for unconditional approval, conditional approval, probation or termination.

It is the responsibility of the Director, Hines CSPCC, to formally nominate members for CSR&D DMC following background checks and to request approval by the Director, CSR&D. The Director, CSR&D, also approves the nomination of the Chairperson to each DMC panel.

The members of the CSR&D DMC, under the stewardship of the DMC Chairperson, are responsible for safeguarding the interests of study participants, assessing the safety and efficacy of all study procedures, and monitoring the progress of CSR&D funded studies. The committee functions as an independent advisory group to the Director, CSR&D, in order to ensure that projects proceed safely and according to schedule.

A determination will be made by the Director, CSR&D, with input from Program Staff as needed, as to whether a study approved for CSR&D funding warrants CSR&D DMC oversight. The level of risk to study participants is considered in determining the need for CSR&D DMC involvement. Once the determination for DMC oversight is made (prior to study initiation), the Director, CSR&D, informs the PI's VA facility Associate Chief of Staff for Research (ACOS/R) and the PI of assignment to a CSR&D DMC panel. The DMC Office then communicates directly with the PI to provide DMC related information. The CSR&D 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; 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
- Review adverse event (AE), serious adverse event (SAE) and unexpected problem (UP) documentation and safety reports and make recommendations regarding maximizing the safety of the study participants

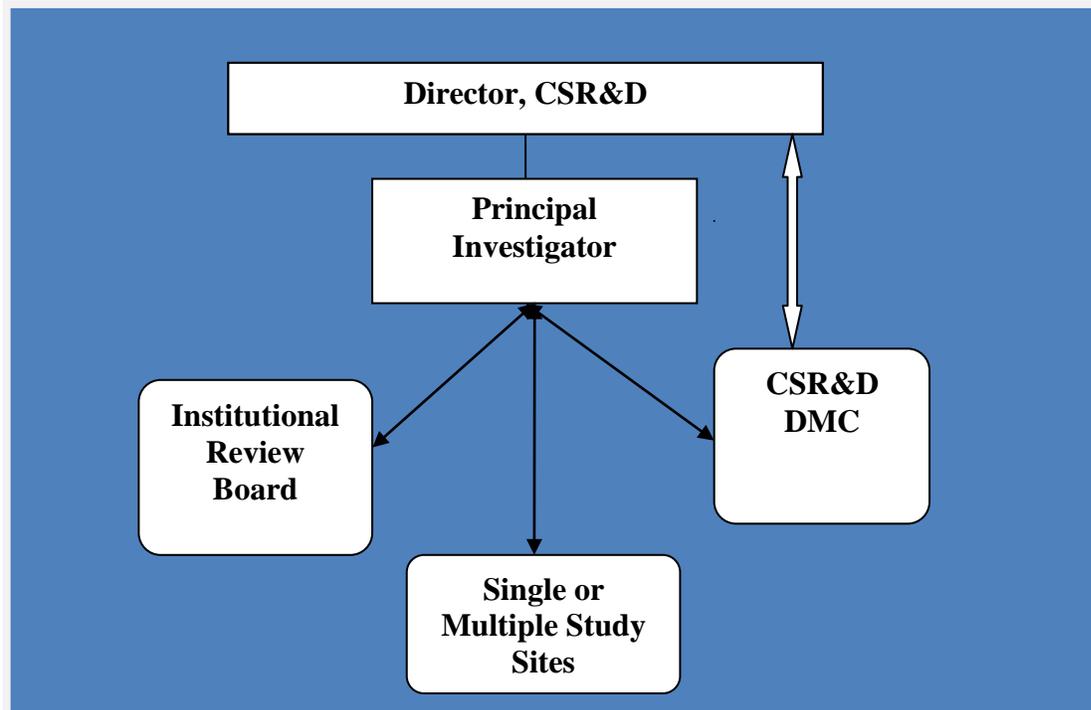
- Report to the Director, CSR&D, on the safety and progress of funded studies through documented committee minutes in a prompt manner
- Evaluate and report to the Director, CSR&D, on any perceived problems with study conduct, enrollment, sample size, and/or data collection
- Provide to the Director, CSR&D, a recommendation regarding continuation conditionally or unconditionally, probation, termination, or other modifications of the study based on its cumulative experience.

Under the stewardship of the CSR&D DMC Chairperson, the DMC will make recommendations to the Director, CSR&D, and Principal Investigators with regards to safety and efficacy of all study processes and overall study progress. The PI will also be made aware at study initiation by the DMC of the statistical and non-empirical benchmarks that will be used as tools for review. In addition, PI's will be informed at study initiation and throughout the study life cycle of data or procedural factors that warrant probationary status and the benchmarks that must be instituted by PI's to reverse probationary and conditional approvals.

