16 Study monitoring and interim analyses

The primary purpose of monitoring a clinical trial is to ensure the safety and well-being of the specific participants entered on the trial. All interventional protocols must include a formal monitoring plan. All randomized phase 2 all phase 3 trials, and some specially-designated trials are formally monitored by a standing Alliance Data and Safety Monitoring Board (DSMB). The monitoring functions for other trials (e.g., phase 1 and non-randomized phase 2), including accrual monitoring, are carried out by the study chair, the primary statistician, and the executive officer along with other members of the study team and Alliance staff.

16.1 Study monitoring by the DSMB

16.1.1 Studies requiring DSMB monitoring

All Alliance-led phase 3 and randomized phase 2 NCTN or NCORP sponsored trials are monitored by the Alliance DSMB. Non-interventional (i.e., Screening) trials do not usually require formal monitoring procedures, however other studies may be monitored by the DSMB if deemed appropriate by the NCTN/NCORP group chair and DSMB chair.

16.1.2 Function of the DSMB

The responsibilities of the DSMB are as follows:

1. The primary responsibility of the DSMB is to review adverse event data in conjunction with protocol-specified interim and final analyses of outcome efficacy data (prepared by the study statistician) and to recommend whether the study needs to continue per protocol or be changed or terminated based on these analyses. For phase 3, phase 2/3, and randomized phase 2 trials, the committee also determines whether and to whom outcome results should be released prior to the public reporting of study results at the time specified in the protocol.

2. The DSMB reviews reports of related studies performed by the network groups or other organizations to determine, considering information and recommendations supplied by the study team, whether the Alliance led study needs to be changed or terminated.

3. The DSMB oversees the safety and accrual data; however it is also the responsibility of the study team (including medical monitoring, as applicable) to review the safety and accrual information on a regular basis. The study chair also oversees safety through processes defined in Sections 8.3 and 8.4.

4. All patient level clinical trial data release requests, including baseline data, or patient level or aggregate outcome data, including projections of analysis milestones outside of the NCI policy, on DSMB monitored studies have to be submitted to the DSMB for review and approval. Per NCI policy, the timing of the final analysis (6 months or less in advance) will be given to NCI (and company partners as applicable).

5. The DSMB reviews major modifications to the study proposed by the study team (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, other major design changes).

16.2 Overview of DSMB procedures

Each study to be monitored requires periodic (at least every 6 months) confidential reports to be prepared by the primary statistician. These reports are submitted to the DSMB, a single standing committee established for the purpose of reviewing all of the individual reports. No individuals other than members of the DSMB receive a copy; specifically, the study chair does not receive a copy.

16.2.1 Confidentiality

All interim and final analyses are carried out in a confidential manner. No one other than those explicitly authorized to be part of the monitoring process have access to the results. All such persons must keep all aspects of their deliberations in strict confidence. Any violation of confidentiality is considered a serious offense.

All members of the DSMB pledge to maintain confidentiality. The Alliance SDMC maintains confidential files of all reports and in conjunction with the Alliance Operations Center retains the meeting minutes and record of actions taken on each study. No communication of the deliberations of the committee, either written or oral, may be made except as provided for in these DSMB policies and procedures. Any violation of confidentiality must be reported to the Alliance group chair.

16.2.2 Membership

The DSMB chair is nominated for a five-year term by the Alliance group chair and confirmed by NCI. The group statistician is a non-voting member of the DSMB. All other members are appointed by the Alliance group chair for three year terms, and include individuals primarily from outside of the Alliance. The majority of the voting DSMB members cannot be affiliated with the Alliance, and voting quorums for a DSMB meeting require that the majority of voting members not belong to the Alliance. Individuals are selected based on their breadth of experience, reputation for objectivity, absence of the actual conflicts of interest or the appearance of conflicts of interest, and knowledge of good clinical trial methodology. There is at least one lay member and a voting statistician from outside the group. One or more NCI physician(s) and a NCI statistician, selected by NCI, are nonvoting *ex officio* members. Members of the DSMB who chair or co-chair studies being monitored by the committee excuse themselves from all DSMB discussions concerning that study and do not receive DSMB reports concerning that study. Members of the DSMB who are leaders (chair or vice chair) of disease or modality committees excuse themselves from all DSMB discussions concerning

studies being conducted by their committee and do not receive DSMB reports concerning those studies.

