

SWOG

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DATA AND SAFETY MONITORING POLICY

1. BACKGROUND

Interim evaluations of comparative trials are necessary in order to monitor for extreme therapeutic and prevention results, as well as for excess toxicity and practical difficulties. Routine reporting of some of these evaluations, those concerning side effects of treatment and study conduct, is necessary to apprise participating physicians of safety issues and to improve study quality. Routine reporting of interim results, however, is not only unnecessary but also detrimental to study quality.

One source of difficulty lies in what constitutes an "extreme result." Investigators might wish to consider a result extreme and close a study whenever the p-value of a test statistic falls below .05. There are at least two major problems with this approach. The first problem has to do with the long term nature of most clinical trials. For instance, early separation survival curves is not convincing evidence of long term survival benefit for the superior arm. If a study is closed on the basis of early differences, the ability to make long term evaluations will be compromised due to the limited sample size. The second problem is that the probability of a false positive is greatly increased by allowing repeated testing at the .05 level. By testing repeatedly and reporting whenever $p < .05$, the probability of obtaining a false positive can increase to over .25.

These problems are addressed by requiring very small p-values to close a study early (e.g., $p < .005$). Using this approach, the ability to compare long term results is given up much less frequently. Furthermore, stringent closing requirements at interim analyses allow final analyses to be performed at nearly the usual .05 level while maintaining an overall 5% chance for false positive results for the entire study.

Another source of difficulty with interim reporting is that a study can be stopped informally as well as formally. Presentation of early results with p-values indicated at the .05 or .01 level (or with no p-values reported but with widely separated curves or identical curves shown) is likely to result in reduced accrual, with many physicians treating according to the current best (or least toxic) regimen rather than randomizing their patients. Furthermore, decisions to close a study are rarely as straightforward as examining a single test statistic; many factors must be carefully considered before a decision to terminate is made.

It is for these reasons that SWOG convenes a Data and Safety Monitoring Committee (DSMC). The DSMC is responsible for carefully considering all relevant information related to a given study, as described more fully below, and then providing a recommendation to the Group Chair concerning whether the study needs to be changed or terminated based on the information. This policy is consistent with the National Cancer Institute's Cooperative Group Data Monitoring Policy.

2. DATA AND SAFETY MONITORING COMMITTEE AND STUDY COMMITTEE

2.1 Membership and Responsibilities

A single DSMC monitors all SWOG Phase III and selected randomized Phase II therapeutic and cancer control trials. For large prevention trials such as SELECT, a separate DSMC will be formed where some members will be chosen due to their expertise outside of cancer. DSMC members are appointed for three-year terms (renewable once, unless special circumstances permit otherwise) by the Group Chair, with the approval of the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), and include members both from within the Group and from outside the Group. A majority of the DSMC are outside members, at least one outside member is a patient advocate, and at least one a statistician. The Group Statistician (or designee), two representatives of CTEP (one physician and one statistician), and one representative of the Division of Cancer Prevention (DCP) are non-voting members. The Group Chair may not be on the DSMC. Members who fail to attend two consecutive meetings (including conference calls) may be replaced.

Each of these trials will also have a Study Committee, composed of the study coordinator, 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.

The DSMC is responsible for reviewing interim analyses of data prepared by the study statistician and for recommending whether the study needs to be changed or terminated based on these analyses. The DSMC also determines when the results of the study should be published or otherwise released to the public. The DSMC reviews any major modifications to the study proposed by the Study Committee prior to their implementation (e.g., dropping an arm based on toxicity or reports of other trials, or changing the accrual goals). The Study Committee is responsible for monitoring the data from the study for toxicity, feasibility, and accrual. The Study Committee is also responsible for initiating minor changes in the study such as clarifications and eligibility refinements, and may request that the DSMC initiate major changes as discussed above. The Study Committee, CTEP 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 weight given to the information relative to making decisions on monitored studies.

2.2 Procedures

The DSMC meets twice yearly. Each year one meeting will be face-to-face in conjunction with the SWOG meetings, and the other biannual meeting will be conducted as a conference call 1-6 weeks prior to the corresponding SWOG meeting. 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. The frequency of DSMC deliberations for a given study are guided by the protocol-specified plans for formal interim analyses. Unplanned monitoring of a given study may be requested by any member of the Study Committee or DSMC. 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.

For those trials which require discussion by the DSMC, the Group Statistician (or his designee) will present the report of the study statistician. Following this presentation, the DSMC will develop its recommendations. DSMC members who are on a Study Committee for a particular study, except for the Group Statistician (or his designee), should absent themselves from the review of that study. The Group Statistician (or his designee), although allowed in the Closed Session, should recuse himself from the Executive Session when studies for which he is the Study Statistician are being discussed. Decisions of the DSMC will be by majority vote of those present, with the tie votes being decided by the DSMC chair.

