

Knowledge Acquisition Session Report

SWOG – Protocol Authoring Tools Development

Session Date: 11/2/00

Session Time: 2:00 – 3:45 p.m.

Session Topic: Southwest Oncology Group clinical trial authoring process

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Session Location: SWOG offices, San Antonio, Texas

Type of Session:

Interview

Task Analysis

Scenario Analysis

Concept Analysis

Observation

Structured Interview

Other:

Documentation: KA Session Report, SWOG Protocol Guidelines

General Topic Area

Southwest Oncology Group (SWOG) processes for authoring clinical trial protocols, with special attention to eligibility criteria

Session Goals

- Document the general process used at SWOG to author clinical trial protocols
- Understand how eligibility criteria are determined and used in protocols at SWOG
- Gather examples of documents and guidelines typically used in the authoring of SWOG protocols
- Gain SWOG impressions on the CDE initiative as it relates to protocol authoring

Summary

Southwest Oncology Group (SWOG) is a large cooperative group that performs cancer research across the United States and Canada. SWOG personnel secure funding, develop protocols, and manage data for cancer clinical trials (among other tasks). SWOG personnel develop clinical trials in four phases: Capsule Summary, Concept Blueprint, Concept Development, and Protocol Development. Clinical trial eligibility criteria are developed, negotiated, and revised throughout this process by all of the individuals involved. Eligibility criteria decisions are driven mainly by scientific intent, patient safety, and patient availability. However, other factors such as Institutional Review Board preferences also affect eligibility criteria decisions. SWOG domain experts expressed concern that common data elements (CDEs) might not provide the specificity and flexibility desired for use in eligibility criteria. They also expressed concerns that that CDEs might be time-consuming to maintain and that their adoption might dilute the diversity of thinking in the cancer research community.

Southwest Oncology Group Background

Southwest Oncology Group (SWOG) performs cancer clinical research across the United States and Canada. SWOG personnel secure funding for clinical trials, develop clinical trial protocols, and manage clinical trial data. Figure 1 shows SWOG's major tasks in performing cancer research.

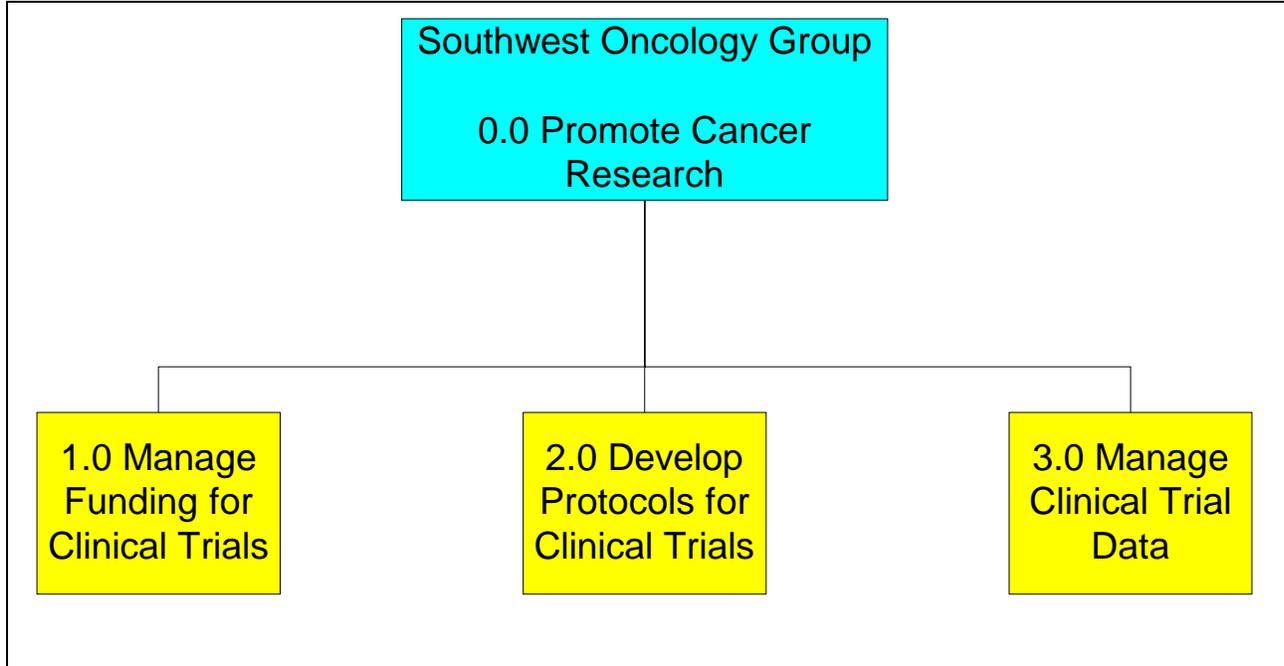


Figure 1: Southwest Oncology Group Tasks

Funding Sources

The National Cancer Institute (NCI) and the non-profit Hope Foundation both fund SWOG activities. Figure 2 shows SWOG funding mechanisms.