16.2.3 Meetings

The DSMB meets at least twice yearly, ordinarily in conjunction with scheduled group meetings (see section 5). Additional DSMB meetings may be held at any time or in any form as decided by the DSMB chair.

The DSMB meeting itself consists of open (optional, per discretion of DSMB chair) and closed (required) sessions for each study under consideration. During the open session, the study chair, primary statistician, and committee chair are available to answer questions posed by DSMB members. During the closed session, the DSMB decides what action, if any, is required. The study chair, primary statistician, and committee chair must absent themselves from the closed session even if they are members of the DSMB.

16.2.4 Recommendations

The results of each DSMB meeting are summarized in a formal report by the group statistician and sent to the Alliance group chair within two weeks of the meeting (urgent matters are addressed immediately). The DSMB report contains recommendations on whether to modify or close each study reviewed, whether to release and report the results, and whether to continue study per protocol. A primary recommendation (e.g., continue with no change; recommended or required modification; release study results and stop further DSMB monitoring) must be included in the document. Upon approval from the Alliance group chair, the recommendations are sent to NCI for review approval before any action is taken.

The Alliance group chair, or designee, is responsible for notifying the study chair, primary statistician, and committee chair before the recommendations of the DSMB are carried out. An edited version of the recommendations is distributed to Alliance membership. The Alliance Operations Center keeps an archive of DSMB recommendations; the SDMC keeps an archive of the DSMB meeting minutes.

16.2.4.1 Study change for patient safety reasons

In the event that the DSMB recommends a study change for patient safety reasons (including early stopping for inferior therapy), the Alliance group chair will act to implement the change as expeditiously as possible. For studies that are being closed based on a DSMB recommendation, although NCI pre-approval is not

required, the Alliance group chair (or his/her designee) must inform and discuss the closure of the study with the NCI leadership before disclosing the study closure to anyone. If the DSMB recommends closure of a study, the NCI physician member of the DSMB will provide the current 24/7 contact information for NCI leadership.

16.2.4.2 Study closure due to slow accrual

In the event that the DSMB recommends a study be closed early due to slow accrual, then the recommendation of the DSMB would be processed as described in 16.2.4.1 above. Note: NCI may have additional closure policies that apply to studies with slow accrual that have not yet had formal interim efficacy analyses presented to the DSMB.

16.2.4.3 Study change for non patient safety reasons

In the event that the DSMB recommends a change in a study for reasons other than either patient safety or study closure due to slow accrual such as extend accrual because of an event rate lower than expected, the DSMB will provide to the Alliance group chair an adequate rationale. In the absence of disagreement, the Alliance group chair (working with the study chair) will be responsible for having an amendment prepared and submitted to the appropriate NCI Protocol and Information Office reflecting the recommendations of the DSMB and providing the rationale for the changes. (This is required even if NCI approval has been obtained prior to the amendment being presented to the DSMB.) NCI approval of the amendment will be required prior to implementation of the change, although it is anticipated that a decision to override the recommendation of the DSMB will be made only in the most exceptional circumstances. In the event that the Alliance group chair disagrees with the DSMB recommendation, the recommendation would be processed as described in 16.2.4.4.

16.2.4.4 Disagreement with Alliance DSMB Recommendations

In the unlikely situation that there is a disagreement with the Alliance DSMB recommendations, the Alliance and NCI leadership will work together with the Alliance DSMB chair and group statistician for a mutual resolution.

Confidentiality will be maintained during these discussions, but relevant data will be shared with the Alliance and NCI leadership, and other parties whom they wish to involve in reaching a decision.

In the exceptional circumstance that a mutually acceptable decision cannot be reached, final responsibility for a decision will rest with the applicable NCI division director.

16.2.5 Study modifications

Major modifications to the study design by the study team not motivated by confidential outcome data or patient safety/toxicity data (e.g., increasing the sample size because of more rapid than expected accrual) must be discussed with NCI before being presented to the DSMB for consideration. If NCI is willing to approve the modifications, the network group informs the DSMB at the next scheduled DSMB meeting.

