

PROTOCOL GUIDELINES

A. 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.
2. Each section title of the protocol should be capitalized and the sections must appear in the order listed below. Standard sections to be included in all protocols are:

- SCHEMA
- 1.0 OBJECTIVES
- 2.0 BACKGROUND
- 3.0 DRUG INFORMATION
- 4.0 STAGING CRITERIA
- 5.0 ELIGIBILITY CRITERIA
- 6.0 STRATIFICATION FACTORS
- 7.0 TREATMENT PLAN
- 8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS
- 9.0 STUDY CALENDAR
- 10.0 CRITERIA FOR EVALUATION
- 11.0 STATISTICAL CONSIDERATIONS
- 12.0 DISCIPLINE REVIEW
- 13.0 REGISTRATION GUIDELINES
- 14.0 DATA SUBMISSION SCHEDULE
- 15.0 SPECIAL INSTRUCTIONS
- 16.0 ETHICAL AND REGULATORY CONSIDERATIONS
- 17.0 BIBLIOGRAPHY
- 18.0 MASTER FORMS SET
- 19.0 APPENDIX

The contents of each section are defined in Section G.

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 the Group administration 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 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 lower priority studies will be actively pursued by SWOG staff as time and competing priorities allow.

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.

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.

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 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.

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.

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.

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.

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.

B. PROTOCOL FORMAT AND CONTENT GUIDELINES

SCHEMA

Schemas are included only for complicated Phase II protocols and all Phase III protocols. The Operations Office will prepare a final schema to be attached to the protocol when it is submitted for NCI review. Given the possibility that investigators may attempt to treat patients using the information provided in the schema without referring to the treatment plan details, any specific treatment details, i.e., treatment dose(s), schedule, must not be included in the schema.

1.0 OBJECTIVES

- 1.1 The objectives should pose important scientific questions to be answered by the study and should be written in terms of clinical benefit rather than statistical terms. These include the value of a new investigational drug or a new combination of treatments, or a comparison between standard therapy and innovative new treatment. The objectives should be attainable with the sample size of the study. Phase II example: "To assess tumor response to esorubicin in patients with advanced breast cancer and one prior chemotherapeutic regimen for advanced disease." Phase III example: "To compare cyclophosphamide plus 5-fluorouracil plus tamoxifen to tamoxifen alone with respect to survival and time to progression in postmenopausal breast cancer patients with recurrent disease."
- 1.2 Do not abbreviate the drugs to be used, and list them by generic name (cyclophosphamide vs. Cytosan).
- 1.3 State the endpoints of interest (response, disease-free survival, time to progression, survival, etc.).

2.0 BACKGROUND

The background justifies the objectives by summarizing the results of similar studies. Background information is required on all experimental modes of treatment which will be used. If non-standard (novel) endpoints are to be used in the study, these must be justified in the background as well.

Adequate preclinical and clinical data to support the study must be provided. Specifically, the Triage review process will focus on how the proposed study will advance the field to improve the care of cancer patients, and, in the case of a Phase I or II study, what the next steps will be. For Phase I studies, most background data will be preclinical; the safety profile in animals and other human studies should be described. For single-agent, single-disease Phase II study proposals, both preclinical as well as Phase I data must be provided to support the proposed patient selection, dose, and schedule. For studies evaluating new combinations, pilot data or a plan for evaluating toxicity in an initial patient subset must be provided. For Phase III studies, significant activity in early phase studies should be described, as well as rationale for patient selection. Combination Phase I/II or Phase II/III should clearly describe how the pilot step will be used to proceed to the next step in development of a new therapy. ALL STUDIES should emphasize the impact of the therapy/new data on the field.

There should be no abbreviated words within the background section and this section should be written in complete sentences. Paragraphs are not numbered. All references should be numbered in the order they appear in the text and included in the bibliography.

The typical background for a Phase II protocol should be limited to one page (front and back single spaced) in length. The background for a Phase III protocol should be limited to one and one-half pages (front and back). However, background length may vary from these guidelines if necessary to provide adequate justification.

3.0 DRUG INFORMATION

The Operations Office will provide the entire drug information section for those drugs which are available commercially, or for those investigational drugs which have been previously used in protocols. The author may put "information supplied by the Operations Office" and the information will be inserted when the final draft is being prepared for NCI review. For the drugs not previously used in a protocol, as mentioned above, the Study Chair must contact the Operations Office to begin the process for developing a drug information section through the Pharmacy Committee.