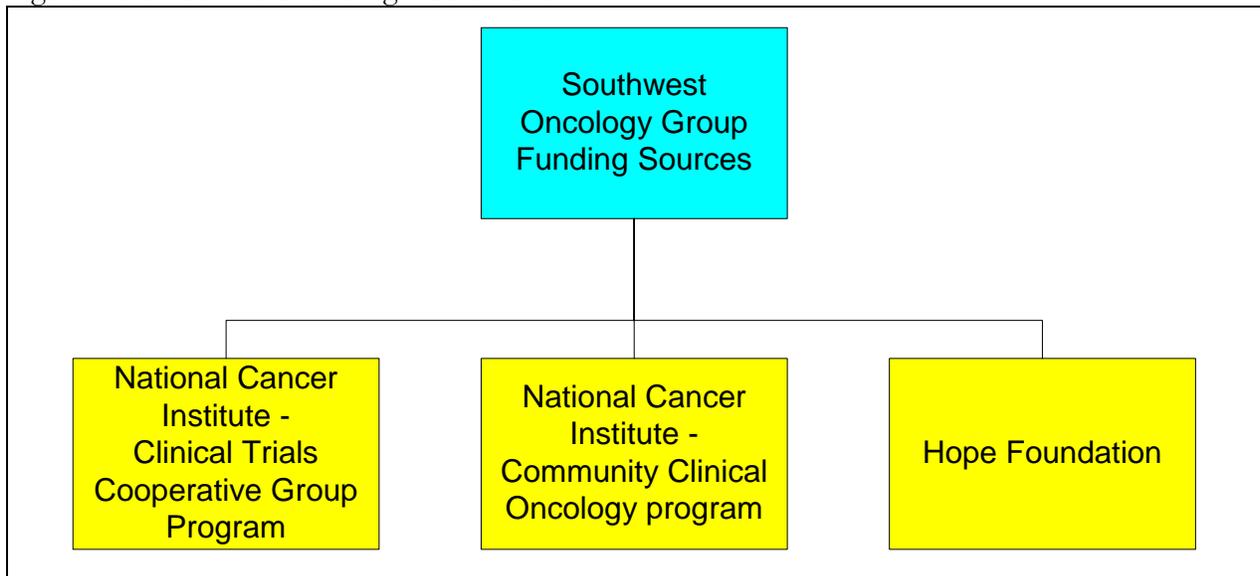


Figure 2: Southwest Oncology Group Funding Sources

National Cancer Institute – Clinical Trials Cooperative Group Program

NCI established the Cooperative Group program in 1955, and SWOG was founded the next year as one of the first cooperative groups. The program allows NCI to fund the development and conduct of large-scale trials in multi-institutional settings. The number of cooperative groups has fluctuated over the years. SWOG is one of the largest of the cooperative groups currently researching adult cancer treatment and prevention.

Cooperative groups must renew their funding every five years. The renewal process includes a full NCI review and a rigorous peer review. Peer review boards consist of NCI personnel, independent researchers, and researchers from other cooperative groups.

National Cancer Institute – Community Clinical Oncology Program

NCI established the Community Clinical Oncology Program (CCOP) in 1983. The CCOP program allows NCI to fund clinical research into the community setting and stimulate improvement in the quality of cancer care in the community. SWOG serves as a CCOP “research base” which designs, organizes, and manages data for clinical trials.

Hope Foundation

SWOG established the Hope Foundation, a non-profit 501(c)-(3) organization, in 1992. The Hope Foundation provides a means for organizations and individuals to financially support SWOG cancer research efforts. The foundation works to increase awareness of SWOG’s cancer research and clinical trial efforts.

Pharmaceutical companies encourage cooperative group participation in clinical trials with the company’s drugs. Cooperative groups receive federal funding, so pharmaceutical companies see no need to pay for research by cooperative groups. Also, federal funding implies that the research is unbiased. Cooperative group trials clinical tend to be less costly than trials sponsored by pharmaceutical companies (about \$1,500 per case accrued versus \$10,000 per case accrued).

Funding and renewal procedures may limit the cooperative groups’ ability to study some rare cancers. Many rare cancers could only be studied in the cooperative group setting, since that is the only way sufficient accruals could be generated. However, even in a cooperative group setting such a study might require many years. Each cooperative group must renew its agreement with NCI every five years, and cooperative groups are discouraged from taking on studies and then not completing them in a timely way. This policy discourages cooperative groups from taking on studies that may take longer than five years to complete.

Organization

The SWOG organization consists of an Operations Office, a Statistical Center, more than 400 cancer research institutions, and over 6,000 individual cancer investigators. Figure 3 depicts the SWOG organization.

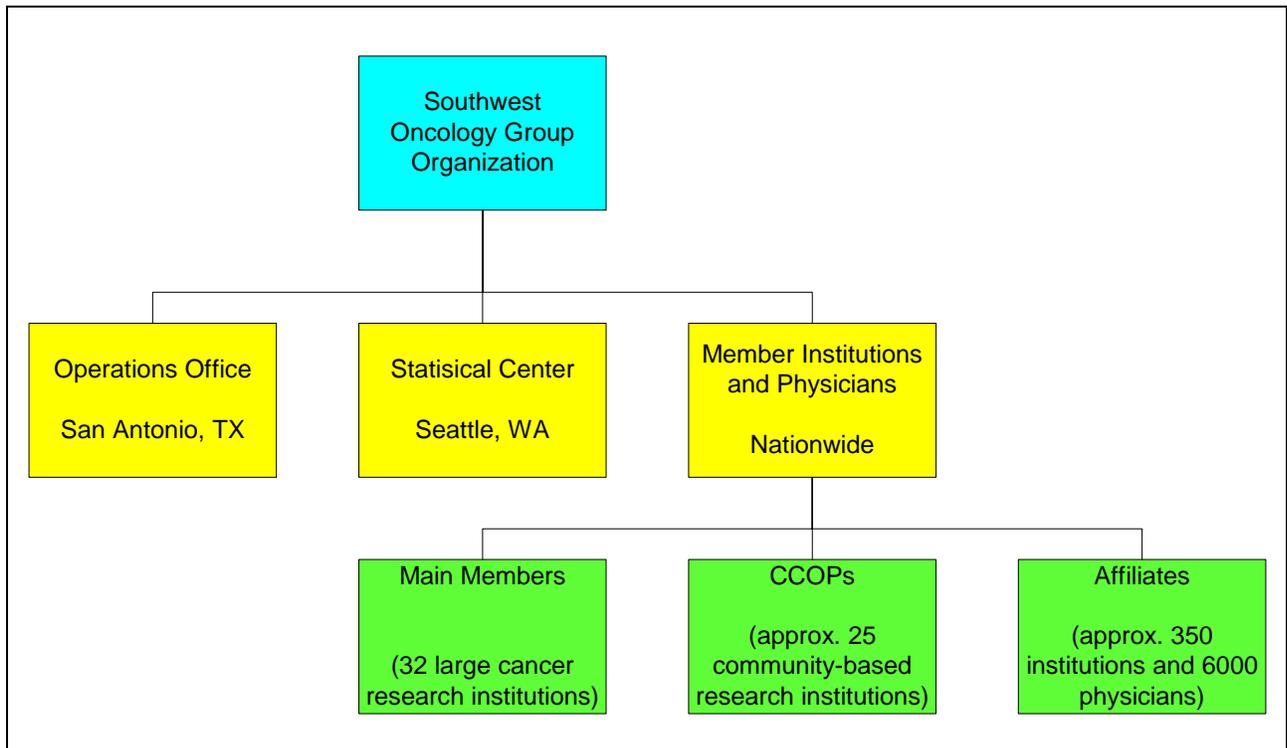


Figure 3: Southwest Oncology Group Organization

Operations Office

The SWOG Operations Office manages the following aspects of cancer clinical trials for the Southwest Oncology Group:

