THE STUDY PROTOCOL

The study protocol is a written document detailing how a clinical trial is conducted. The elements of a protocol include:

1. Trial design and organization;
2. Study objectives;
3. Background information;
4. Patient population descriptions; and
5. Treatments to be studied.

The requirements for patient entry, treatment and evaluation, plus data collection procedures should be clearly stated.

Protocol Development

Protocol development and activation is coordinated by the Operations Office. Any SWOG member or committee can initiate a protocol, but only one of the disease and research committees can sponsor a protocol. An investigator with a treatment proposal for a particular disease site submits it to the committee chair. If the committee decides to pursue the study, a capsule summary is submitted to the Operations Office for consideration at the Executive Conference for decision and comments. The idea may then be further developed and eventually, when applicable, a concept or formal letter of intent is submitted to the National Cancer Institute (NCI). If the NCI approves the idea, a formal draft is developed and circulated for review to the study chair(s), committee chair, discipline designates, intergroup participant(s) (if applicable), statistician(s), data coordinator(s), patient advocate, an oncology research professional representative, and an executive officer. Several drafts of a protocol may be circulated before a consensus is reached. After this review process, a final draft is submitted to the NCI for review and approval. When approved by the NCI, the study opens for patient accrual. A detailed account of the steps included in protocol development follows.

1. The idea is sent by an investigator to one of the disease and research committee chairs for consideration.

2. Depending upon the approval of the committee, a capsule summary is submitted to the Operations Office for consideration at the Executive Conference for decision and comments.

3. If the decision is made to develop the study, the idea may be further developed and a concept sheet or letter of intent is submitted by the protocol coordinator to the Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP) of the NCI for review.
4. Upon the NCI's approval of the concept sheet or letter of intent, the originator of the concept becomes the study chair and is responsible for writing and directing the development of the protocol.

5. The protocol is formatted by the protocol coordinator using SWOG standards, and is circulated for review and comments to the study chair(s), statistician(s), data coordinator(s), an oncology research professional representative (if applicable), discipline committee chair(s), and any other relevant designates. This process may be repeated several times with the protocol coordinator serving as central contact for comments and changes to the protocol document.

6. After a final draft of the protocol is agreed upon by all relevant designates, the protocol coordinator submits the study to CTEP for treatment studies, or, for cancer control studies, to the NCI's Division of Cancer Prevention (DCP), for review. The study is reviewed and returned with consensus review comments and/or approval.

7. Revisions are made, and the CTEP (or DCP) review process is repeated until the study receives final approval. Depending on the type of study, the NCI's Central Institutional Review Board (CIRB) may review the study. When this is the case, final NCI approval will not be granted until CIRB approval is received.

8. Following approval of the study, the protocol is activated. At the time of activation, the protocol coordinator adds the study to the disease committee priority list.

Considerations for Protocol Development of Intergroup Studies

Intergroup studies are protocols that target patients through multiple cooperative groups. Communication between groups about protocol development and activity should be clear, concise, and thorough. Whenever possible, all potentially participating cooperative groups should be involved as early as possible in the planning stages of an intergroup trial.

The “coordinating group” or “lead group” is responsible for assuring that all other participating groups have reviewed the study and have provided input throughout the development of the protocol. The coordinating group’s statistical office is also involved to aid in study design, assist in the establishment of realistic goals, and to determine registration and data flow procedures.

One contact person (the protocol coordinator) is designated in each group to receive each draft and distribute it to the appropriate members within that group. The contact person is, in turn, responsible for returning comments at each stage of the review to that group’s study chair, and eventually to the coordinating group.

The protocol coordinator for the coordinating group is also responsible for finalizing the protocol draft in conjunction with the study chair (the coordinating group’s primary study investigator), and will serve as sole administrative liaison with the NCI. All formal communication between the study chair and participating group coordinators should be via the protocol coordinator at the coordinating group. Hence, all appropriate personnel are involved in development at all stages, and the mechanics and logistics of implementing the trial can be negotiated along with the
scientific aspects of the protocol. As a liaison with the NCI, the protocol coordinator advises the
NCI on group participants (study number, activation date for each group, and actual participants),
provides updates during the stages of study development, and provides the formal draft for review
and approval. One protocol document must be developed for use by all participating groups.

