OFFICE OF DATA QUALITY
450 BROOKLINE AVENUE, OS200
BOSTON, MA 02215-5450

Overview

A centralized Data Safety Monitoring Board (DSMB) has been created to review DF/HCC investigator-initiated randomized protocols that otherwise do not have an independent DSMB assigned. These trials include both the National Cancer Institute (NCI)- and industry-sponsored randomized studies, typically Phase III trials, which have a DF/HCC investigator as the lead investigator. The Office for Data Quality (ODQ) coordinates the meetings. The charter describes the authority, responsibilities and membership of the DSMB, and the schedule and structure of its meetings.

Authority

The DF/HCC DSMB is an advisory committee to the DF/HCC Senior Vice President for Research and study principal investigators. When the DF/HCC DSMB determines that a change should be made to an existing trial, it will make those recommendations to the study team, with a copy to the DFCI IRB and the DF/HCC Clinical Investigations Leadership Committee (CLC). The DFCI IRB will adjudicate disagreements between the DSMB and a study team.

Responsibilities

The study team will prepare a DF/HCC Data and Safety Monitoring Report for each protocol being monitored by the DSMB. The reports will be sent to the DSMB by ODQ staff at least two weeks in advance of the meeting. This report will summarize the current status of the study, including enrollment and toxicity information, and may also contain recommendations regarding on study-related issues for consideration by the DSMB. The report will follow a template distributed by ODQ staff to the study teams. The mailings may also include the full protocol document (new protocols), and, at the discretion of the DSMB, continuing renewal applications and SAE reports to the DFCI IRB.

The members of the DSMB will: (1) Familiarize themselves with the research protocol(s) and plans for the data and safety monitoring. (2) Evaluate study summary data to determine protocol progress and whether the trial should continue as originally designed, should be changed, or should be terminated based on these data. (3) Review reports of related studies to determine whether new information means the monitored study needs to be changed or terminated. (4) Review major proposed modifications to the study prior to their implementation (e.g. termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

Following each meeting, the ODQ staff will prepare the DSMB meeting minutes. These minutes will be sent to the DSMB members for review and approval, and copies will be sent to the DFCI IRB and DF/HCC Clinical Investigations Leadership Committee (CLC). The DFCI

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IRB will acknowledge receipt of the DSMB minutes to the ODQ staff. Following each meeting, the DSMB chair will also send memorandum to each study PI summarizing the DSMB recommendations regarding the study. The protocol Principal Investigator (PI) will be required to submit an acknowledgement of receipt of the DSMB report to the ODQ staff.

Typically the DSMB minutes and PI reports will not include confidential outcome data. For studies that remain blinded, outcome data will not be made available to individuals outside of the DSMB. Any special release of this data should be approved by the DSMB. In instances where the DSMB recommends changes to the design of a study (including early stopping of enrollment because of the results of an interim analysis or changes in one or more of the treatments), the DSMB will provide in writing to the protocol PI a rationale for these recommendations.

Outcome data for protocols still enrolling patients are considered confidential and are not to be discussed outside the DSMB meetings. Outcome data may be released to the study team for manuscript preparation or planning of future studies only after review and approval by the DSMB. No communications of the deliberations (either written or oral) or recommendations of the DSMB will be made outside the DSMB except as provided for in this policy.

The protocol assigned statistician and ODQ Data Managers will address any requests for distribution of interim data reports, including toxicity data. As indicated above, no blinded data will be released without the expressed approval of the DSMB.

The study team should implement recommendations from the DSMB expeditiously. When requested by the DSMB, the protocol PI will respond in writing to the DSMB and DFCI IRB of the actions taken regarding the recommendations and the reasons for that decision. The DFCI IRB will adjudicate any disagreements between the DSMB and the protocol PI.

The DFCI IRB should evaluate recommendation from the DSMB expeditiously. When the DSMB recommends accrual suspension as a result of patient safety concerns, the Chair of the IRB is responsible for ensuring that the study is closed as soon as possible, but no longer than 24 hours after receiving the recommendation.