- funding
- membership
- regulatory tracking
- publications tracking
- public relations
- grant submissions
- communication
- quality assurance
- meetings management
- adverse event tracking
- administrative protocol development

Protocol Coordinators, who are administrative personnel responsible for moving concepts and protocols through the development process, work in this office. Marjorie Godfrey manages the Operations Office, which is located in the Cancer Treatment and Research Center in San Antonio, Texas

Statistical Center

The SWOG Statistical Center manages statistical scientific protocol development, data management, and data analysis for cancer clinical trials. John Crowley, PhD directs the Statistical Center, which is located on the campus of the Fred Hutchinson Cancer Research Center in Seattle, Washington.

Member Institutions and Physicians

SWOG member institutions include 32 large cancer research institutions, which are referred to as “main member” institutions. About 25 additional institutions are Community Clinical Oncology Programs (CCOPs) associated with SWOG through its status as a CCOP research base. Many smaller cancer research institutions and individual physicians are associated with SWOG through the NCI Affiliate program. The Affiliate program encourages individual physicians and groups of physicians to take part in cancer research clinical trials.

SWOG disease committees are responsible for focusing the scientific efforts of the cooperative group. Each committee will prioritize all proposed clinical trials in its disease area. Figure 4 shows the current SWOG disease committees.

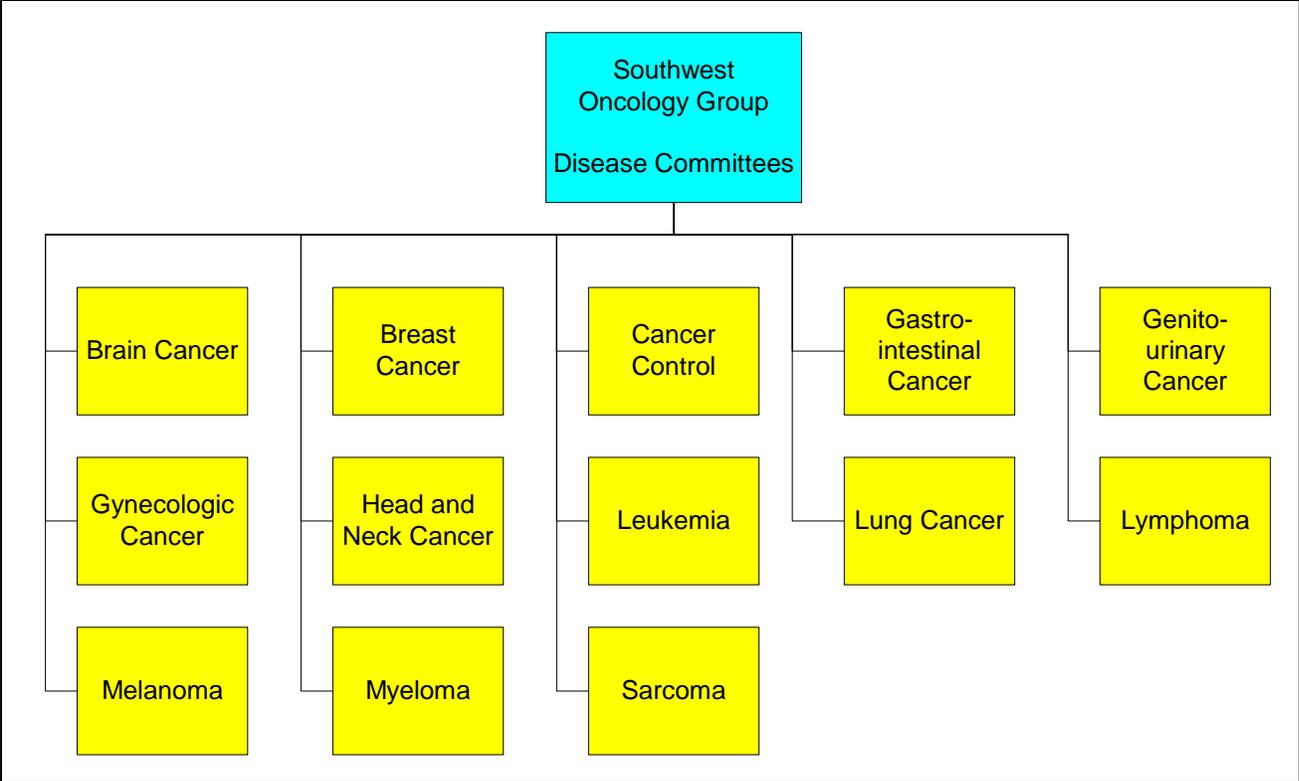


Figure 4: Southwest Oncology Group Disease Committees

Clinical Trials

SWOG generally has 100-125 active clinical trials at any time. This is managed by concentrating development resources on the two or three highest priority trials in each disease committee. SWOG participates in both cancer therapy trials and cancer prevention trials.

SWOG currently follows over 32,000 patients in various cancer treatment trials. SWOG is also following more than 18,000 patients in the Prostate Cancer Prevention Trial, a \$60 million multi-year study. In 2001 SWOG will kick off the SELECT study, a 14-year prostate cancer prevention trial involving more than 32,000 patients.

SWOG Clinical Trial Development Process

Southwest Oncology Group (SWOG) divides its clinical trial development process into four distinct phases:

- Capsule Summary Phase
- Concept Blueprint Phase
- Concept Development Phase
- Protocol Development Phase

Figure 5 shows an ideal timeline for the SWOG clinical trial development process.