Prior to submission of the intergroup protocol to the NCI for review, all participating groups
should agree on procedures for the following items:

* Registration/randomization, data flow, data management.
* Data quality control responsibilities (routinely assigned to the coordinating statistical
  office), and modality quality control procedures.
* Analysis (assigned to the coordinating statistical office).
* Response criteria.
* Data collection forms to be used.
* Drug distribution procedures.
* Toxicity criteria and procedures for reporting adverse drug reactions.
* Guidelines for presentation of data, publications and authorship.
* Identification of contact personnel and demographics on the participating cooperative
  groups (i.e., participants within the Group, study chairs and modality representatives for
  each group, and projected activation dates).

Usually, an eligibility checklist/registration form is developed for the protocol and is used by all
participating groups to verify eligibility requirements. The checklist/registration form should be
reviewed by all participating groups to assure agreement and compliance.

The coordinating group’s office should be the only office to distribute new versions of protocols to
the participating group offices. The cover pages and face sheet of the study should be used by
all participating groups and should indicate the protocol number, the study chairs for the
coordinating group and their telephone numbers, and the study chairs for participating groups.

When one cooperative group joins another cooperative group’s active protocol (automatically
making the study an intergroup effort), operational details should be finalized prior to activation of
the study by the joining group. When the active protocol is already an intergroup study, the
operational procedures established for the joining group should be as consistent as possible with
ongoing procedures. The details outlined in the list above should be addressed prior to notifying
the NCI of the intergroup collaboration. Organizational procedures, modes of communication and
decision making should be clearly defined.
The Cancer Trials Support Unit (CTSU) systems will be used in order to centralize registration and data submission responsibilities for intergroup studies. When this occurs, communication with participating groups is facilitated by CTSU.

SWOG Protocol Components

The following is a brief description of the content of each section contained in a SWOG protocol. Further documentation on what is included in each section is found in Policy Memorandum No. 13.

Title page lists the study title, the activation date, the current version date of the protocol document, the eligible participants, the agent(s) used in the study, the study chairs(s), and the statistician(s) responsible for the study analysis.

**Schema** provides a diagrammatic overview of a protocol from registration to the end of the protocol treatment. In SWOG protocols, a schema is included only in Phase III studies or complicated Phase II studies.

**1.0 Objectives** states the study purpose, a brief outline of the therapy under evaluation and the endpoints of interest (survival, response, time to progression, etc.).

**2.0 Background** supplies justification for conducting the study (justifies the objectives) and cites results of similar studies or pilot data. This section also provides information justifying assumptions made in the Statistical Considerations section.

**3.0 Drug Information** describes the drugs used in the study, their known toxicities, storage requirements, drug stability, administration, and supply information.

