

**POLICY OF THE NATIONAL CANCER INSTITUTE
FOR DATA AND SAFETY MONITORING
OF CLINICAL TRIALS**

Introduction

All clinical trials supported or performed by NCI require some form of monitoring. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the principal investigator/project manager or NCI program staff to a data and safety monitoring board (DSMB). These monitoring activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Throughout this policy, the term "awardee" means the awardee institution. In the case of NCI intramural research, the comparable institutional unit is the NCI.

Responsibility for Data and Safety Monitoring

Responsibility for data and safety monitoring depends on the phase of the study and may be conducted by NCI program staff or contractor, by the principal investigator/project manager conducting the study, or by a DSMB. Regardless of the method used, monitoring must be performed on a regular basis. Oversight of the monitoring activity is the responsibility of NCI program staff. In the case of extramurally funded research, adherence to this NCI policy and any data and safety monitoring policies of the NCI Division making the award will be made a condition of the award.

Phase I and Phase II studies may be monitored by the principal investigator/project manager, by NCI program staff or a designee, or jointly. When conducted by the principal investigator/project manager, the awardee must have written policies and procedures describing the monitoring and reporting processes in place. The awardee's policies must be consistent with any policies of the NCI Division making the award. NCI program staff from the awarding NCI division will determine the acceptability of the awardee's policies and procedures. These will be documented in the grant, cooperative agreement or contract file and become part of the award.

All Phase III randomized clinical trials supported or performed by NCI require monitoring by a DSMB. The organization, responsibilities, and operation of the DSMB are described below.

For studies co-funded with other NIH Institutes or Centers (IC), the lead NIH IC will be responsible for monitoring the study and establishing a DSMB if necessary. Oversight of the DSMB will be the collaborative responsibility of the lead NIH IC and NCI.

Requirement for Data and Safety Monitoring Boards

Data and Safety Monitoring Boards must be established to monitor all Phase III randomized clinical trials supported or performed by NCI. Funds to support the functions and operations of the DSMBs will be provided by NCI in a fashion to be determined by each NCI Division.

Responsibilities of the DSMB

1. Familiarize themselves with the research protocol(s) and plans for data and safety monitoring.
2. Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data. The DSMB reviews trial performance information such as accrual information. The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
3. Review reports of related studies to determine whether 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).
5. Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. A copy of this information will be provided to the NCI Division Director or designee. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRBs.

Membership

The DSMB voting members will be appointed for a fixed term by the principal investigator/project manager or designee. Proposed DSMB members must be reviewed and approved by the awarding NCI Division Director or designee prior to their appointment. The Chair of the DSMB will be selected from among the voting members. Voting members of the DSMB should include physicians, statisticians, other

scientists, and lay representatives selected based on their experience, reputation for objectivity, absence of conflicts of interest (and the appearance of same), and knowledge of clinical trial methodology.

Voting members may be from within or outside the institution¹, but a majority should not be affiliated with the institution. Staff affiliated with the institution who are members of the DSMB should view themselves as representing the interest of patients and not that of the institution. Voting members directly involved with the conceptual design or analysis of a particular trial must excuse themselves from all DSMB discussion of the particular trial and must not receive that portion of the DSMB report related to the particular trial.

Program and statistical staff from the NCI may be permitted to serve as *non-voting NCI representatives* to the DSMB at the request of the NCI Program Director since NCI has a critical stewardship responsibility with regard to the clinical trials that it supports. NCI representatives are not considered “members” of the DSMB and should be limited in number.

The roles, responsibilities, and rationale for attendance of NCI staff at closed or executive sessions should be clearly articulated in the specific DSMB policy for a NCI Clinical Trials Program or individual NCI-sponsored trial commiserate with the stewardship/oversight functions required for that Program or trial (e.g., programmatic, scientific and/or administrative functions). NCI staff should be objective about the outcome of the trial(s), abide by all confidentiality requirements as well as the conflict of interest policy of the DSMB, and should function only to ensure that the DSMB members have all appropriate information to make independent recommendations about the trial(s).