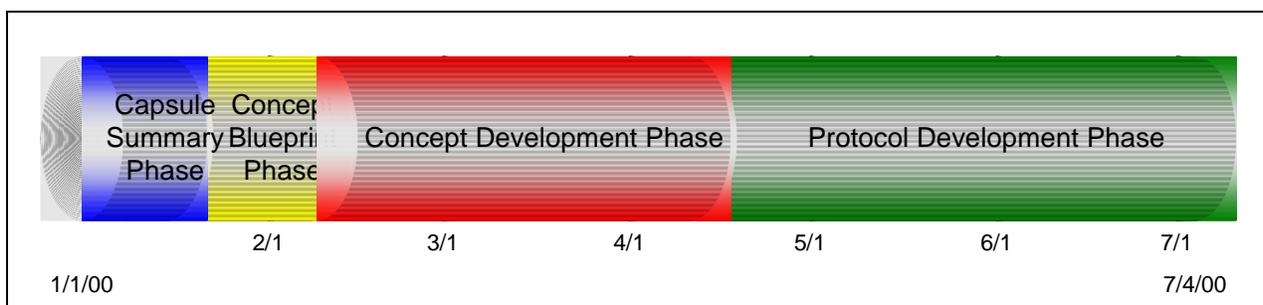


Figure 5: Ideal Timeline for the SWOG Clinical Trial Development Process

The process is designed to take six months from initial idea to study activation, under ideal conditions. In practice, a study will require about eight or nine months to complete the process. The National Cancer Institute (NCI) has recently made efforts to speed up the process.

Capsule Summary Phase

The Capsule Summary Phase begins when the Study Coordinator (a physician member of SWOG, also known as the principal investigator) submits a new idea to SWOG and the appropriate disease committee. If the disease committee chair approves, the Study Coordinator creates a capsule summary.

The Executive Conference is comprised of leaders from the Operations Office and the Statistical Center. It meets once a week to evaluate and approve studies, and all detailed notes of these meetings are retained. If the Executive Conference approves the capsule summary, the disease committee chair assigns a priority to the study. Figure 6 shows the elements of the Capsule Summary Phase.

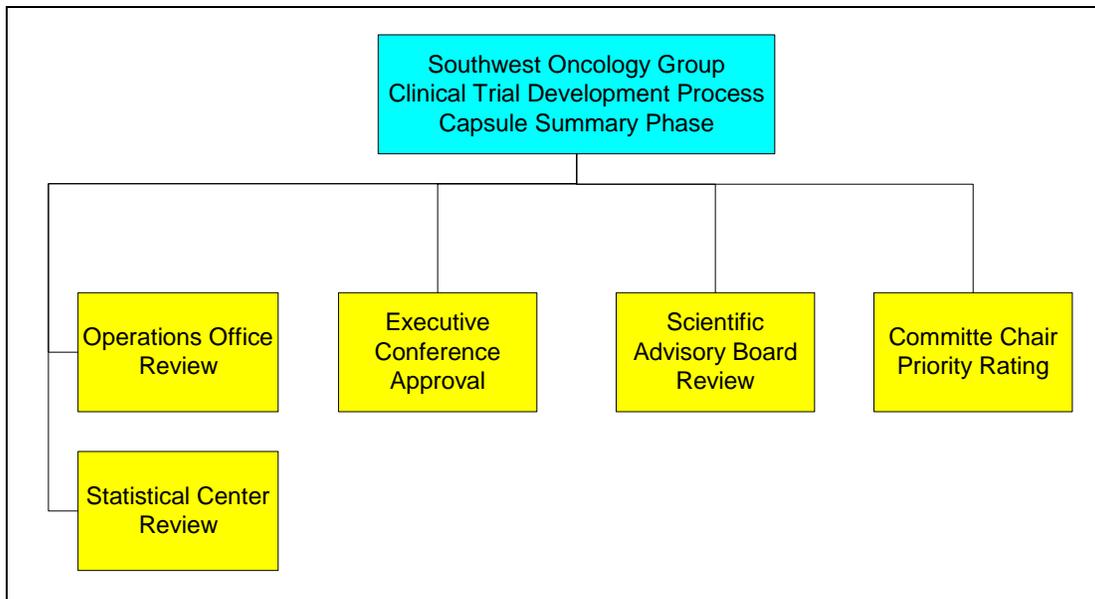


Figure 6: Southwest Oncology Group Capsule Summary Phase

Concept Blueprint Phase

In the concept blueprint phase, the Study Coordinator develops the capsule summary into a concept (phase III study) or a letter of intent (phase I/II study) for submission to NCI. This development follows two parallel sections: administrative and scientific.

The administrative section resolves such issues as sponsorship, drug supply, regulatory filings, and funding. The scientific section handles such issues as experimental design, dose regimen, study endpoints, and eligibility criteria.

The concept blueprint phase ends when all the elements in this phase have been specifically identified for the trial. Figure 7 shows the elements of the Concept Blueprint phase.

