Policy Memorandum No. 21
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DATA AND SAFETY MONITORING POLICY

Studies to be Monitored

A single DSMC monitors all SWOG-coordinated Phase III and randomized Phase II therapeutic, advanced imaging, and cancer control trials. For large prevention trials, a separate DSMC may be formed where some members will be chosen due to their expertise outside of cancer.

Responsibilities

1) The primary responsibility of the DSMC is to review interim analyses of outcome data (prepared by the study statistician) and to recommend whether the study needs to be changed or terminated based on these analyses. For phase III, phase II/III, and blinded randomized phase II trials, the committee also determines whether and to whom outcome results should be released prior to the reporting of study results at the time specified in the protocol.

2) The DSMC reviews reports of related studies performed by the Network Groups or other organizations to determine, considering information and recommendations supplied by the study committee, whether the group study needs to be changed or terminated.

3) The DSMC reviews interim toxicity data although that is primarily the responsibility of the study committee.

4) The DSMC reviews major modifications to the study proposed by the study committee prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size).

Membership

DSMC members are appointed for three-year terms (renewable once, unless special circumstances permit otherwise) by the Group Chair with the approval of the Chief, Clinical Investigations Branch (CIB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD) at the NCI or his/her designee. The nominees should be reviewed and approved by NCI/DCTD with written confirmation by the Chief, CIB prior to their official appointment and participation in DSMC activities. The committee will include physicians and statisticians from within and outside SWOG selected based on their experience, reputation for objectivity, absence of conflicts of interest (or the appearance of same), and knowledge of good clinical trial methodology. The committee will include a consumer representative and a voting statistician from outside the group. A NCI/DCTD physician and a NCI/DCTD Biometric Research Branch (BRB) statistician, as designated by the Chief, CIB will be non-voting members and will be free to attend all sessions of the DSMC including closed and executive sessions. The SWOG Group Statistician, or his or her designee, will also be a non-voting member of the DSMC. Since SWOG is also funded as NCORP Research Bases, a designee named by the Division of Cancer Prevention (DCP) Community Oncology and Preventive Trials Research Group (COPTRG) program director will be a non-voting member and is free to attend all sessions.

The DSMC is constituted by voting members who are either members of SWOG or external to SWOG; however, the majority of the voting DSMC members are not affiliated with SWOG, and voting quorums for a DSMC meeting require that the majority of voting members not belong to SWOG.

SWOG members who are members of the DSMC must see themselves as primarily representing patient interests and not the interests of SWOG or the SWOG Group Chair. Members of the study team or the

leadership of the disease committee or scientific research committees of the Network Group (e.g., chair or vice-chair of the disease committee) conducting a study will recuse themselves from all DSMC discussions concerning that study and will not receive DSMC reports concerning that study. Additionally, the study statistician will not be a voting member of the DSMC for his/her trial. The SWOG Group Chair, Principal Investigator on the SWOG Group Operations Center grant using the multiple Principal Investigator option, or any member of the executive leadership of SWOG (including vice-chairs and executive officers, but not disease-committee chairs or members of SWOG executive committees, as long as they are not also vice-chairs or executive officers) cannot attend closed or executive sessions of the DSMC. In addition, the SWOG Chair, Principal Investigator(s)/Program Director(s) on the SWOG Operations Center grant using the multiple Principal Investigator option, or any member of the executive leadership of SWOG, cannot be a member of SWOG's DSMC.

Each of these trials will also have a Study Committee, composed of the study chair, study statistician, any discipline coordinators, and the disease committee chair. The Study Committee for Intergroup trials will also have a representative from each of the participating Groups.

Meetings

The DSMC meets twice yearly. Each year, one meeting will be face-to-face in conjunction with the SWOG meeting and the other biannual meeting will be conducted as a conference call within six weeks prior to the corresponding SWOG meeting. Members who fail to attend two consecutive meetings (including conference calls) may be replaced. The DSMC Chair may choose to convene the DSMC "conference call" meeting as a face-to-face meeting if the agenda merits it. Other communications (conference calls, e-mails, etc.) take place as determined by the DSMC Chair. For a given study, the frequency of DSMC deliberations is guided by the protocol-specified plans for formal interim analyses. Prevention DSMCs may plan to meet yearly and additionally only as needed.

Every six months a written report outlining the current status of each trial being monitored will be developed by the study statistician and sent to the DSMC members at least three weeks prior to the bi-annual DSMC meeting. The Study Chair may prepare a report addressing specific toxicity concerns or other concerns about the conduct of the study. The statistician's report may contain recommendations on whether to close the study, whether to report the results, whether to continue accrual or follow-up, and/or whether a DSMC discussion is needed. Unless a DSMC discussion is requested by a DSMC member, the recommendations will be accepted without discussion. Major modifications to the study design not motivated by confidential outcome data or patient safety/toxicity data, however, must be discussed with CTEP before being presented to the DSMC for consideration. If CTEP is willing to approve the modifications, the Group may then seek DSMC approval before submitting an official amendment to CTEP.

