

PROTOCOL GUIDELINES

GENERAL INFORMATION FOR PROTOCOL DEVELOPMENT AND ADMINISTRATION

By reviewing and following these guidelines, a protocol author helps to ensure prompt and efficient processing of the study.

1. To be a Study Chair, an individual must be a member of SWOG and must have completed the Group's online Study Chairs' Workshop or the SWOG Young Investigator course.
2. The format of the protocol will follow the SWOG protocol template. Suggested content and prompts are included in the online template to be found on the Protocol Workbench on the SWOG website.
3. Protocol Development and Administration

The goal of centralized protocol development in SWOG is to speed development and standardize quality and format of the most important studies in the judgment of the Committee Chair within every research committee of the Group. This process includes central review of all studies by Group leadership at the earliest possible time in the development process. Protocol status reports will be maintained on the Group web site and development time will be tracked for all studies in development by committee, and provided to the respective Study Chairs and Committee Chair at least semi-annually, and more often upon request (they are always available on the SWOG web site). The Group's Executive Committee will review development time for studies on a quarterly basis (or more often as particular situations warrant) and will recommend a corrective action plan involving action by the Protocol Coordinator, the Clinical Trials Project Manager, the Executive Officer, the Study Chair and/or the Committee Chair – as needed – for any study where the Executive Committee identifies that intervention is needed. If corrective action is not taken within the timeframe specified in the corrective action plan, the protocol may be moved lower in priority and/or tabled.

Protocol development for the highest priority trials (generally 3, as a rule of thumb) per committee will be pursued as expeditiously as resources allow. Protocol development for lower priority studies will be actively pursued by SWOG staff as time and competing priorities allow.

TIMING CONCERNS

Please see <http://ctep.cancer.gov/SpotlightOn/OEWG.htm> for a summary of issues related to required milestones and timeframes related to study supported by the Cancer Therapy Evaluation Program of the National Cancer Institute.

PERSONNEL INVOLVED IN PROTOCOL DEVELOPMENT

Protocol Coordinator/Operations Office

The protocol development responsibilities of a Protocol Coordinator for SWOG are:

- To coordinate and assist in the development and activation of studies to be performed within SWOG and to ensure that this is done in a timely fashion.
- To assist the Study Chairs by sending them information, answering questions and providing clarification regarding the protocol development process and Group procedures.
- Specifically, to coordinate the development of each proposed study through activation including:
 - putting proposed studies into a proper and acceptable format, and

- making sure that all pertinent physician coordinators, Statisticians and Committee Chair perform a detailed review of the study and incorporate comments and changes into the study.
- To serve as a liaison between the National Cancer Institute (NCI) and the Committee.
- To ensure that the study is consistent in content and contains all the information that is required by the NCI and the Group.
- To submit the study to the NCI for review and distribute information about the study (such as approval or disapproval) to the appropriate individuals.

Clinical Trials Project Manager/Operations Office

The Clinical Trials Project Managers provide direct supervision to the protocol department staff (including the Protocol Coordinators) and assist the study teams in defining and tracking protocol project components, necessary resources and associated deadlines.

Director of Operations and Protocols/Operations Office

The Director of Operations and Protocols is responsible for assisting the responsible Protocol Coordinator in the prompt development of the priority protocols per Committee, and providing overall leadership, training and consistency across Committees in protocol development and maintenance.

Study Chair

The Study Chair is the primary advocate for an idea within the Group. The Study Chair is the Group member who proposes a study, is the primary force in developing the capsule summary into an activated protocol in a timely fashion, is responsible for answering questions regarding medical and scientific issues that arise during the conduct of the study, expeditiously responding to requests from the Statistical Center and analyzing the data in conjunction with the Committee Statistician, and writing the manuscript summarizing the results of the trial. Investigators in SWOG who coordinate a Group trial must adhere to the requirements listed herein. In addition, the investigator must complete the Group's Study Chair Workshop prior to receiving approval to coordinate a SWOG trial. This workshop provides a detailed overview of each responsibility (Protocol Development, Study Monitoring, Study Evaluation, Reporting of Results, etc.). Except in unusual circumstances, a Study Chair may not be primary Chair of more than one SWOG-coordinated Phase III clinical trial at a time. The detailed job description of a Study Chair is found in SWOG Policy Memorandum No. 11.