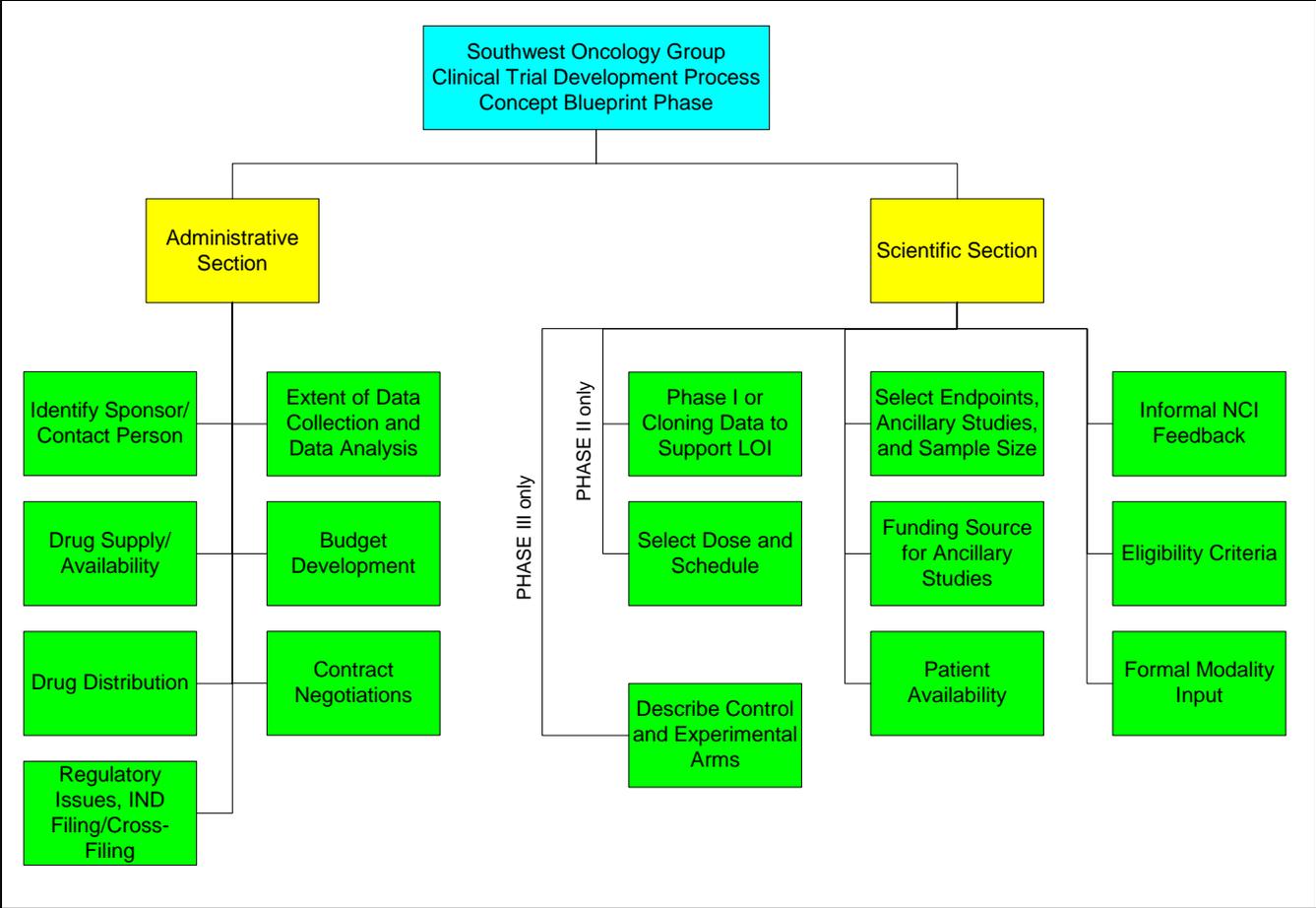


Figure 7: Southwest Oncology Group Concept Blueprint Phase

Concept Development Phase

The concept development phase begins when the Study Coordinator develops a concept or letter of intent for submission to NCI. Cancer therapy studies are submitted to the Cancer Therapy Evaluation Program (CTEP). Cancer prevention studies are submitted to the Division of Cancer Prevention.

During this phase NCI will review the concept or letter of intent. NCI reviewers may request changes to the document before approval. The Study Coordinator will incorporate changes into subsequent drafts of the document and resubmit the document for review. This phase ends when NCI approves the concept or letter of intent. Figure 8 shows the elements of the concept development phase.

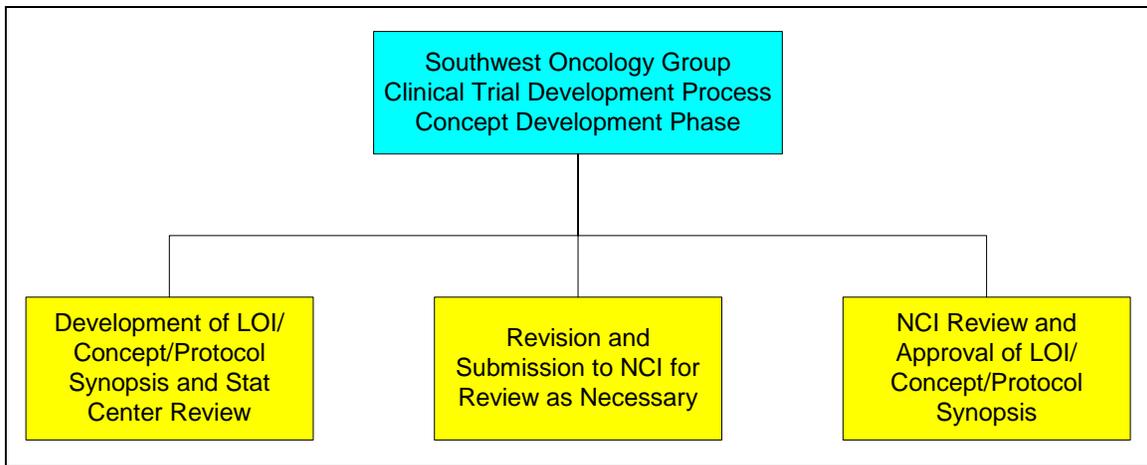


Figure 8: Southwest Oncology Group Concept Development Phase

Protocol Development Phase

The protocol development phase begins when the Study Coordinator receives NCI approval to develop the protocol. The protocol coordinator then manages the process of creating the protocol from all the existing elements. Previous protocols, concept/letter of intent information, and NCI comments all feed the creation of the protocol document.

The protocol coordinator, Study Coordinator, Statistical Center, and disease committee chair will all review the protocol before submission to NCI. SWOG has set a goal of two rounds of internal review, with each round taking about two weeks. NCI reviewers may require changes before approving the protocol. If so, Study Coordinator and Statistics Center will respond to NCI comments, and the protocol coordinator will incorporate changes into a new draft of the protocol.

Once NCI reviewers have approved the protocol, the study may be activated. This ends the protocol development phase. Figure 9 shows the elements in the protocol development phase. The protocol development elements must occur in the sequence indicated by the numbers in Figure 9. No element may begin until its preceding element has been completed.