With respect to implementation of phase II decision rules in phase II/III designs of clinical trials, any protocol-specified phase II decision-rule analysis must be performed within six weeks from the date the required number of events are observed. If the trial follows the decision rule (i.e., continues or stops depending on whether the continuation threshold is met), then SWOG notifies the DSMC and Chief, Clinical Investigations Branch (CIB) of the status of the trial (i.e. continuing or stopping) based on the protocol-specified phase II decision rule. In the unlikely event that the study statistician wishes to request permission not to follow the protocol pre-specified decision rule, such a request must first be discussed with NCI/DCTD/CTEP by conference call within two weeks. This request (change in the design of the trial) needs to be approved by the CTEP Associate Director or his/her designee in consultation with the Chief, CIB who will notify the SWOG Operations Center in writing of NCI decision regarding the request. If NCI/DCTD/CTEP is willing to approve the request, SWOG must then seek DSMC approval within three weeks before submitting an official amendment to CTEP's Protocol and Information Office to change the design of the trial regarding the phase II decision rule.

The review of each trial may include three parts. The first part will be an open session in which members of the study team and disease committee and NCI/DCTD staff not on the DSMC may be present at the request of the DSMC to answer questions. In this part, the focus is on accrual, compliance and toxicity issues, and no outcome results may be presented. Following the open session, there will be a closed

session limited to DSMC members and possibly the study statistician in which outcome results will be presented either by a member of the DSMC, the designated SWOG Statistician, or the study statistician. It is generally recommended that outcome data be presented to the DSMC in an unblinded manner. However, if SWOG desires to keep outcome data blinded (perhaps on some specific trials), then this is acceptable provided that any DSMC member request for unblinding for a trial will be honored. Following this closed session, there will be a fully closed, executive session in which the DSMC discusses outcome results, and then votes. At the executive session, those present are limited to DSMC members. Decisions of the DSMC will be by majority vote of those present, with the tie votes being decided by the DSMC chair.

Recommendations

DSMC recommendations should be based upon results for the current study being monitored as well as upon data available to the DSMC from other related studies. The study committees, NCI/DCTD staff, and individual DSMC members will assure that the DSMC is advised about relevant non-confidential results from other related studies that become available. It will be the responsibility of the DSMC, with advice from the study committee, to determine the extent to which this information is relevant to decisions to continue or modify the current study.

The DSMC will provide recommendations to the SWOG Group Chair to change a study or to continue a study unchanged. In the event a change is recommended by the DSMB/DMC, the study statistician may send his/her written report that was prepared prior to the DSMB/DMC meeting to the SWOG Group Chair, who may seek the advice, in a confidential manner, of the Study Chair, Disease Committee Chair, and/or SWOG Group Statistician.

1) In the event that the DSMC recommends a study change for patient safety reasons (including early stopping for inferior therapy), the SWOG Group Chair will act to implement the change as expeditiously as possible. For studies that are being closed based on a DSMC recommendation, although CTEP pre-approval is not required, the SWOG Group Chair (or his/her designee) must inform and discuss the closure of the study with the Chief, CIB or his/her designee before disclosing the study closure to anyone. If the DSMC recommends closure of a study, the NCI/DCTD physician member of the DSMC will provide the current 24/7 contact information for the Chief, CIB or his/her designee.

In the unlikely situation that the SWOG Group Chair does not concur with the DSMC recommendation, the Group Chair must discuss his/her reasons for not accepting the DSMC recommendation with the Chief, CIB. The Chief, CIB will then inform the CTEP Associate Director of the recommendation of the DSMC and of the Group Chair's reasons for disagreeing with the recommendation. The CTEP Associate Director, Chief, CIB, and the Group Chair, in consultation with the DSMC Chair, will be responsible for reaching a mutually acceptable decision about the study. Confidentiality will be maintained during these discussions, but relevant data will be shared with the Group Chair, Chief, CIB, CTEP Associate Director, 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 CTEP Associate Director in consultation with the Director of the Division of Cancer Treatment and Diagnosis.

2) In the event that the DSMC recommends a study be closed early due to slow accrual, then the recommendation of the DSMC would be processed as described in 1) above. Note: NCI/DCTD/CTEP may have additional closure policies that apply to studies with slow accrual that have not yet had formal interim efficacy analyses presented to the DSMC.