In an event that the study team wishes to request permission not to follow the protocol pre-specified decision rule and/or a major redesign, such a request must first be discussed with the NCI, and the DSMB notified. This request (change in the design of the trial) needs to be approved by the NCI, including assignment of an independent statistician as appropriate following the NCI policy for major redesign. The study team works with the group statistician and the independent statistician on the redesign proposal, with consultation from NCI. Upon receiving NCI approval, the DSMB is notified of the redesign and an official amendment is submitted to the appropriate NCI Protocol and Information Office.

16.2.6 Release of data & results

For phase 3, phase 2/3, randomized phase 2 trials, and any other trial monitored by the DSMB, ***any*** release of outcome data (either internal to the network group, to NCI personnel not members of the DSMB, or external [e.g., a paper presented at professional society meetings, seminars, papers, etc.]) prior to the final approval of general dissemination of results must be reviewed and recommended for approval by the DSMB to the Alliance group chair. In general, outcome data from phase 3, phase 2/3, and randomized phase 2 trials would not be routinely made available to individuals outside of the DSMB until accrual has ceased and all patients have concluded their randomized treatment and completed study follow-up and/or reached a protocol-specified endpoint. After this time point, the DSMB may recommend the release of outcome data on a confidential basis to the study chair for planning the preparation of manuscripts, and/or to a small group of individuals for purposes of planning future trials. The DSMB will consider

special requests for information from the disease committee chair prior to that time point. The DSMB should be made aware of any communication of analysis results from phase 3, phase 2/3, and randomized phase 2 trials outside of the SDMC at any time. The Alliance group chair may not be able to accept the recommendation of the DSMB to release data for a specific trial if the Alliance and/or NCI has a binding agreement with a company collaborator (or other entity) that specifies data exclusivity for the trial without discussing the release with NCI (for Alliance trials with a NCI binding agreement) and/or the company or other collaborator (for Alliance studies that are under other binding agreements).

16.2.7 Presentation of results by intervention group

The DSMB assesses relative efficacy according to the protocol specified interim and final analyses; therefore, results by intervention are presented and discussed. No intervention-specific results, coded or not, are released to anyone not on the DSMB.

16.2.8 Phase 2/3 trials

With respect to implementation of phase 2 decision rules in phase 2/3 designs of clinical trials, any protocol-specified phase 2 decision-rule analysis must be performed timely when the required number of events are observed and reported in the database, and report submitted to the DSMB. If the trial follows the decision rule (i.e., continues or stops depending on whether the continuation threshold is met), then the DSMB review and decision of the status of the trial (i.e., continuing or stopping) based on the protocol-specified phase 2 decision rule is communicated to Alliance and NCI leadership. Any deviations from the protocol specified design specifications follows the NCI policy for a major redesign, see 16.2.5 above.

16.2.9 Industry-supported studies

Studies supported by industry are also covered by these policies and procedures. Industry representatives may not serve on the Alliance DSMB.

16.2.10 Conflict of interest

Individuals invited to serve on the DSMB are subject to the Alliance Conflict of Interest policy (see section 3.5).

16.3 Monitoring phase 1 and 2 studies

16.3.1 Phase 1 studies

Phase 1 studies are ordinarily limited access studies. Routine monitoring is carried out via conference call among representatives of each participating institution, the primary statistician, the study chair and members of the study team. A representative from each institution must participate whenever the institution has any participants currently receiving protocol therapy. Institutions that fail to submit adverse event data as required or that do not participate in the conference calls will be prohibited from continuing to enroll participants on the study.

16.3.2 Phase 2 studies

Non-randomized phase 2 studies are routinely monitored by the study team (study chair, primary statistician, executive officer, protocol coordinator, data management personnel) following the protocol specified plans for efficacy and adverse event monitoring, as well as other Operations Center staff (e.g. director of regulatory affairs), as applicable.

All patient level clinical trial data release requests, including baseline data, or patient level or aggregate outcome data, including projections of analysis milestones cannot be shared outside of the statistical team. Requests for this data would have to be submitted to the study statistician who will consult with group statistician and Alliance leadership for review and approval. The timing of the final analysis (6 months or less in advance) can be given to the study chair (and company partners as applicable), NCI may be notified.