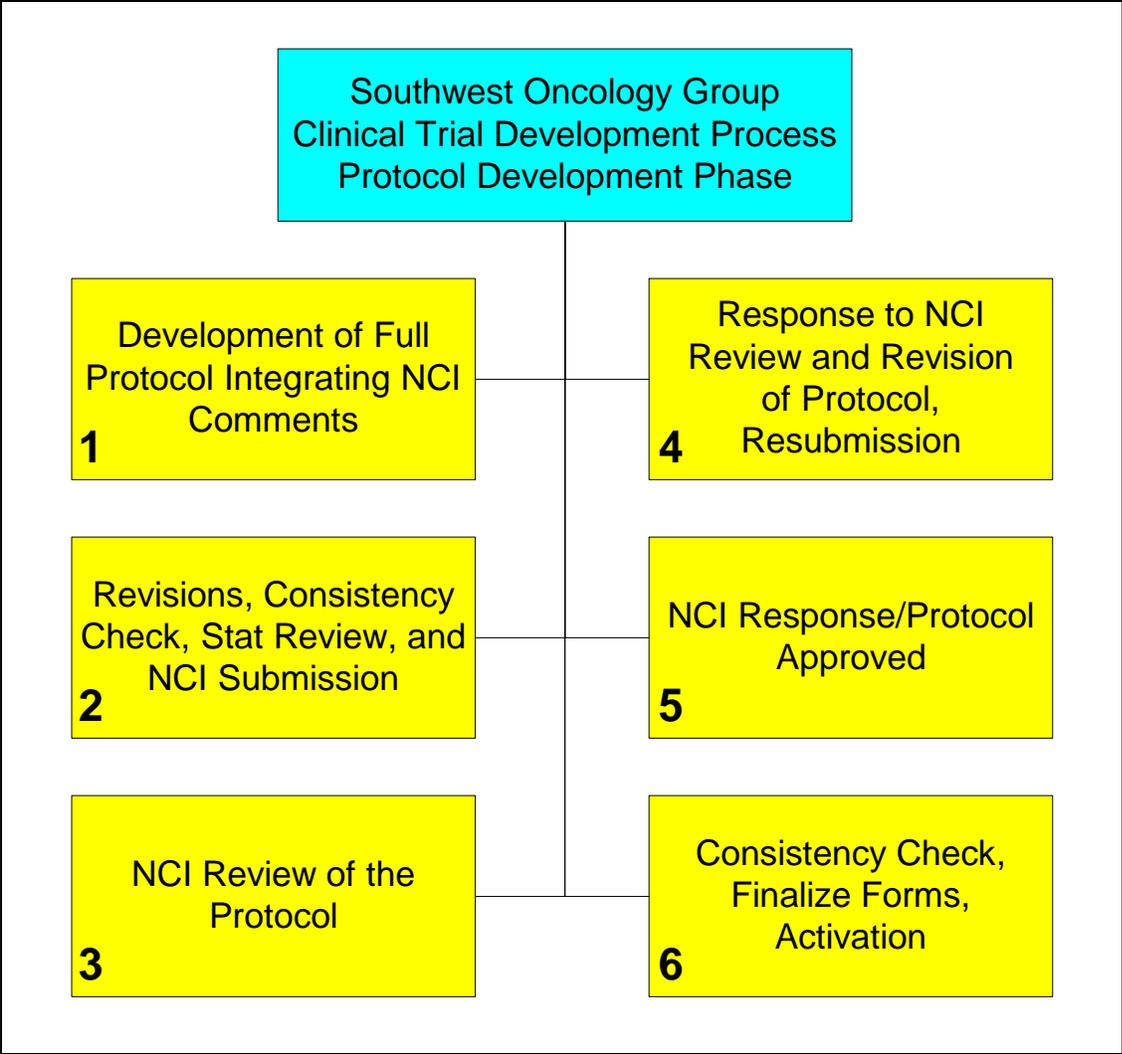


Figure 9: Southwest Oncology Group Protocol Development Phase

Protocol Coordinator Role

The Protocol Coordinator drives the entire SWOG clinical trial development process. This person serves as the central collection point for all questions, testing, and problems that may arise. Once the concept/letter of intent (LOI) is approved, the Protocol Coordinator drafts the protocol. The Protocol Coordinator combines sections from previous protocols, details from the concept/LOI, and comments from NCI to create the first draft of the protocol. A single Protocol Coordinator has between 20 and 30 studies in development at any one time.

Protocol Authoring

In the past SWOG personnel developed protocol templates specific to each disease. However, these templates proved impractical in actual use. SWOG has replaced the templates with standard statements that may be used in any protocol regardless of disease. SWOG uses the standard NCI consent forms, modified to include study-specific details.

By the end of 2000 SWOG intends to test an online protocol development system. The system will initially be based on Microsoft Word templates, but later versions of the tool may include database components. Some investigators do not have many technical computer skills, and this may be an obstacle to acceptance of online protocol development.

Concept/LOI and Protocol Reviewers

The same individuals are typically involved in all the concept and protocol reviews throughout the development of a particular SWOG clinical trial. The reviewer roles are:

- Disease Committee Chair
- Study Coordinator (the principal investigator and first author on publication)
- Primary Statistician
- Secondary Statistician
- Pharmaceutical Company Representative (if a pharmaceutical company is involved through a contract)
- Statistics Center Data Coordinator

Additional individuals may participate in certain reviews because their special expertise is required.

Eligibility Criteria and Common Data Elements

Eligibility criteria define the population of patients that may participate in a clinical trial. Southwest Oncology Group's (SWOG) protocol development guidelines show "Eligibility Criteria" as a small section of the Concept Blueprint Phase. In practice however, the eligibility criteria are proposed, negotiated, and revised throughout the entire clinical trial development process. Almost anyone involved in the writing or review of a protocol may have input on the development of eligibility criteria.

Factors Affecting Eligibility Criteria

SWOG guidelines state that each eligibility criterion requires a strong scientific basis for inclusion. If a criterion does not affect patient safety or data interpretation, it should probably not be included. Many of SWOG's eligibility criteria guidelines drive towards improving patient accrual rates without harming the scientific integrity of the study. Figure 10 shows the factors affecting eligibility criteria development in SWOG clinical trials.