In cases where an immediate judgment is necessary based upon the severity of patient safety issues, the Chair of the IRB is empowered to suspend or close the study. In other situations that are less urgent in nature and that require additional clarification, the Chair of the IRB may confer with the Chair of Scientific Progress Review Committee (SPRC) as well as with the DF/HCC Medical Director, Clinical Trials Operations. The purpose of this step is to provide an extra layer of validation of the DSMB's recommendation before accepting the recommendation as final. This process is expected to occur within 24 hours and should permit time to methodically review the data that formed the basis of the DSMB's recommendation.

In cases where the DSMB recommendation does not involve trial closure for patient safety, the Chair of the IRB may decide to place the DSMB recommendation on the IRB agenda for a more complete discussion (if it is not time dependent). Alternatively, the DSMB recommendation may be referred to SPRC or to the Scientific Review Committee (SRC) if it involves accrual or scientific design issues, respectively, that are not sufficient to recommend study closure, but sufficient enough to warrant a more in depth evaluation.

In any case where the Chair of the IRB is not available, the DF/HCC Medical Director, Clinical Trials Operations is responsible for receiving and acting upon the DSMB recommendations. For administrative management, all communications to the Chairs of the IRB, SRC or SPRC will be copied to the Director of the Office for Human Research Studies.

Trials being monitored by the DF/HCC DSMB will remain under the DF/HCC DSMB review until either the last enrollment occurs, or until the DSMB feels there are no patient safety concerns that require further monitoring. The DSMB will determine the length of continued review on a study-by-study basis.

The DF/HCC expects that the DSMB will act in a way that is consistent with the intent of the design of a protocol and in the best interests of the study participants. In some instances, the DSMB may recommend changes to the design of a protocol, the timing of data collection or the details of an analysis because either the assumptions made in the original design are not true, or because of data external to the study. The deliberations of the DSMB should not be influenced by special interests of either the study team or the protocol sponsor.

Each member of the DSMB must sign a confidentiality agreement. DSMB members will be expected to follow the Harvard Medical School guidelines for disclosing conflicts of interest and will sign a statement agreeing to that policy at every meeting.

Membership

The DSMB membership includes both voting and non-voting members. The Senior Vice President for Research appoints all members of the DSMB. The DSMB chair is selected from the voting members by the voting members. There will be five permanent voting members of the DSMB, at least three of who must come from institutions outside the DF/HCC. Voting members will include physicians, statisticians, other scientists, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trial methodology. For studies requiring special expertise, the Senior Vice President for Research may appoint ad hoc non-voting members to provide advice on protocols. The voting members of the DSMB will normally come from the following disciplines and institutional affiliations:

Medical Oncologist (External, outside DF/HCC)
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Other Scientist (radiation oncologist or surgeon – within DF/HCC)
Statistician (External, outside DF/HCC)
Ad hoc membership (if special expertise is needed)

The Chair of the Department of Biostatistics and Computational Biology or his designee will serve *ex officio* as a non-voting member of the DSMB.

A quorum consists of the DSMB Chair, at least one other medical oncologist and the external statistician.

The DSMB members, both internal and external, are indemnified by DFCI against possible liabilities. DFCI's general and professional liability policies, under the insurer CRICO, cover DFCI and non-DFCI DSMB members serving in a volunteer capacity.

With the prospective permission of the DSMB Chair, guests may attend a DSMB meeting to observe for educational purposes. The invited guest will be required to sign a confidentiality agreement prior to the meeting. If the invited guest is affiliated with any of the trials under review, he/she will be asked to leave for the closed session review of that trial.

Meeting Structure

Meetings will be held at least twice each year. Depending on the nature and volume of the trials being monitored, one of these meetings may take place by conference call. Each protocol will be discussed in both an open and a closed session. In the open session, members of the study team, including the study statistician, may be present to review the conduct of the trial and to answer questions from members of the DSMB. The focus of this open session will be on accrual, protocol compliance, and general toxicity issues. Outcome results will normally not be discussed during the open session. The closed session of the DSMB will include only the voting, non-voting and ad hoc members, along with ODQ staff, and will include discussion of the general conduct of the trial and outcome results, including toxicities, and adverse events. The study statistician may be asked to present outcome data during the closed session.

The DSMB meeting will close with an executive session to summarize and evaluate the overall meeting, finalize recommendations, and plan the next meeting.