ETHICAL AND REGULATORY CONSIDERATIONS

Office for Office for Human Research Protections

The Office for Office for Human Research Protections (OHRP) is an administrative subdivision within the U.S. Department of Health and Human Services (HHS) designed to protect human research subjects. OHRP is located in the Office of the Secretary of HHS in Rockville, Maryland. OHRP functions include establishing criteria for and approving assurances of compliance for the protection of human subjects and providing guidance on ethical issues concerning human subjects involved in biomedical or behavioral research.


Regulations included in 45 CFR 46 require that prior to involvement of a human subject in any aspect of research where the provisions of 45 CFR 46 apply, the following conditions must be met:

* OHRP has approved an appropriate assurance of compliance;
* Proper IRB review has occurred;
* Informed consent has been administered and documented.

The Assurance Program

An assurance is a binding commitment between an institution and the Department of Health and Human Services. It documents the institution's intent to comply with 45 CFR 46. OHRP acts on behalf of HHS in negotiating these assurances. The Assurance Program was changed in 2001, eliminating a three-tiered Project Assurance Program to one assurance: Federal/Wide Assurance (FWA) to cover all institutions that have grant funding from DHHS.

Institutional Review Board (IRB)

An institution's IRB is composed of a minimum of five members with professional competence, experience, and qualifications. The members should include both males and females from a variety of backgrounds, racial and cultural identities.

At least one member must be a non-medical professional (e.g., lawyer, clergy) and one person must have no direct affiliation with the institution performing the research (i.e., layperson, community representative). This diversity in an IRB is critical to maintain objectivity in assessing the ethical considerations of human research projects.

An IRB reviews research protocols using these ethical principles:
* Respect for persons (autonomy).
* Minimization of risk and maximization of benefit to subjects (beneficence).
* Fairness in the distribution of research burdens and benefits (justice).

These principles are the basis of "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" which was developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. They are commonly known as The Belmont Report.

The assurance program requires that all cooperative oncology group clinical protocols be subjected to full IRB review prior to accruing human research subjects and at least annually thereafter (≤ 365 days).

Institutional Review Board Functions

1. Main functions are:
   * Review all research protocols, including the informed consent document;
   * Assess benefit/risk ratio for patients;
   * Ensure patients are informed of the research and their rights;

2. Review proposed research at a meeting that:
   * Convenes with a majority of members;
   * Includes one member whose concerns are of non-scientific areas;
   * Approves research with a majority vote of those present;

3. Report to the appropriate institutional authorities any continuing noncompliance by investigators with the requirements and determinations of the IRB. IRB have the authority to:
   * Approve, disapprove or modify the protocol and informed consent form;
   * Conduct continuing review of the protocol and informed consent form;
   * Observed and verify changes in the protocol and informed consent form through amendments and revisions;
   * Suspend or terminate approval

Institutional Review Board Process

Oncology studies which accrue and actively treat subjects must be reviewed by the entire IRB at least once per year. Some research that involves no more than minimal risk such as some cancer control studies may qualify for expedited review.

A typical review process consists of the following two stages:
1. **Pre-review**: One or more board member(s) receives a protocol two to three weeks prior to the board meeting. The protocol and informed consent form are carefully reviewed and questions or problems are presented to the investigator to be addressed prior to the board meeting.

2. **Full Board Review**: Following investigator response to pre-review, the protocol is reviewed by all board members, resulting in the protocol and the informed consent form being approved, disapproved, or approved with stipulations. The IRB also decides how often the project must be reviewed based on risk/benefit ratio to the patient.

The IRB is also responsible for reviewing changes to the protocol while it is in process. Once all patients are in follow-up, it may be appropriate (at the discretion of the IRB) to allow an expedited process for subsequent annual reviews.

**Central Institutional Review Board (CIRB)**

The Central Institutional Review Board (CIRB) was initiated to reduce the administrative burden on local IRBs and investigators by partnering with local institutions to provide a high level of protection for study participants in NCI-sponsored clinical trials. The CIRB Initiative is sponsored by the NCI in consultation with OHRP. The CIRB enables an investigator to enroll patients into NCI-sponsored clinical trials significantly faster than when employing the traditional method of IRB review.

Each participating institution grants authority to the CIRB when the Institutional Official signs the Authorization Agreement and OHRP has accepted an FWA designating the CIRB as an IRB for that institution. The CIRB is informed of local context considerations via the Annual Signatory Institution Worksheet About Local Context and the Annual Principal Investigator Worksheet About Local Context. The Signatory Institution has two main responsibilities: 1) to report to the CIRB potential unanticipated problems or serious or continuing noncompliance and 2) the merging of the CIRB-approved local boilerplate text into the CIRB-approved consent document.

**Informed Consent**

The principle of informed consent is based on a 1974 Supreme Court decision which stated that every adult human being of sound mind has the right to determine what shall be done with their own person.