**4.0 Staging Criteria** when required, this section details staging criteria used in the study.
<table>
<thead>
<tr>
<th>Study Protocol</th>
<th>Chapter 14</th>
<th>Revised: December 2017</th>
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<tbody>
<tr>
<td><strong>5.0 Eligibility Criteria</strong></td>
<td>outlines patient and disease characteristics required for participation in the study. From these criteria, the SWOG Statistics and Data Management Center (SDMC) creates a study specific onstudy form, which is placed online and also in the forms set of the protocol activation. This onstudy form will be used to help document patient eligibility on the protocol along with other baseline forms and reports (e.g. baseline tumor assessments and pathology reports).</td>
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<tr>
<td><strong>6.0 Stratification Factors (randomization scheme)</strong></td>
<td>lists patient characteristics key to study design. Stratification factors are pretreatment patient characteristics which are balanced across treatment arms for randomization or used to determine the initial dose. The type of randomization scheme used in the study is also described briefly if necessary.</td>
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<tr>
<td><strong>7.0 Treatment Plan</strong></td>
<td>provides a detailed description of the entire treatment or study plan, including dose, schedules, number of courses for each treatment modality, and reasons for discontinuing treatment.</td>
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<tr>
<td><strong>8.0 Toxicities Monitored &amp; Dosage Modifications</strong></td>
<td>lists the anticipated toxicities and guidelines for dosage adjustment.</td>
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<tr>
<td><strong>9.0 Study Calendar</strong></td>
<td>outlines, in a chart form, time frames for all parameters, tests, and treatment administration required while the patient is on study.</td>
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<td><strong>10.0 Criteria for Evaluation &amp; Endpoint Definitions</strong></td>
<td>provide definitions for patient performance status, and study endpoints which may include progression of disease, response to treatment, time to treatment failure, and survival.</td>
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<tr>
<td>Section</td>
<td>Description</td>
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<td>11.0 Statistical Considerations</td>
<td>reiterates the study objectives, defines accrual goals and describes the study design used to address the objectives of the study. Guidelines for early closure and data and safety monitoring may also be outlined.</td>
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<tr>
<td>12.0 Discipline Review</td>
<td>includes information regarding pathology, radiation therapy, imaging or surgery review requirements and, when required, includes details regarding submission of materials. The necessity for discipline review is determined by the appropriate discipline committee prior to the protocol's activation.</td>
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<tr>
<td>13.0 Registration Guidelines</td>
<td>provides detailed registration instructions including when and how to register, how many registration steps are required for the study, and registration policies.</td>
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<tr>
<td>14.0 Data Submission Schedule</td>
<td>provides a detailed schedule for all required data submission, and how to submit them.</td>
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<tr>
<td>15.0 Special Instructions</td>
<td>outlines other aspects of protocol participation that are not otherwise specified, including special shipping or handling procedures for study specimens or other materials, if applicable.</td>
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<tr>
<td>16.0 Ethical and Regulatory Considerations</td>
<td>describes ethical and regulatory issues for the study. Informed consent, IRB, drug accounting and serious adverse event reporting information are presented.</td>
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</tr>
<tr>
<td>17.0 Bibliography</td>
<td>lists references used in the protocol.</td>
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<tr>
<td>18.0 Appendices</td>
<td>contain all appendices referenced in the text.</td>
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Model Informed Consent
a sample informed consent for use by institutions in drafting their own.

Protocol Activation, Modification and Closure

The Operations Office distributes group-wide website postings on the first and 15th of each month. The postings include protocol opening and closure notices, protocol amendments and revisions, changes in the Priority Lists, and any general communications on such items as policy clarifications and general news that will affect the entire Group.

Activation

Following NCI final approval, the Operations Office assigns an activation date and notifies the SDMC of protocol activation. The final protocol and an activation memorandum will be sent to the SDMC and all participating institutions in the website posting. All requests for copies of protocols should be directed first to the Group website and then to the Operations Office.

Modifications

When any action is taken on a protocol, information is circulated to the group which identifies the action (see below) and details the actual changes, corrections, etc. When applicable, updated protocol pages that reflect the changes accompany the memorandum. The memorandum is attached to the front of the protocol and all amended/revised pages are inserted in the protocol and the corresponding previous protocol pages discarded (or retained in a separate file according to institutional procedures).

SWOG has defined revisions and amendments as outlined below. In addition, protocol changes may be classified into several different categories for the type and timing of IRB review (regardless of whether they meet the criteria for a revision or an amendment). Each protocol change will include some specific wording regarding the need for and timing of IRB review. This wording outlines the minimum review level and timing required by SWOG (your IRB may have additional requirements).

Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. The changes are effective upon approval by the local IRB; however, changes to eligibility are effective 6 weeks after distribution of the notice. If approval is not granted within 6 weeks, accrual must be suspended until approval is obtained.