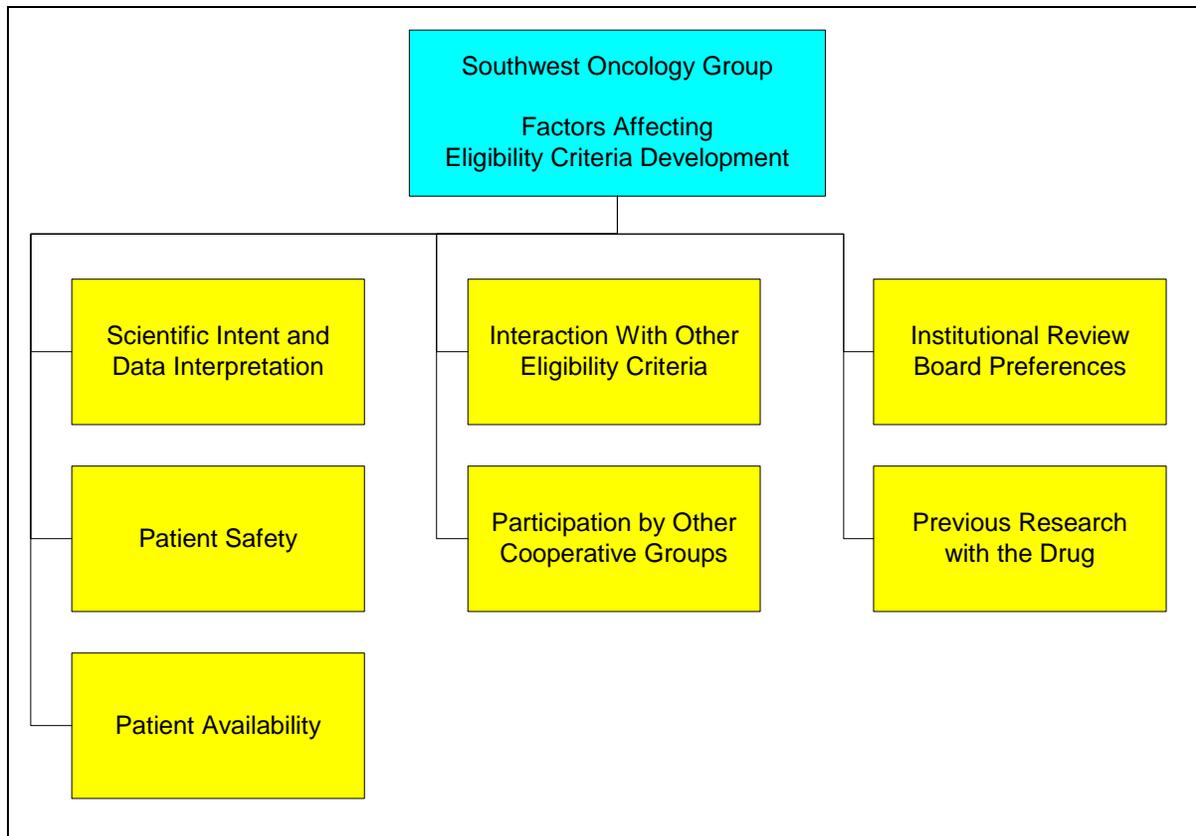


Figure 10: Factors Affecting Eligibility Criteria Development

Scientific Intent and Data Interpretation

Eligibility criteria must define the population(s) in a clinical trial so that the questions of scientific interest may be answered. Eligibility criteria must also be stated in a way that allows results to be interpreted for each primary and ancillary study in the clinical trial.

Patient Safety

Eligibility criteria must screen out patients for whom participation might pose unreasonable risk.

Patient Availability

Eligibility criteria should be written to maximize the number of potential participants, consistent with patient safety and the study's scientific rationale. The total pool of potential patients is limited, and the rate of patient accrual limits the speed with which clinical trials may be concluded. If a study's eligibility criteria are too restrictive, or if another study is competing for the same group of patients, the study may accrue patients at an extremely slow rate.

Interaction with Other Eligibility Criteria

Some eligibility criteria are interdependent. When one criterion is changed, the protocol author must also review other criteria for possible changes.

Participation by Other Cooperative Groups

Some clinical trials require so many patients that SWOG cannot complete the trial using just its own institutions. This is especially true for phase III trials that test the overall effectiveness of a therapy. In these cases, SWOG will work with other cooperative groups to generate the desired number of accruals. However, the other cooperative groups may have different eligibility criteria standards, and SWOG must address those differences when writing the protocol.

Institutional Review Board Preferences

The Institutional Review Board (IRB) of each cancer center must approve each protocol before the center begins accruing patients onto the study. Different institutions have different standards and preferences with regard to eligibility criteria, and SWOG must address those differences when writing the protocol.

Previous Research with the Drug

Some clinical trials involve slightly new uses for drugs already approved by the FDA. Certain eligibility criteria for these trials may be written as guidelines rather than as strict criteria.

Types of Eligibility Criteria

SWOG domain experts identified the following types of eligibility criteria used in cancer clinical trials:

- Tumor type
- Stage
- Prior therapy
- Performance Status
- Measurability of disease
- Receptor positivity/negativity
- Hormonal status
- Organ function
- Demographics (age, gender if scientifically indicated for the study)

The domain experts noted that organ function eligibility criteria were much more standardized in the past. At one time the toxicity standards were based on institutional normal values. Since the implementation of the Common Toxicity Criteria, organ function measurement per protocol requirements is less standardized.

Interpreting Eligibility Criteria

In the past, questions about the meaning of eligibility criteria arose at patient registration. Clinicians posed these questions to Statistical Center Data Coordinators. They in turn passed the questions to the Protocol Coordinators, who consulted with the Study Coordinators to clarify the criteria as necessary.

Today registration is more commonly completed by telephone or online, and questions about eligibility criteria are not reviewed at that point. Eligibility criteria reevaluation is now a retrospective review.

SWOG now uses the protocol standard statements to address issues that have caused the greatest confusion in eligibility criteria wording. These standard statements contain the correct wording for the problematic issues. The standard statements in SWOG’s protocol guidelines deal with:

- Participation by pregnant or nursing women
- Participation by men or women of reproductive potential
- Prior malignancy allowed
- Informed consent
- Institutional Review Board approval

Using Common Data Elements for Eligibility Criteria

SWOG domain experts identified a number of issues that should be addressed when applying a common terminology to eligibility criteria. Figure 11 shows the issues that were raised.