- 3.1 All drugs being utilized in the proposed study should be described. Standard sections required by the NCI are: Human Toxicity, Pharmaceutical Data, Administration, Storage & Stability, and Supplier.
- 3.2 The drugs should be listed in alphabetical order.
- 3.3 The National Service Center (NSC) number should be given along with other standard names for the drug. If the drug is investigational, the Investigational New Drug (IND) number should also be supplied.
- 3.4 The supplier should be correctly given. Many of the drugs standardly obtained from the NCI in the past are now available by commercial means only.

4.0 **STAGING CRITERIA**

The criteria by which patients should be staged should be provided, or state if staging is not applicable. Reference standard criteria instead of reproducing them, when appropriate. Define only those stages needed to determine eligibility.

5.0 **ELIGIBILITY CRITERIA**

This section of the protocol must be carefully written assure all information required for patient eligibility is appropriately included. This section will contain all pertinent medical history as well as the functional, hematologic, biochemical, symptomatic and cancer specific prior treatment of the patient. Specific hematologic and biochemical test results that are necessary to assure patient safety must be spelled out clearly (i.e. normal, twice the upper limit of normal, etc.). The timing for performing pretreatment tests including scans or MRIs must be well thought out to avoid unnecessary duplication of tests. Required histologic characteristics of the tumor for patient eligibility must be spelled out. If necessary, required availability of tumor samples for correlative studies called for the protocol must be clearly spelled out. Care must be given to avoid copying and pasting eligibility criteria of one protocol to another since this section is unique to each protocol. The eligibility criteria should ONLY include items that are absolutely necessary to describe disease specifications, provide for patient safety, and minimize factors that will confound the study endpoints. The study Chair should make the eligibility criteria as short, simple, and "auditable" as possible.

The SWOG Data Operations Center will not make exceptions to the eligibility criteria in the protocol without a written amendment to the protocol from the SWOG Operations Office. No one in the Group is authorized to make an exception to eligibility criteria unless an error is discovered in the protocol relating to the exception. In case of such error, the protocol will be amended to correct the error. Registration of a patient based upon an exception granted by the Study Chair without a subsequent amendment to the protocol will result in a major eligibility deficiency during an audit. For additional rationale for this position, please see http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm.

While the wording for certain criteria has been standardized and may be added by the Operations Office, the Study Chair has the option (and the responsibility) to edit these as needed. In order to prevent impediments to clinical trial participation from arising and to help increase accrual to clinical trials, Study Chairs are asked to simplify eligibility criteria by following these guidelines:

- 5.1 There should be a sound scientific basis for every eligibility requirement listed in Section 5.0 of the protocol. If any of the requirements is not likely to have a significant impact on issues of patient safety or data interpretation, strong consideration should be given to leaving that criterion out of Section 5.0.
- 5.2 Every effort should be made to limit the requirements for studies or procedures performed outside of the immediate pre-registration evaluation period since many of these procedures are performed by non-Group members (e.g., specific criteria for

staging and debulking procedures, numbers of lymph nodes sampled, etc.). Inclusion of such requirements should be based on evidence that non-adherence to these standards will have a substantial impact on the course of disease, response to therapy, or interpretation of the data.

- 5.3 Careful consideration should be given as to whether central pathology review should be required for the study. In most diseases, there is general agreement between pathologists regarding essential aspects of diagnosis (tumor grade, histologic subtype, etc.), and central pathology review is not necessary.

Availability of specimens that are required for eligibility (i.e. for central pathology review or for correlatives that are an integral part of the study objectives) must be verified prior to registering the patient. Eligibility criteria must be written so that this expectation is clear.

- 5.4 SWOG has identified timeframes for the performance of prestudy tests that appear to be reasonable and strike a good balance between the avoidance of repeating tests that would not be medically warranted and obtaining an accurate assessment of the baseline tumor status. Specifically, baseline evaluation of tumor dimensions within 28 days (for measurable disease) or 42 days (for non-measurable disease) are the current standards. However, the Study Chair should always evaluate these timeframes for their applicability to standard practice in this patient population. It should be recognized that diseases with a tendency for rapid growth or dissemination may require more stringent time frames.
- 5.5 More liberal criteria are needed to allow patients with a prior diagnosis of another malignancy to be enrolled on SWOG trials. Specifically, the five year disease-free criterion from other malignancies (outside of superficial squamous cell carcinoma of the skin or cervix) is unnecessary for patients with Stage IV disease in whom the median survival is usually less than one year. Study Chairs should consider whether there is any need to restrict eligibility for patients with previous malignancies.
- 5.6 In order to reduce the need for repetition of expensive imaging studies, SWOG will limit the requirement for scans performed to confirm objective responses to Phase II trials of Investigational New Drugs (INDs) in which objective response rate is the primary endpoint. This means that objective tumor responses do not need to be “confirmed” at 4 weeks, which was previously a common practice.
- 5.7 Eligibility for patient registration is not specifically captured in study forms at the time of registration. The registration process is designed to capture essential demographic information and a simple “yes/no” question to determine whether the patient has met the eligibility requirements of the trial. However, each eligibility criterion is subject to quality assurance audit, and should be written in a way that will allow QA confirmation by source documentation, that the criterion is met.