The study PI will submit reports to the DMC Office for distribution to DMC members, no later than 30 days prior to committee meetings. Following the DMC meeting, minutes or review reports will be made available to the Director, CSR&D, who has to officially approve the recommendations of the committee. Upon approval by the Director, CSR&D, the recommendations will be sent to the PI and the PI's VA facility ACOS/R. The PI will have up to 30 days to respond to DMC recommendations and action items, if necessary, in writing through the DMC Office. These responses will then be forwarded to committee members for their review and acceptance.

3. Organizational Diagram

The following diagram depicts the general relationships between the Director, CSR&D; the CSR&D DMC and other stakeholders involved in a trial.



4. Membership of the DMC

4.1 Members

The CSR&D DMC panels are independent multidisciplinary groups, whose members have collectively through education, training, experience, and expertise, the requisite knowledge pertinent to the subject area to be reviewed.

DMC panels establish membership through an approval process based on nomination. Upon committee member nomination by the CSPCC Director, following nominee background checks, the Director, CSR&D, will determine approval or non-approval of a nominated committee member. The Director, CSR&D, may also suggest alternative nominations.

CSR&D DMC membership terms will be staggered and no member will serve for a period longer than six years. If any committee members leave the DMC during the course of a trial, Hines CSPCC, in consultation with the Director of CSR&D, will promptly appoint replacements.

The members of the CSR&D DMC are broadly divided into two main functional groups: voting members and non-voting members.

Voting Members: CSR&D DMC voting members, which include the Chairperson, will serve for a period of no more than six years. Voting DMC members will be selected based on their expertise in the subject areas to be reviewed.

Non-voting Members: CSR&D DMC non-voting members include the Director of CSR&D, CSR&D Central Office (CO) Program Staff, and Hines DMC representatives. Committee members who provide additional scientific expertise on a non-regular or ad hoc basis will also be considered as non-voting members. Non-voting members will not have any formal term of appointment.

CSR&D DMC oversight will cover the period from initial review until final study completion and subject assessments. Once the final review for a study is completed, committee members, whether voting or non-voting, are forbidden to participate in any primary or secondary data analysis.

4.2 Authority of the DMC

The CSR&D DMC is authorized by the Director, CSR&D, to evaluate research projects funded through various research funding mechanisms. Studies assigned to a DMC will be reviewed mainly for recruitment and retention on a schedule determined by the DMC. All studies will at least have a full review annually. 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. Full reviews may involve the review of aggregate safety data. The DMC will determine at its initial review whether full reviews will also include aggregate efficacy data and or interim analytic assessments. This is to ensure that the CSR&D project is not an exercise in futility. The DMC has the authority to recommend study continuation unconditionally or conditionally, probation or termination.

Once the committee has made a recommendation regarding the safety and progress of a funded trial, the Director, CSR&D, receives the recommendation through the submission of finalized minutes from the DMC office, to approve or disapprove. After the Director, CSR&D, approves or disapproves the DMC recommendations, the minutes become official documentation.

4.3 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. Voting committee 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 action by motion or vote. At the discretion of the DMC Chairperson and/or DMC Office Staff, such members may participate in the discussion of the protocol prior to any committee actions. Upon appointment to the DMC, all committee members, voting or non-voting, must declare any conflicts of interest to the DMC Manager 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.

DMC members will disclose to the Chairperson any conflicts they consider relevant. It is important to recognize that a conflict of interest may exist if a DMC member has a substantial financial, consultancy or contractual interest in an

ongoing study under review. It must also be recognized that a conflict of interest applies when these relationships or interests exist or appear to exist.

No person who participates in the planning of a study under review, or is from the PI's institution, or plays key roles in the execution of a DMC assigned protocol, should be nominated to the committee. Persons from industry should not be nominated as committee members for studies that involve the evaluation of industrial products of potential commercial value.

The DMC members will be responsible for notifying the Chairperson of any changes in consulting agreements or financial interests that occur during the course of a trial. Any DMC member who develops significant conflicts of interest during the course of reviewing a trial must recuse himself or herself from the review prior to recommendations being made or actions being taken.

5. Authority of the Sponsor

CSR&D, as sponsor, may grant certain special approvals to funded projects monitored by the DMC. The Director, CSR&D, 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, CSR&D, may, however, take into account the DMC's recommendations. The PI must submit all requests for special approval to the Director, CSR&D, through his or her ACOS/R. The DMC will direct PI's who wish to obtain any special approvals to submit their requests as described above, to the Director, CSR&D; a copy of the request must be sent to the DMC Office simultaneously.