A manuscript outlining the results of the study is required from the principal Study Chair within one year of closure date, unless publication at that time as advised by the Committee Statistician or Data and Safety Monitoring Committee is premature. Refer to Policy Memorandum No. 24, Publication Guidelines, for the proper procedure.

By Group definition, coordinating a clinical trial means involvement from the capsule summary stage to the submission of a manuscript. Study Chairs are required to submit a disclosure of any significant financial conflict of interest that they may have in conformity and compliance with the Group's Conflict of Interest Policy #35.

Executive Officers

The protocol development responsibilities of the Executive Officers are:

- To continually assess the committee priorities in relation to Group priorities.
- To evaluate each study proposal's merit in terms of its fit with the Group mission.
- To provide leadership consistency across committees.
- To participate in protocol review.
- To assist in the review of protocol development timelines.

Committee Patient Advocate

The protocol development responsibilities of the Patient Advocate are:

- To participate in committee discussions regarding potential new trials and prioritization.
- To review the capsule summary and concept/LOI prior to submission to assess potential obstacles to accrual and the desirability of the trial for the patient's perspective.
- To review the study's final eligibility requirements and the study's Model Informed Consent Form to ensure that expectations are realistic and are conveyed appropriately.

The role of the Committee Chair is described in Policy #10.

PROTOCOL DEVELOPMENT PROCESS

CAPSULE SUMMARY PHASE

The Study Chair is initially responsible for proposing a new idea to the Committee and the Group. The Study Chair must receive approval from the Committee Chair of the responsible committee to proceed with development of a capsule summary. When a new protocol (or an amendment to an existing protocol) is identified where the eligibility crosses traditional committee boundaries, the Protocol Coordinator will take the following steps:

- 1) contact the chair of the proposing committee to find out whether the chair of the "secondary" committee has agreed that this protocol, committee assignment and inclusion criteria are appropriate
- 2) contact the chair of the "secondary" committee to assign a secondary Study Chair from their committee
- 3) ensure that both the "secondary" committee chair and assigned Study Chair are copied on circulation of all formal protocol drafts - to ensure opportunity for comments
- 4) enter the involvement of the additional committee into the publication tracking system to ensure that each committee is recognized for its input.

The Study Chair will additionally seek input in a similar manner from any involved Research Support Committees through contacting the relevant Committee Chair(s) and soliciting input on the proposal.

The Protocol Coordinator will serve as a resource for information and distribution of information during this phase. The Protocol Coordinator will assist in preparing a capsule summary from information provided by the Study Chair. Any SWOG member wishing to begin putting together a capsule summary may contact any Protocol Coordinator in the Operations Office at any time to request a copy of the capsule summary format. There are special requirements regarding proposing translational medicine studies as part of a clinical trial. The Protocol Coordinators are also able to assist in deciding whether to include a translational medicine proposal submission with your capsule summary, or not.

Things to think about while completing a capsule summary:

- Is this proposal as complete and clear as it can be (providing scientific rationale for the questions being asked)?
- Does this study build on a previous trial within SWOG?
- Will the study result in a new direction or build toward a subsequent definitive trial?
- What is the likelihood of successful accrual? What evidence do you have to support accrual estimates?
- What is the practicality of endpoint assessment within SWOG?

Scientific Issues

The scientific section of Phase III trials will involve detailed description and justification for selection of the control and experimental arms. The control arm should be selected so that it

conforms to best standard therapy that has been defined in previous clinical trials and/or represents standard of care in the community. Selection of the drugs, doses and schedules for the experimental treatment arm should be based on the results of Phase II (or in rare instances, completed Phase I) clinical trials. Modification of the drugs, doses, or schedules from the Phase II experience is to be discouraged. The Study Chair should then contact the Committee Statistician to discuss determination of primary and secondary endpoints, ancillary study endpoints, and sample size for the trial.

In the case that ancillary studies are to be done, it is the Study Chair's responsibility to identify sources of funding to accomplish those ancillary studies and to notify the Director of Operations and Protocols and the Protocol Coordinator of the contact personnel with whom contract negotiations or grant submission can be initiated. Potential funding sources include R-O1 or R-O3 grants from the National Cancer Institute, supplemental funding to the SWOG U-O1 grant, institutional grants, and a pharmaceutical sponsor, to name but a few. It is imperative that funding sources be obtained prior to the initiation of the development of the protocol document.