Eligibility criteria must be written by the Study Chair. These define:

- 5.8 Patient population: allowable disease sites, cell types, stage, and any other appropriate disease descriptors. Any exclusions should be stated. Since the statement *histologically confirmed advanced disease* is ambiguous, provide specific histologic confirmation instructions:
- * a biopsy of the metastatic site or recurrence is required, or
 - * prior histologic confirmation of the malignancy is required and there must be clinical evidence of recurrent or metastatic disease.
- 5.9 Acceptable disease status: measurable only, or measurable and non-measurable.

- 5.10 Prior therapy: Any previous therapies that would exclude patients should be listed. Clarify if these exclusions pertain to previous therapy for the current cancer only, or for any prior disease. Those agent(s) or modes of therapy which are either required, or allowable for eligibility should be defined. If eligibility requirements include a minimum period of time since the end of prior treatment, specify the time period in days rather than months or weeks to ensure compliance.
- 5.11 Performance status: A numeric value is required to be documented to reflect the patient's functional status pre-treatment. Subsequent evaluations during a study must have a numeric representation of patient's performance status. SWOG traditionally uses Zubrod criteria for scoring performance status
- 5.12 Multiple registrations: Include a separate section to define eligibility requirements for re-registrations (e.g., at crossover).
- 5.13 Concurrent treatment: Eligibility Criteria are intended merely to determine eligibility at a fixed point in time, and may not proscribe or prescribe something that may happen in the future. If another therapy is expected to occur, not as part of the experimental question, but as part of the standard of care (for example, adjuvant endocrine therapy in ER positive breast cancer), it should be described in the treatment plan, and not as an eligibility criterion.

6.0 STRATIFICATION FACTORS

Stratification is not applicable if there is no randomization or stratification. Otherwise, the stratification factors should be identified. This section must appear in all protocols.

Stratification factors are pretreatment patient characteristics which will be balanced across treatment arms. Stratification factors should be limited to two or three of the most important variables.

7.0 TREATMENT PLAN

The entire treatment or treatments should be outlined. For those studies which will include randomization, the separate regimens should be labeled with suitable abbreviations consistent with the rest of the protocol. It should be stated if the patients will be restaged and if a second registration will be required at that time. Indicate when any other registrations/randomizations should occur, such as for start of radiation therapy. Make sure this is consistent with the registration guidelines. **Do not include disease assessment information in this section; it belongs in the Study Calendar.**

When different modes of therapy are being utilized, such as surgery or radiation therapy, each should be given in one complete section of the treatment plan. Radiation therapy guidelines have been formulated, and all protocols must have the standard format before approval will be given for NCI review. For the more complex protocols (Phase III) which contain two or more treatment modalities, the different modalities should be divided and included under separate headings, such as:

- 7.1 Treatment Plan - Surgery
- 7.2 Treatment Plan - Radiation Therapy
- 7.3 Treatment Plan - Chemotherapy

The dose(s) of drugs utilized, the schedule of the agents, and the number of courses should be clearly outlined for each treatment. Doses should always be expressed in terms of daily dose and not in terms of the cumulative dose.

The following format will be used:

AGENT	DOSE	ROUTE	RE RX DAYS	INTERVAL	NOTES
Adriamycin	50 mg/ M ²	IV over 5 min.	1	4 weeks	Maximum cumulative dose 500 mg/ M ²
Cisplatin	60 mg/M ²	IV over 2 hr in 1000 ml 1/2 normal saline + 25 gm Mannitol	1	4 weeks	Give Adriamycin before Cisplatin
Pred- nisone	30 mg	PO	1-7	4 weeks	

- 7.4 Criteria for removal from protocol treatment are to be outlined. Examples of standard criteria follow. Make sure that the treatment program for all patient subgroups has a clearly defined stopping point, or if treatment is to continue indefinitely, that this is stated. This section should be consistent with any off treatment criteria outlined in the dose modification section.