6. Quorum Establishment, Organization and Format of DMC Meetings

6.1 Quorum Establishment

All decisions made by the DMC must be taken via quorum; no decisions can take place without the availability of more than 50 percent of the committee's membership. Although the number of DMC members may vary, the DMC membership will always consist of a quorum of 51 percent of the committee's voting membership. At least two clinicians and one biostatistician are always needed as part of the committee's membership and must be part of the quorum for recommendations to be made. While formal votes may be taken, recommendations routinely are made via consensus of the voting members present.

Non-voting membership of the committee must include the CO Program Staff member(s) who is responsible for writing meeting minutes and the CSR&D DMC Office Manager who is responsible for processing and maintaining the committee minutes. 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 upon request, but should not be present when consensus is reached or during the executive session when recommendations are made.

6.2 General Format of Meetings

The format of the initial CSR&D DMC meeting for a **newly convened** DMC will be face-to-face. This meeting will focus on explaining the role and responsibilities, scope of authority, and conventions of the DMC, as well as identification of a person or persons willing to be nominated to serve as Chairperson. Newly assigned protocols may also be reviewed at an initial meeting of a newly convened DMC. The PIs of new protocols reviewed by the DMC can participate by teleconference.

Subsequent meetings will be held either face-to-face or via teleconference. These meetings are generally scheduled every 4 months (three times per year), but the frequency may increase or decrease depending on the current workload of the DMC or other factors. A decision on the format for each meeting will be reached by consensus of the CSR&D DMC and the DMC Office based on anticipated workload for a given meeting. Study PI's and their teams may be invited to participate by teleconference whether the DMC itself is meeting in person or via teleconference.

Each meeting will include the following:

- General business, including items such as introductions of new members, key sections of DMC policy which may require discussion and vote (e.g., threshold for consideration of probation, new methods of SAE reporting), changes in VA regulations that may impact DMC function, and any global or other concerns of the committee members
- Initial review of newly assigned protocols.
- Comprehensive progress reviews of ongoing studies, including enrollment/retention, AE's/SAE's, safety issues and statistical considerations
- Updates of studies under assigned to DMC but not scheduled for review at a particular meeting
- Recommendations to CSR&D Director
- Action items for the PI.

6.3 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 lead the review of the protocol before the full DMC. The review of a newly assigned protocol will include: 1) an initial DMC executive session to discuss the proposal and to identify questions they have for the PI, 2) an open teleconference with the PI, and 3) a final executive session to summarize recommendations. The PI will submit the following to the DMC at least 2 weeks prior to the review:

- A copy of the original protocol submitted to Merit Review
- If the protocol has subsequently been modified, a list of proposed revisions to the original protocol or a copy of the revised protocol
- If not specified in the protocol, how AEs, SAEs and UPs will be defined in the protocol and how they will be assessed.
- If not specified in the protocol, the proposed interim monitoring plan for the primary outcome measure or justification why the PI believes interim monitoring is not needed.

The review process will include:

- Review of the protocol
- Review of the safety monitoring plan
- Review of proposed recruitment methods
- Determination of the frequency of full reviews. These will be conducted at least annually, but the DMC may decide more frequent reviews are necessary.
- Determination of whether full reviews will include open and closed reports or only open reports. 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. If only open reports are requested, they will contain safety data but no efficacy data. Since safety data will not be reported by treatment group in an open report, 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.
- 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 in closed reports, review of the statistical monitoring plan.
- Establishment of study progress benchmarks and development of recommendations and action items for the investigator.

6.4 Recruitment Reviews of Ongoing Studies

All studies will undergo regular recruitment reviews, which are a portion of the regular progress report template developed for the DMC, usually scheduled every 4 months. If a study has been recruiting below 75 percent of its target levels, for one or more reporting periods, the PI will be instructed to submit a recruitment report no more than 30 days in advance of each review, allowing for the most up-to-date numbers to be presented. This will be expected for each month of the recruitment period. This report will include the number screened, the number randomized, and the number withdrawn. If a study has been recruiting at or above 75 percent of projected in previous reports, the DMC Office may request the recruitment figures be submitted only 30 days prior to a meeting. The DMC office will determine whether the report indicates recruitment targets are being met. When recruitment is below target, the DMC

Office will consult with the DMC membership to determine what additional information the PI should provide for the upcoming meeting. In addition, the PI will be contacted to teleconference with the DMC at the upcoming meeting.