In conjunction with discussions with the Committee Statistician, Executive Officer, the Committee's Patient Advocate and the Committee Chair, the Study Chair must assure that the eligibility criteria for the study are written in such a way that there will be adequate patient availability to complete the planned accrual in an appropriate period of time. If any significant differences of opinion develop, they should be discussed among all participants through a conference call. The final eligibility criteria for the study are then developed with input from other modality chairs (e.g., surgical oncology, radiation oncology), where appropriate.

In trials involving multimodality therapy as part of the therapeutic protocol, input from all involved modalities must occur throughout the capsule summary, concept blueprint and protocol development phases. Modality input during the concept blueprint phase refers to defining modality-specific criteria for inclusion in the concept.

The process for development of a Phase II trial proceeds along a somewhat similar pathway. Selection of the drug, dose and schedule should be based on the results of Phase I or preliminary Phase II data. From that point on, the elements in protocol development are similar up to the point of preparation of an LOI for submission to CTEP by the Protocol Coordinator.

Administrative Issues

Some studies may involve investigational new drugs (INDs) obtained directly from a pharmaceutical company, or ancillary or other studies that require additional financial support. Such protocols require additional administrative support. Should the study involve an investigational new drug obtained directly from a pharmaceutical company, the Study Chair should provide the Operations Office with the name of a contact person at the company who will be able to provide us with information to begin identifying issues to negotiate a contract for support of the study.

It will be the responsibility of the Group Chair's Office and the Operations Office staff to ensure adequate drug supply for the study, to arrange drug distribution, to address regulatory issues such as IND filing, to determine the extent of data above and beyond Group norms that will be required for this study, and to develop a budget and contract that will cover the costs for these elements in the conduct of the study. The SWOG staff will be responsible for keeping the Study Chair and the Committee Chair apprised of the status of these negotiations. The SWOG staff will also work within National Clinical Trials Network (NCTN) mechanisms to establish a national coverage analysis that addresses issues related to cost containment. For more detail regarding these principles, see Policy Memorandum No. 17.

In the event of ancillary or other studies, it will be the responsibility of the Study Chair to identify sources of financial support for these studies. SWOG staff are available to assist with this process.

When the capsule summary is completed and approved by the Committee Chair, the Protocol Coordinator provides the capsule summary to the Director of Operations and Protocols for placement on the agenda for the Executive Conference, comprised of leadership from the Group

Chair's Office, Operations Office and Statistical Center. Approval of the capsule summary will depend on feasibility and priority within the Group, and current workload in the Operations Office and Statistical Center.

Following review by the Executive Conference, the decision and specific comments will be communicated to the Study Chair and Committee Chair with a copy to the Protocol Coordinator, and to other individuals involved in the review process, for official record-keeping.

Upon receiving the Committee Chair's priority ranking, the Protocol Coordinator will contact the Study Chair and the Committee Biostatistician with specific information on the study's priority ranking and its significance. The Protocol Coordinator will provide the Study Chair with information about proceeding with study development. Studies may be re-prioritized at the discretion of the Committee Chair. The Committee Chairs will be asked to re-prioritize the studies within development in their Committee whenever a new capsule summary is approved.

The first step in continuing this process will be to hold a Feasibility and Financing (F&F) call that is specific to the protocol. This call will ensure that all study team members have a common understanding of study development processes, timelines, logistics and financial questions and plans.

CONCEPT DEVELOPMENT

In this phase, the capsule summary is expanded to provide information for a formal Letter of Intent (LOI) or concept submission. The Protocol Coordinator will then assist the Study Chair in finalizing the requirements of the scientific planning for the study and will begin working with the Director of Operations and Protocols toward fulfilling the detailed requirements of the administrative issues. Budget development and contract negotiations begin simultaneously with finalizing the details for concept submission. The Study Chair and Committee Chair will be kept apprised of progress and problems and/or delays in addressing the administrative issues.