Criteria for Removal from Protocol Treatment

- a. *After eight weeks of treatment (two courses), patients with progressive disease will be taken off treatment. Patients with complete or partial responses or stable disease will continue treatment.*
 - b. *Progression of disease (as defined in Section 10.____).*
 - c. *Unacceptable toxicity.*
 - d. *The patient may withdraw from the study at any time for any reason.*
- 7.5 *All reasons for discontinuation of treatment must be documented in the Study Forms.*
- 7.6 *All patients will be followed for five years or until death, whichever occurs first.*

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE), will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

- 8.1 Chemotherapy (or hormonal, biologics) toxicities to be monitored. Note that if both experimental and standard therapies are to be applied sequentially (for example experimental chemotherapy then standard hormonal therapy), the study need only monitor toxicity of the experimental therapy. The specific therapies and toxicities to be monitored, and the duration of monitoring, should be spelled out. When standard and experimental therapies are applied simultaneously, toxicity must be reported for the combination regimen, and should not be assumed to be due to just one component of the regimen.

List major expected toxicities (long term and short term).

8.2 Radiation toxicities (if applicable).

List major expected toxicities (long term and short term).

8.3 Surgery toxicities (if applicable).

List major expected toxicities (long term and short term).

8.4 If a toxicity is not included in the CTCAE Active Version, grades must be developed, reviewed and approved by SWOG. If a standard definition exists, other definitions of the toxicity may not be used. Instructions for dose modification should be inclusive of all possible toxicities and, whenever possible, should be based on the numeric toxicity grades of the CTCAE Active Version.

8.5 Dose changes (increases and decreases) should be presented in levels to minimize confusion. Providing a precise amount of drug to be administered for a defined condition reduces error and promotes consistent treatment. Indicate whether dose modifications are based on toxicity on the day of treatment versus worst toxicity during the previous treatment. Combination regimens can present additional challenges in defining which drug should be reduced for a specific toxicity, and should be carefully reviewed for clarity. See tables below for examples.

Dose Adjustments based on Day of Treatment Counts:

Granulocyte		Platelet	5-FU
≥ 1,500	and	≥ 100,000	Starting Dose
1,000 - 1,499	and	≥ 75,000	Dose Level -1
≥ 1,000	and	75,000 - 99,999	Dose Level -1
< 1,000	or	< 75,000	Hold drug one week*

*If sufficient hematologic recovery has not occurred, (i.e., granulocytes ≥ 1,000 and platelets ≥ 75,000) after holding drug one week, hold radiation therapy in addition to the drug for an additional week. If hematologic recovery has not occurred after a total of two weeks, contact the Study Chair.

Dose Levels (mg/M²):

Drug	- 2	- 1	Starting Dose
5-FU	500	750	1,000

8.6 The following provisions for dose modification should be addressed in all protocols:

- a. Define any prestudy condition that necessitates modification of initial dose.
- b. Define retreatment parameters (e.g., AGC ≥ 2,000/μl, platelets ≥ 100,000/μl, creatinine ≤ 1.5 mg%). If toxicity has not resolved at time of retreatment, define acceptable delay, dose at resumption of treatment, and what should be done if the toxicity has not resolved at the end of the delay.

- c. If toxicity persists after one dose modification, indicate what further dose changes are required. If additional dose decreases are indicated, the dose table should accommodate multiple level decreases. If the agent is eventually permanently discontinued, or if at some point there are no further reductions, indicate this as well.
- d. Indicate if dose increases are allowed after dose decreases. If so, to what grade of toxicity must the patient recover, what is the minimum duration of recovery prior to dose increase, how large is the dose increase and how many increases are allowed. NOTE: Tables which indicate dose levels when counts are normal should specify that dose level should be at previous dose rather than starting dose, *unless increases to starting dose after a previous decrease are actually intended.*
- e. Indicate what dose level should be used if there are multiple toxicities. (For instance, the lowest dose indicated for any individual toxicity.)
- f. If instructions are to use ancillary treatments, e.g., antiemetics. rather than dose reductions, indicate what measures are to be taken when the ancillary treatment is not effective.
- g. If instructions are to delay treatment rather than reduce dosage what should be done if the toxicity has not resolved at the end of the delay, to what grade of toxicity must the patient recover, what is the minimum duration of the recovery period prior to retreatment, what dose level should be used after the delay?
- h. Use of G-CSF must be addressed.