A subject (or the subject's legally authorized representative) must give his or her written consent to participate in the study. This consent must be signed by the patient, dated and retained by the investigator as part of the study records for inspection at any time. In addition many IRBs and regulatory agencies recommend the signature of all three persons listed below:

1. A witness
2. The investigator
3. The person conducting the informed consent process
Failure to obtain informed consent may result in suspension of patient entry privileges for the institution and termination of access to investigational drugs. In instances of fraud or severe misconduct, action may include replacement of the principal investigator, termination of the grant, cooperative agreement or contract, re-analysis or retraction of published results, formal investigation by the National Institutes of Health (NIH) or disbarment of the investigator from future participation in NIH clinical trials.

Federal guidelines stress two critical components in obtaining informed consent:

1. The participant must be given complete information; and
2. Participation must be voluntary.

The OHRP (Protection of Human Subjects code of the Federal Regulations 45 CFR 46) and the Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) describe the following elements of informed consent.

These elements must be included to comply with FDA/OHRP regulations for the conduct of clinical trials and help to ensure that the subject is completely informed.

1. A statement that the study involves research, an explanation of the purpose of the research, the expected duration of the subject's participation, a description of the procedures and identification of any experimental procedures.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that the possibility exists that SWOG, the NCI, and/or the FDA may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation or medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
9. When appropriate the following elements shall also be provided:

a. Statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) which are currently unforeseeable.

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

c. Any additional cost to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

e. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

f. The approximate number of subjects involved in the study.

The circumstance under which consent is obtained is also important. A participant's decision can be profoundly influenced by the way information is given. The following guidelines ensure that the consent will be as voluntary as possible.

Information given to the subject must be provided in their own language.

The investigator must verify that the subject understands what they have read and heard by asking questions of the subject to determine the subject's level of understanding and clarify any misunderstandings.

* The subject should have adequate time to evaluate the pros and cons of participation.

* Allow the participant to take the consent form home to review if necessary.

* The subject should be encouraged to discuss the study with anyone they wish, particularly family and friends who might be affected (e.g., person who might be needed to provide transportation).

* Family members of the subject may raise questions and considerations that the subject is likely to overlook; questions that concern the family are better answered sooner than later. Furthermore, there is evidence to suggest that family support increases the probability of subject cooperation during the course of the study.

* The setting in which the consent is obtained should be as private as possible so the subject can freely ask questions without embarrassment. If other persons can hear the conversation, the subject may be reluctant to ask appropriate questions.

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1The CARET (Carotene and Retinol Efficacy Trial, Seattle, Washington) Study Manual
To avoid pressuring the subject, only one person associated with the study should be present when the subject reviews the consent form.

The subject should be given a copy of the consent form after it is signed.

The subject should be encouraged to keep the consent form because it contains useful information about the study he or she can review from time to time.

A protocol specific model consent form is included in every SWOG protocol.

An IRB may approve a consent form which alters the basic elements of informed consent. However, the following policy has been developed to ensure that all patients on SWOG trials are fully informed regarding their participation in a clinical trial.

1. All model informed consent documents for protocols will be prefaced with the following statement.

"This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study."

2. The objectives of each study, the risks, and the alternative treatments as included in the model informed consent document will be placed in bold type to identify them as crucial and they should be included in the local consent document in their entirety.

3. Any changes and justifications for changes submitted to the Operations Office by local IRBs will be reviewed and approved by the protocol coordinator for that study with input (as needed) from quality assurance personnel and/or the Executive Officer.

4. Institutional consent forms are subject to review on a specific case-by-case basis during regularly scheduled quality assurance audits.

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule went into effect on April 14, 2003. The Privacy Rule places restrictions on how Covered Entities may use and disclose Protected Health Information (PHI).

Please be aware of these key points:

- All patients (initially) registered to SWOG-coordinated studies on or after April 14, 2003 must have signed a patient authorization form giving permission for PHI to be released to SWOG and its designates.
• PHI for patients registered to SWOG-coordinated studies prior to April 14, 2003 may be released without further authorization, according to the HIPAA Transition Provisions which say that a consent form signed prior to April 14 may act as an authorization after April 14, 2003.

• SWOG expects that patient authorization forms will be specific to the local institution’s requirements, and will comply with local laws. Current protocols include study-specific patient authorization forms that sites may use as a template.

• With the exception of patient initials and dates, the only PHI SWOG collects is at registration. These data are stored under an additional layer of security in the SWOG database, and access is severely restricted. Some older forms may still request full patient name, but we continue to require that only initials be provided now and in the future on all data submitted. This will be enforced at the Statistical Center. Repeated infractions will be reported to the institution’s Privacy Officer.

Questions regarding HIPAA and privacy protection may be addressed to Dana Sparks at the Operations Office (210) 450-8808 or Angela Smith at the Statistical Center (206) 652-2267.