NCI Program Directors should provide NCI staff training related to their roles and responsibilities of oversight monitoring when attending DSMB meetings. The NCI Program Director or his/her designee should be available to discuss **any** concerns related to DSMB functions, including the role of NCI staff.

The awardee may name a chief statistical officer to be a non-voting member of the DSMB if the DSMB has been established to oversee multiple NCI-sponsored clinical trials supported under the award.

Meetings

DSMB meetings will be held at least annually and more often depending on the nature and volume of the trials being monitored. Each meeting should be divided into three parts.

First, an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. The focus in the open session may be on accrual, protocol compliance, and general toxicity issues. Outcome results must not be discussed during this session.

Following this session, a closed session involving the DSMB members, designated NCI representative(s) to the DSMB (if attendance permitted by the NCI Program Director), and the coordinating

center/statistical office statistician(s) handling the trial should be held. The statistician(s) should present and discuss the outcome results with the DSMB. In order to meet the responsibilities for monitoring the safety of participants and the integrity of the data, DSMBs must be able to access unmasked data whenever masked data are presented. It is generally recommended that all data be presented to the DSMB in an unmasked manner; however, if the awardee leading the trial(s) desires to keep some data masked, then this is acceptable provided that any DSMB member's request for unmasking of trial data is honored.

A final executive session involving only DSMB members and designated NCI representative(s) to the DSMB (if attendance permitted by the NCI Program Director) should be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

A written report containing the current status of each trial monitored, and when appropriate any toxicity and outcome data, should be sent to the attendees for the closed session by the coordinating center/statistical office allowing sufficient time for them to review the report prior to the meeting. This report should address specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow up.

Recommendations from the DSMB

DSMB recommendations should be based on results for the trials being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the coordinating center/statistical office, trial investigator(s), NCI program staff and statisticians, and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available, and of any programmatic concerns related to trials being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to specific trials.

DSMB recommendation(s) will be given to the trial principal investigator/project manager² with a copy provided to the NCI Division Director or designee. If the DSMB recommends a study change for patient safety or efficacy reasons, or that a study be closed early due to slow accrual, the trial principal investigator/project manager must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator/project manager does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for disagreement. The trial principal investigator/project manager, DSMB Chair, and the NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and NCI staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision. In the absence of disagreement, policies of the NCI Division that made the award under which the trial is supported should be followed in regard to amending the protocol or changing the award.³

Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial principal investigator/project manager for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. **Any** release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

Confidentiality Procedures

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to **any** non-member of the DSMB, except as indicated above in the Meetings and Recommendations sections, until the recommendation to release the results are accepted and implemented. All DSMB members and designated NCI representatives must sign a statement of confidentiality.

Conflict of Interest

DSMB members are subject to the awardee's policies regarding standards of conduct. Individuals invited to serve on the DSMB as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the trial principal investigator/project manager and the appropriate institutional officials(s), in accordance with the institution's policies. Conflict of interest can include professional interest⁴, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94. Potential conflicts which develop during a member's tenure on a DSMB must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institution's policies.

¹ "Institution" is defined for this purpose as the awardee(s) institution and any institutions collaborating scientifically in the conceptual design or analysis of the study (beyond merely referring patients),

including Cooperative Group member institutions participating in the trial, or consortia member institutions participating in the trial.

² "Trial principal investigator/project manager" means the individual primarily responsible for the project, i.e., the principal Chair of a Cooperative Group, the principal investigator listed on a U10, UM1, P01 or R01 award, or the project manager listed on a contract award.

³ This policy in no way affects any legal appeal rights of the awardee.

⁴ "Professional interest" is used in the sense of the trial outcome benefiting the individual professionally.

The above was approved by the NCI Clinical and Translational Research Operations Committee (CTROC) on 9/30/2014.