- 8.7 A standard statement will be added by the Operations Office to refer all treatment related questions to the Study Chair. If the Study Chair will be unavailable to be contacted due to vacation, travel, or other reasons, he/she must make arrangements for backup coverage.

For treatment or dose modification related questions, please contact Dr. _____ (name) at _____ (telephone number) or Dr. _____ (name) at _____ (telephone number).

- 8.8 A standard statement will be added by the Operations Office addressing the procedure for reporting of adverse drug reactions as follows:

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via ADEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

A sample Study Calendar is included in chart form in this policy. These calendars should outline every parameter/test and treatment that is required for evaluation of study eligibility, study treatment and endpoint evaluation (including safety, efficacy, quality of life, etc.) The study calendar should not include any other items not related to the above.

Categories to be listed are as follows (in this order): Physical; Laboratory; Specimens; X-rays and Scans; and Treatment. Each test, whether it is being done prestudy only or continuously throughout the study, should be noted. It is not necessary to list every day or week throughout the life of the study; rather, only those days in which either therapy or tests are being performed. Asterisk and footnote special instructions. All tests which will be continued after the patient stops therapy should also be indicated along with the time point at which they should be performed.

Typically, most clinic visits studies for toxicity monitoring and efficacy assessment are "standard of care". If visits/tests fall outside of standard of care (such as research blood submission, and

“research only” biopsies), separate funding will be required. Such “research only” calendar items should be clearly specified in the study calendar.

Check the Study Calendar's consistency with eligibility (all tests required for eligibility must be on the calendar), treatment plan (treatment days, tests and follow-up must match) and dose modifications (tests for toxicity monitoring must be included). A standard NOTE appears at the bottom of the calendar to refer the reader to the Master Forms Set and the Data Submission Schedule for forms submission guidelines.

The Study Chair is responsible for determining that the frequency of examinations and testing required for this study is the minimal necessary for evaluating patient safety and response to treatment. Apart from the allowed window for scheduling of assessment intervals, patients must not continue to receive protocol treatment unless they have undergone assessments as required in the Study Calendar. Treatment may be delayed as outlined in Section 7.0 of the protocol until the required assessments are done. There are no exceptions allowed.

9.0 STUDY CALENDAR

S9708, Evaluation of Gemcitabine (Gemzar®) in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

REQUIRED STUDIES	PRE	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23	Wk 24	
PHYSICAL																	X									
History and Physical Exam	X			X					X				X				X					X				
Weight and Performance Status	X			X					X				X				X					X				
Disease Assessment #																										
Toxicity Notation		X	X	X			X	X		X	X	X		X	X	X						X	X	X		
LABORATORY [∞]																										
WBC/Differential/Platelets	X	X	X	X			X	X		X	X			X	X	X						X	X	X		
Serum Calcium	X								X					X			X					X				
Serum Creatinine	X				X									X												
Calc Creatinine Clearance ^f	X				X				X					X			X					X				
Bilirubin	X				X				X					X			X					X				
SGOT or SGPT	X				X				X					X			X					X				
X-RAYS AND SCANS																										
X-Rays and Scans for																										
Disease Assessment#	X								X																	
TREATMENT																										
Gemcitabine (Gemzar®)		X	X	X			X	X		X	X	X		X	X	X						X	X	X		

NOTE: All forms to be utilized for this study are listed in Section 18.0. Form submission guidelines are found in Section 14.0.

- [∞] All labs should be done prior to each gemcitabine administration.
- ^f Either serum creatinine or creatinine clearance (24 hour OR calculated) may be used to document adequate renal function.
- [#] Measurable and evaluable disease must be assessed after two cycles (every 8 weeks) using the same techniques as for baseline assessment. Response of CR or PR must have a second confirmation at least three weeks after the first documentation of response (see Section 10.3). X-rays and scans for disease assessment should be done on Day 50 and every second cycle thereafter.
- [√] Gemcitabine therapy and parameters will continue at these intervals until progression of disease occurs or patient goes off protocol treatment (see Section 7.2). Once off-treatment, patients should be followed every 3 months for the first year, every 6 months for the second year, and every 12 months thereafter.