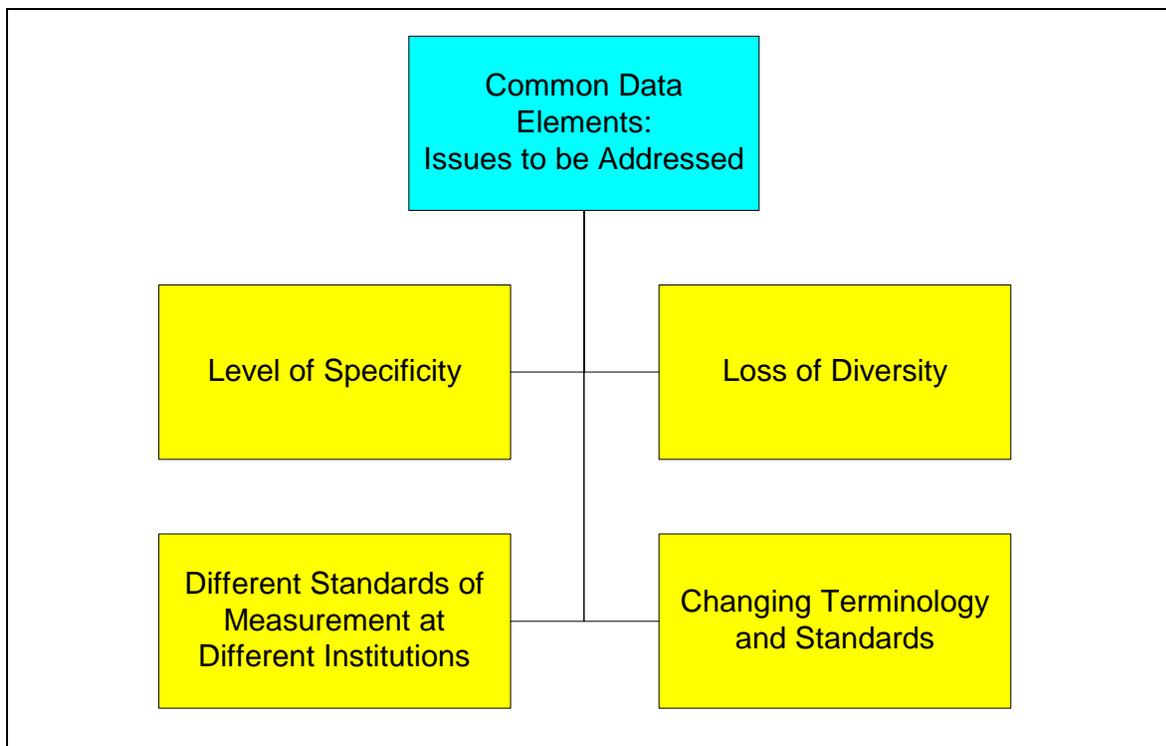


Figure 11: Issues to Address in the Use of Common Data Elements for Eligibility Criteria

Level of Specificity

In some cases common terms will demand either more specificity or less specificity than required for the task at hand. For example, the current Cancer Therapy Evaluation Program concept submission for requires a standard code for disease site. The code is too specific on one score. It allows for one disease site, while some trials involve multiple disease sites. At the same time, this code is not specific enough in other respects, such as indicating the number of nodes involved for a breast cancer trial.

Loss of Diversity

SWOG experts felt that a strength of the cooperative group system is that it encourages diverse groups of researchers to further cancer research knowledge in. Some of the best information might

be contained in alternate approaches rather than in an arbitrarily standardized approach. The SWOG experts expressed concern that standardized terminology would dilute such diversity.

Different Standards of Measurement at Different Institutions

This issue breaks down into two parts:

1. What should be measured? In some cases, investigators disagree among themselves about whether something in the cancer research domain even exists. Some agreement must be attained in this area first.
2. How should it be measured? Different investigators and institutions prefer different metrics. For example, some institutions prefer that menopausal status to be measured in terms of a lab test value, while others prefer it be measured in categories (pre-menopausal, post-menopausal).

Changing Terminology and Standards

Cancer research terminology is constantly changing as the science improves. This presents difficulties in developing and maintaining a set of common data elements. The SWOG experts expressed concern that more time might be spent maintaining a common terminology than using it.

Within the Southwest Oncology Group, if new science causes eligibility criteria terms to change early in a clinical trial, the protocol is amended to reflect the new terminology. If the terms change when the trial is three-quarters or more done, the trial will probably be completed as written (though explanations may be provided in the manuscript). However, accruals may slow or stop on the trial, and the results may be skewed. The SWOG experts noted that interim analysis of trial results is misleading. The study statistics are powered to require a certain number of accruals in order to reach conclusions. Conclusions drawn from fewer accruals may be incorrect.

Implications for Common Data Element Technology

Based on SWOG expert input, in order to successfully apply common data elements to protocol authoring, a technology solution should:

- Be available throughout the entire clinical trial development process, from initial review of the idea through protocol amendments
- Be accessible to all individuals involved in the clinical trial development process
- Accommodate in some fashion the diverse measurement approaches preferred by various investigators and institutions
- Accommodate the varying levels of specificity that may be required to support the science behind different clinical trials
- Be easily updated and maintained as the science behind the terminology changes
- Be considered as "data elements" rather than specified forms or formats

Other Issues Related to SWOG Clinical Trials

Clinical Trials Support Unit

Cooperative groups tend to register about 3 percent of cancer patients on clinical trials. The National Cancer Institute (NCI) would prefer that this percentage be higher. NCI will soon implement a Clinical Trials Support Unit (CTSU) to help cooperative groups accrue more patients.

The SWOG domain experts were as yet uncertain about how CTSU will help accrue more patients. They did express the opinion that CTSU will encourage better communication between cooperative groups, which often view each other as competitors.

SWOG Training for Investigators

Cancer investigators and clinical trial authors possess a wide variety of backgrounds and experiences. SWOG provides a Study Coordinator workshop to help investigators prepare for leading a clinical trial. SWOG also provides a course through the Hope Foundation for young investigators. Older researchers are conducting much of the cancer research, and this course is a means of stimulating young investigators.

Entries for the Domain Dictionary

Committee Chair: At Southwest Oncology Group a Committee Chair leads each disease committee. The Committee Chair prioritizes all study ideas in his area of responsibility.

Disease Committee: At Southwest Oncology Group, disease committees are responsible for focusing the scientific efforts of the group. Each disease committee is responsible for protocols addressing certain types of cancer.

Hope Foundation: The Hope Foundation is a non-profit group that provides a means for organizations and individuals to financially support Southwest Oncology Group cancer research efforts.

Protocol Coordinator: At Southwest Oncology Groups, the Protocol Coordinator administratively drives the entire clinical trial development process. This person serves as the central collection point for all questions, issues, and problems that may arise.

SELECT Study: A 14-year prostate cancer prevention trial beginning in 2001. It involves more than 32,000 patients and is led by the Southwest Oncology Group.

Study Coordinator: At Southwest Oncology Group, the Study Coordinator is the physician who proposed the initial study idea, serves as the principal investigator, and is first author on the publication of results.