3) In the event that the DSMC recommends a change in a study for reasons other than either patient safety (e.g., to extend accrual because of an event rate lower than expected) or study closure due to slow accrual, the DSMC will provide to the Group Chair an adequate rationale. In the absence of disagreement, the Group Chair will be responsible for having an amendment prepared and submitted to CTEP’s Protocol and Information Office reflecting the recommendations of the DSMC and providing the rationale for the changes. (This is required even if NCI/DCTD/CTEP approval has been obtained prior to the amendment being presented to the DSMC.) NCI/DCTD/CTEP 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 DSMC will be made only in the most exceptional circumstances. In the event that the Group Chair disagrees with the DSMC recommendation, the recommendation would be processed as described in 1) above.

For DSMC recommendations specific to cancer prevention and control trials funded by a NCORP Research Base grant, the appropriate NCI staff to include and report to are the DCP/COPTRG Program Director (instead of the NCI/DCTD physician member of the DSMB/DMC), the Chief of COPRTRG (instead of the Chief, CIB) and the Associate Director for Clinical Research in DCP (instead of the CTEP Associate Director), and the Director of the Division of Cancer Prevention (instead of the Director of the Division of Cancer Treatment and Diagnosis).

Confidentiality Procedures

No communication of the deliberations or recommendations of the committee, either written or oral, should be made outside of the committee except as provided for in these policies and procedures. Statements of confidentiality should be signed by all DSMC members. Outcome (efficacy) results from phase III, phase II/III, and blinded randomized phase II trials are strictly confidential and must not be divulged to *any* non-member of the DSMC (excepting the Group Chair, Chief, CIB, and CTEP Associate Director as described above) without the approval of the DSMC until the recommendation to report the results are accepted and implemented.

The actual contact information for the DSMC membership is not publicly shared; however, the Group will describe their roles as needed.

Release of Results

For phase III, phase II/III and blinded randomized phase II trials, ***any*** release of outcome data [either internal to SWOG, to NCI personnel not members of the DSMC, 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 DSMC to the designated Group Chair. In general, outcome data from phase III, phase II/III, and blinded randomized phase II trials would not be routinely made available to individuals outside of the DSMC until accrual has ceased and all patients have concluded their randomized treatment. After this time point, the DSMC 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 DSMC will consider special requests for information from the disease committee chair prior to that time point. The DSMC should be made aware of any communication of analysis results from phase III, phase II/III, and blinded randomized phase 2 trials outside of the statistical center at any time. The Group Chair may not be able to accept the recommendation of the DSMC to release data for a specific trial if SWOG and/or NCI/DCTD/CTEP has a binding agreement with a company collaborator (or other entity) that specifies data exclusivity for the trial without discussing the release with CTEP (for SWOG trials with a CTEP binding agreement) and/or the company or other collaborator (for SWOG studies that are under other binding agreements).

Conflict of Interest

Individuals invited to serve on the DSMC (voting and non-voting) will disclose to the Group Chair any potential, real or perceived conflicts of interest (see SWOG policy #35). These will include professional interest, proprietary interest and miscellaneous interest considerations as described in the NCI/DCTD/CTEP Conflict of Interest Policy for NCTN Program Phase III Trials (formerly known as the NCI Conflict of Interest Policy for Cooperative Group Phase III Trials). The SWOG Group Chair, with the advice of the SWOG Conflict of Interest Committee, will review possible conflicts and determine whether there is sufficient basis to exclude the individual from serving on the DSMC. Potential conflicts which develop during the conduct of a trial should also be disclosed to the Group Chair.

NCI/DCTD Oversight

In order to satisfy its objectives of protecting patients, ensuring study integrity and assuring public confidence in the conduct of clinical trials, it is essential that the DSMB/DMC function in a manner that demonstrates competence, experience and independence from SWOG, career or financial interests. If

NCI/DCTD determines that a DSMC for SWOG is not functioning in this manner, it will discuss with the Group Chair what changes are needed to the composition or structure of the DSMC.

Membership of DSMC and Attendance at Sessions

	Open session	Closed Session	Executive Session
Voting member of DSMC	Present	Present (except if member of the study team or leadership of the disease committee for the study under consideration)	Present (except if member of the study team or leadership of the disease committee for the study under consideration)
NCI/DCTD (non-voting) member of DSMC	Present	Present	Present
Study statistician	Present	Present	Absent
Designated Group statistician (non-voting)	Present	Present	Present (except if study statistician for the study under consideration, in which case, the designated Group Statistician can name another statistician from SWOG as his/her non-voting designee for the executive session)
Group Chair or any member of the executive leadership	Present (if he/she desires)	Absent	Absent