10.0 CRITERIA FOR EVALUATION

There are standard endpoint criteria, such as RECIST response rate, distant disease-free survival, progression-free survival, time to progression, and overall survival, which can be inserted by the Operations Office as appropriate. Within the endpoint criteria, disease specific references will be supplied in conjunction with the Study Chair and the Statistical Center. The RECIST criteria are typically used for metastatic solid tumor disease assessment; however other criteria may be allowed, if justification is provided. Novel endpoints are not discouraged but will be subject to additional scrutiny for their veracity and clinical relevance. Novel endpoints should be supported in the Background (Section 2.0).

11.0 STATISTICAL CONSIDERATIONS

The Study Chair should send the concept sheet and initial draft of the protocol to the disease site statistician who will write the statistical section.

The statistical section will typically include:

- a recapitulation of study objectives
- the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate
- the study design, including contingencies for early stopping, any stratification factors, and characteristics to be incorporated in analyses
- the power of the study to address the major objective(s), the assumptions involved in the determination of power, tables of power under various alternatives
- the power of the study to address the other objective(s), the assumptions involved in the determination of power
- the criteria for study monitoring

To write this section, the Study Chair must discuss with the statistician the expected accrual rate, reflecting recent experience with the disease, and background information for each study objective. For non-comparative (single arm) studies with the objective of ESTIMATING toxicity, response rate, survival time, response duration, time to progression, etc., the statistician will need at least an idea of the expected rate (duration) and the desired precision of the estimate. Useful information to provide would be results from other studies. If the objective is to EVALUATE an endpoint, specify what values would be of interest/not of interest to discern with the study.

12.0 DISCIPLINE REVIEW

There must always be a Discipline Review section in all protocols whether it will be performed or not. If discipline review is not to be performed, the following statement should appear in Section 12.0:

Discipline Review is not required for this study.

The necessity for discipline review is determined by the appropriate discipline committee. Standard information for pathology review, surgery review or radiotherapy review, will be inserted by the Operations Office.

13.0 REGISTRATION GUIDELINES

Certain information is standard for this section and will be supplied by the Operations Office when the protocol is formatted. This section may include information about simultaneous registration to ancillary studies.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Certain information for this section is standard and will be supplied by the Protocol Coordinator when the protocol is formatted
- 14.2 Submission of any data for the study must be referenced here (including timing for submission of specimens).
- 14.3 The submission schedule for each form must be stated.
- 14.4 RE-REGISTRATION AND DATA SUBMISSION REQUIREMENTS: If the protocol requires re-registration, re-registration instructions must be specified. If re-registration will necessitate submission of forms, films, specimens, slides, etc., the Study Chair must communicate this to the Statistical Center so that appropriate instructions can be written.

15.0 SPECIAL INSTRUCTIONS

Examples of items for this section include instructions to the institutional data managers/clinicians/nurses for submission of specimens, or other protocol-specific instructions that do not otherwise fit into the standard table of contents. **DO NOT** include a description of the methods/procedures that will be used by the laboratory performing the tests; detailed methodology to be used by the reference laboratory should be included as an appendix to the protocol.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

This section is standard for all SWOG protocols and will be provided by the Operations Office. It includes information for reporting Serious Adverse Events, and general references regarding ethical concerns.

17.0 BIBLIOGRAPHY

All references must be complete. They should be numbered and listed in the order that they appear in the protocol.

Examples:

- 1. Journal: Bodey GP, Hewlett JS, Coltman CA Jr, Rodriguez V, Freireich EJ. Adriamycin in the treatment of childhood solid tumors. *Cancer*; 36:1572-1576, 1975.
- 2. Book: Freireich EJ. *Childhood Solid Tumors*. Second edition. Baltimore: Williams and Wilkins, 1972:110-147.
- 3. Book Chapter: Huguley CM, Calch CM. The chronic leukemias. In: HF Conn, ed. *Current therapy*. Philadelphia: WB Saunders, 1972:286-288.
- 4. Abstract: Glucksberg H, Rivkin S, Rasmussen S. Adjuvant chemotherapy for operable breast cancer with positive axillary nodes. *ASCO*: #C-367, 1981.

18.0 MASTER FORMS SET

The Statistical Center will create study-specific data collection forms. This section of the protocol includes a list of all of the data collection forms to be used in the study.

18.1 MODEL INFORMED CONSENT FORM: The Protocol Coordinator will supply the standard template and will draft an initial version using all resources available. The Study Chair must ensure that the information included in the Model Informed Consent Form is complete and accurate. The Protocol Coordinator will assist in ensuring that lay language is used.

19.0 APPENDIX

This section includes charts, special forms or additional information that are referenced in the protocol, but do not fit into the standard table of contents.