The Protocol Coordinator is responsible for development of an LOI (if it is a smaller trial, see http://ctep.cancer.gov/protocolDevelopment/docs/loi_form.doc) or concept (if it involves a larger - usually a randomized - Phase II or Phase III trial, see http://ctep.cancer.gov/protocolDevelopment/docs/Concept_Submission.doc) which is reviewed by the Executive Officer, the Study Chair, the Committee Chair, the Committee Statistician and the Statistical Center review committee for accuracy and completeness. Note: The scientific rationale for the study must be sufficiently supported in the concept/LOI document. The concept/LOI is then submitted to CTEP for review. If substantial changes are suggested or mandated by CTEP, the concept/LOI may need to start over from the Capsule Summary phase. A traditional intergroup study should have formal commitment from the other participating group(s) before proceeding with submission of the concept.

PROTOCOL DEVELOPMENT

If the concept is approved by the NCI with no significant changes to elements of the blueprint, protocol development may now proceed. The Protocol Coordinator now becomes the pivotal person in the development process. All important elements of the study should be in place to develop the concept into a full protocol. The Protocol Coordinator will be responsible for completing the remaining steps in development and activation in a timely fashion. CTEP's comments regarding the concept or LOI will be forwarded to the Study Chair, Committee Chair, Committee Statistician, and Executive Officer for review. The Study Chair and Committee Statistician in conjunction with the Protocol Coordinator will be responsible for integrating those revisions into the full protocol. Once the full protocol has been developed, it will be circulated among the Study Chair, Committee Statistician, Committee Chair, Executive Officer and others on the study team (e.g., liaisons from other Disease and Research Committees or Administrative Committees) for revisions, consistency check, and statistical and data coordination review prior to submission of a full protocol to CTEP. Upon receipt of CTEP's review of the protocol, those comments will be circulated to the study team for review. The study team will be responsible for responding to all of CTEP's comments and the Protocol Coordinator will be responsible for generation of a revised protocol. The revised protocol will once again be circulated to the study

team for review and comment prior to submission to CTEP. Barring any additional comments or concerns by CTEP, the protocol will be activated within SWOG upon final approval from CTEP or DCP.

It is critical that the Study Chair personally review all materials and references during protocol development and throughout protocol conduct to ensure scientific integrity and to provide appropriate attribution when required.

POST-ACTIVATION

During the course of the study, occasions may arise to change parts of the study. The Protocol Coordinator remains the primary liaison to ensure that protocol changes are adequately documented and distributed. The study team remains involved in reviewing protocol changes. The following is a list of protocol actions and their definitions:

- a. Amendment: A change to the protocol that directly affects patient care or treatment and may substantively increase the patient's risk/benefit ratio.
- b. Revision: An administrative or editorial change that does not affect patient care or treatment, or a scientific or medical change that does not substantively increase the patient's risk/benefit ratio.
- c. Memorandum: Explanation of a study concept or other information about the study that do not change the study itself.
- d. Temporary Closure: Initial accrual goals on a study have been met, or death or severe toxicity that may be related to treatment has been reported, or other logistical reason for closure.
- e. Permanent Closure: The accrual goal has been met for the study, or the required tumor response has not been seen to reopen a study that was temporarily closed, or a decision has been made that the accrual goal for the study is not likely to be met.

TO ALLOW ADEQUATE NOTICE, NOTIFICATIONS REGARDING ROUTINE CLOSURES ARE POST-DATED BY TWO WEEKS (I.E., A NOTICE WILL BE DISTRIBUTED ON SEPTEMBER 1 NOTIFYING THAT THE CLOSURE WILL BE EFFECTIVE SEPTEMBER 15). EMAIL DISTRIBUTIONS OF CLOSURE NOTICES WILL BE ROUTINELY SENT TO THE PRINCIPAL INVESTIGATORS OF ALL GROUP INSTITUTIONS TO ALLOW MORE TIME FOR PROCESSING.

Priority Lists are committee specific lists of all open and temporarily closed protocols within that committee. Disease sites are grouped together and studies are placed in the order of their priority for patient entry. Institutions will not routinely be able to participate on competing studies for the same type of tumor. The list is distributed via the web site and shows which institutions can enter patients on each study. Priority lists are updated only when there has been a change such as activation of new study, a temporary or permanent closure, or change in participants.