A table is provided at the end of this policy showing the ability of DSMC members and any Group leaders to attend DSMC meetings.

2.3 Recommendations

The DSMC will provide recommendations on each trial being monitored to the Group Chair based on results for the trial as well as other data available to the DSMC from related studies. The study statistician may send his written report prepared prior to the DSMC meeting to the Group Chair at this time.

In the event a change in a trial is recommended for patient safety reasons, including early stopping of inferior therapy, the Group Chair will act to implement the change as rapidly as possible. He may seek the advice, in a confidential manner, of the Study Chair, Disease Committee Chair, and/or Group Statistician. If the Group Chair does not concur with the DSMC recommendation, then the CTEP Associate Director and Group Chair, in consultation with the DSMC Chair, will be responsible for reaching a mutually acceptable decision.

For studies that are being recommended for closure prematurely, although CTEP pre-approval is not required, the Group Chair must inform and discuss the closure of the study with the responsible NCI Program Director before disclosing the study closure to anyone. Relevant data will be shared with the Group Chair, CTEP Associate Director, and other parties whom they wish to involve in reaching a decision on treatment studies. For DSMC recommendations specific to cancer prevention and control trials funded by a CCOP Research Base grant, the appropriate NCI staff to include and report to are the DCP/COPTRG Program Director, the Chief of COPTRG and the Associate Director for Clinical Research in DCP. If a change in a trial is recommended for reasons other than patient safety, the Group Chair will be responsible for communicating the recommendation and the DSMC rationale to CTEP on treatment studies (or DCP on prevention studies), whose approval is required prior to implementation.

2.4 Access to and Release of Data

The DSMC and the study statistician will be the only individuals with regular access to the primary outcome data (typically survival, progression, and/or response), although toxicity and accrual information will be presented to the general membership in the Report of Studies. Release of data to anyone else for any purpose until the trial is published must be approved by the DSMC. Release of data to a small, specified group of investigators for planning purposes is acceptable after the last randomized patient has completed treatment, or otherwise as explicitly determined by the DSMC. The Group Chair may not be able to accept the recommendation of the DSMC to release data for a specific trial if the Group and/or 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 and/or the company collaborator.

2.5 Conflict of Interest and Confidentiality

On an annual basis, the members of the DSMC and of each Study Committee will disclose to the Group Chair any potential conflict of interest (see SWOG Policy #35), as well as disclosing any potential conflicts arising during the year or during the conduct of a Group trial. The Group Chair, with the advice of the Conflict of Interest Committee, will determine whether there is sufficient basis to exclude a DSMC member from participation in the discussion and decisions with respect to a given trial or from serving on the DSMC entirely. DSMC members involved in the Study Committee for a trial, except for the Group Statistician, will not participate in the DSMC discussions of that trial.

No communication of the deliberations or recommendations of the DSMC should be made outside of the DSMC except as otherwise permitted in the policy. DSMC members will be required to sign confidentiality agreements. Outcome (efficacy) results are strictly confidential and must not be divulged outside of the DSMC members, except as permitted to the Group Chair and CTEP Associate Director provided herein, without the approval of the DSMC until the recommendation to report the results are accepted and implemented. Premature disclosure of confidential data, deliberations or recommendations, except as provided for in this policy, will result in removal from the DSMC. The actual contact for the DSMC membership is not shared; however, the Group will describe their roles.

2.6 Intergroup Trials

These guidelines apply also to intergroup trials. The DSMC of the Group whose statistical center is coordinating the trial will monitor the trial. The term “Group Chair” in this policy will apply to the Chair of the coordinating Group.

3. INSTITUTIONAL RESPONSIBILITIES

The SWOG Data and Safety Monitoring Policy is available to local Institutional Review Boards (IRBs) on the Group website at <http://swog.org>. As outlined in the “GUIDANCE ON REPORTING ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS FOR NIH-SUPPORTED MULTICENTER CLINICAL TRIALS,” the NIH requires that summary reports of adverse events be communicated from the DSMC to the IRBs at participating institutions. The interim toxicity reports for SWOG studies are thereby posted on the Group website as are the minutes of the DSMC most recent deliberations, with access to such minutes limited to Group membership.

Table 1: 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)
CTEP (non-voting) member of DMC	present	present	present
Study statistician	present	present	absent
Group Statistician (non-voting)	present	present	present (except if study statistician for the study under consideration)
Group Chair or any member of the executive leadership	present (if he/she desires)	absent	absent
Prevention DSMC			
DCP Leadership	Present (if he/she desires)	absent	absent