In extremely rare cases, a protocol change may be considered a “showstopper”. These are used when we have a requirement to prove that all registrations after a specific date occurred after IRB review of the necessary change. This is usually to implement a new study design or if a regulatory or safety situation is sensitive or important enough to warrant the need to keep close record and ensure the actual implementation date of the change. In these cases, the web registration program will not allow a registration to begin unless the current IRB date has been updated based
on the Version Date of the protocol change. The protocol change itself will clearly indicate when this is required.

Revisions

Administrative editorial changes to a protocol that do not affect patient care or patient treatment, or a scientific change which does not substantively increase the patient’s risk/benefit ratio. Examples of revisions include change of study coordinator, addition or deletion of a participating institution, or correction of a typographical error. Expedited IRB review is usually allowed.

Amendments

Changes to the protocol that directly affect patient care or treatment and may substantively increase the patient’s risk/benefit ratio; these usually constitute changes in the treatment plan, dosage modifications, eligibility criteria, or study parameters. Amendments must be recommended by the study chair, approved by, at a minimum, the disease committee chair, the executive officer, and the statistician of record. Justification for the amendment is required. Amendments will generally require full board review and approval by an institution’s IRB.

Memoranda

Used to reiterate or clarify a section of the protocol that may be overlooked, or be a source of confusion, or to provide additional information. Memoranda are not accompanied by any protocol replacement pages.

Permanent and Temporary Protocol Closures

The SDMC monitors accrual and notifies the Operations Office and the study chair when interim and final accrual goals are attained. Typically, Phase II studies have a two-stage accrual design. After initial accrual, the study is temporarily closed and the patients are evaluated. If a pre-specified number of responses is not observed, the study is permanently closed. Otherwise, the study is re-activated until full accrual is met. Phase III studies typically have early stopping rules that allow for permanent closure of the study if extreme results are observed. Once accrual has been reached, the Operations Office will send a written notice of temporary or permanent protocol closure to all participating institutions. A study may also be temporarily or permanently closed when exceedingly high or unanticipated toxicities are encountered.

To allow adequate notice, closures are post-dated by two weeks (i.e., a notice will be posted on September 1 notifying that the closure will be effective September 15). Group emails of closure notices are routinely sent to the Principal Investigators and Head CRAs of institutions to allow even more time for processing.
Exceptions to this policy include instances where there is an emergency closure, or when intergroup studies coordinated by cooperative groups other than SWOG are closed. Temporary closures will include the effective date of the closure and be noted on the priority list in the same mailing in which the closure notice is distributed. Permanently closed studies, although the closure is post-dated by two weeks, will be deleted from the priority list at the time the closure notice is distributed.

**Modifications to Active Intergroup Protocols**

Following activation, the coordinating group is responsible for circulating all amendments, revisions, terminations, suspensions, etc., to the participating institutions for each participating group via the CTSU, and the NCI. Modifications to the protocol must originate from the coordinating group; therefore, changes requested by participating groups must be forwarded to the coordinating group. The coordinating group will also obtain approval from the study chair(s), and CTEP and the CIRB (when appropriate).

**SWOG Priority List**

Priority lists are committee specific lists of all open and temporarily closed protocols within that committee and identify the institutions allowed to register patients to each study. Institutions will not routinely be able to participate on competing studies for the same type of tumor. Each protocol has a separate entry that includes the following:

* Sub-category of disease.
* Study number.
* Treatments.
* Study chair name.
* Limited eligibility information (cell type/overall stage).
* Study phase.
* Activation date.
* Institutions eligible to register patients.
* Cancer control credits if applicable.

The priority list is produced by the Operations Office on the Group website, and is updated in group mailings only when there has been a change such as activation of a new study, a temporary or permanent closure, or change in participants. Prior to beginning a pre-study patient work up, the institution should use the Priority List to verify that a particular study is open to patient registration from that institution. The Priority List should be used as a reference of potential studies. The protocol must be reviewed to identify specific criteria and eligibility.

SWOG protocols and a list of open studies, activations, closures, priority lists, amendments and revisions are accessed through the SWOG website ([https://www.swog.org/](https://www.swog.org/)).