At the meeting, the DMC will review the actual recruitment data in comparison with recruitment targets required to complete recruitment within the period specified by the protocol. Additional information provided by the PI pertinent to recruitment will also be reviewed. The DMC will then teleconference with the PI to discuss methods being used and suggest additional strategies for recruitment that may be helpful. Potential protocol modifications, such as revisions to exclusion criteria, may also be discussed. The DMC may also request a reexamination of the assumptions used for the original sample size estimates and other statistical information, to evaluate the likelihood the study will be sufficiently powered to assess the primary hypothesis if the final sample size is less than the original target.

The DMC will consider in executive session whether the study should be placed on **probation** for inadequate recruitment and the terms of the probation. For studies that subsequently do not meet the terms of the probation, the DMC may recommend **termination** of the study.

6.5 Comprehensive Progress Reviews of Ongoing Studies

The comprehensive progress review of an ongoing study will be scheduled at least annually. 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 a comprehensive progress review. The PI and, when necessary, the study biostatistician may participate in the review meeting via teleconference.

The PI will submit to the DMC office a copy of the open 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 office 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 will meet in closed session to review the progress report and other information provided by the PI and the study biostatistician. If appropriate, the PI will 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 and the DMC will go into executive session to summarize recommendations and decide whether the DMC recommends the study can continue.

6.6 Protocol Modifications

At each convened meeting the DMC will review protocol modifications submitted by individual investigators for feasibility, justification, and relation to DMC recommendations made to that study.

6.7 Overview of Safety Reviews

Individual SAEs will be reviewed by the DMC Office and directed to the assigned reviewers for the particular study with the Director, CSR&D, also being notified. Aggregate AE and SAE safety data will be reviewed at comprehensive progress reviews.

The DMC office will request from the committee Chairperson an emergency meeting of the DMC when it receives information, either external or internal to the study, indicating significant new risks to study patients 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 patients. In these instances, the DMC may recommend to the CSR&D Director temporary suspension of patient intake until the DMC has met to review the new information, decide whether the study can resume, and decide whether protocol modifications are needed.

7. 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 trial. 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 of the trial, the statistical integrity of the trial and the subsequent successful conduct of the trial. The following principles guide the functions and communication of the DMC:

- a. The DMC is independent of the PI and study team, but supportive of the aims and methods of the study
- b. The DMC serves in an advisory role to the Director, CSR&D
- c. The DMC and PI with the office of the Director, CSR&D, work collaboratively to ensure rigorous and timely conduct of the study
- d. The Director, CSR&D, receives DMC recommendations under advisement. Recommendations are final once approved by the Director, CSR&D
- e. The DMC Office is the conduit of information for communications between the PI and DMC members (outside of formal teleconference exchanges or convened meetings).

7.1 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 8 of this guidance.

Closed reports are made available only to those attending closed sessions of the DMC. Closed reports are prepared by the primary trial 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 patients should not have access to closed reports or any other treatment comparison summaries. Contents of closed statistical reports are described in Section 8 of this guidance.

7.2 Minutes of the DMC Meeting

CSR&D CO Program Staff in collaboration with the DMC Administrator, under the oversight of the Chairperson, will prepare minutes of the meetings. The DMC Chairperson or designee will review and approve the draft minutes before they are forwarded to the CSR&D Director for approval. Minutes will be made available to the CSR&D Director no later than 10 working days after each DMC meeting. Upon receipt by the DMC office of approved minutes from the CSR&D Director, the DMC Office will provide the study PI and the PI's ACOS/R a copy of the approved minutes that include recommendations and action items. The DMC Office may elect to append a document providing additional explanatory information that may be helpful to the PI in responding to DMC recommendations.

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 unblind the efficacy and safety data if the DMC is not recommending early termination.

If the DMC also conducts closed reviews, then 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, CSR&D; CSR&D CO Program Staff; and primary trial biostatistician during the course of conduct of the trial. Copies of the closed minutes will be archived by the DMC Office and the primary trial biostatistician.

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

7.3 Recommendations to the Director, CSR&D

At each meeting the DMC will make one of four types of recommendations to the Director, CSR&D. The recommendation will be made for unconditional approval, conditional approval, probation or termination. This recommendation will be based primarily on safety and efficacy considerations as stated in the study charter. A recommendation to suspend enrollment will be for permanent enrollment suspension, temporary suspension until the DMC has completed an emergency review of new safety information, or suspension of enrollment until approval of a protocol modification.

8. Content of Open and Closed Statistical Reports

8.1 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 patient 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
- Withdrawals from treatment and withdrawals from study.

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

8.2 Closed Statistical Report

Closed statistical reports 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.