A Manual for Participants in Clinical Trials of Investigational Agents Sponsored by DCTD, NCI

1. Introduction

The Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) has developed policies concerning various aspects of the therapeutic development of new agents. They are intended to ensure patient safety and to provide the National Cancer Program with the most effective new agent development program possible. In this handbook, we explain the policies and procedures of the DCTD with respect to the clinical use of its investigational agents. Some DCTD policies are a direct result of the regulatory requirements of the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS). Others are not directly mandated by law or regulation but are the result of a consensus among DCTD staff, the NCI Board of Scientific Advisors, and leaders in the community of clinical investigators.

We have also described in this handbook the specific procedures that the NCI has in place to implement its policies. Oncologists, nurses, pharmacists, research administrators, and data managers should find the information presented here useful in practical matters connected with protocol writing and submissions, reporting requirements, agent accountability, and a host of other subjects. Specific policies and procedures continue to evolve; through them NCI aims to provide a flexible and responsive system within the constraints imposed by regulation and the size and scope of the program.

With respect to new agent development, NCI acts both as a funding agency and as a sponsor (in the sense used by FDA) of clinical research. The DCTD has broad responsibility for this effort. Within the DCTD, the Cancer Therapy Evaluation Program (CTEP) designs and implements the development plans for new agents. Aside from the purely scientific and medical issues involved in such planning, CTEP utilizes two particular administrative tools:

(1) It submits Investigational New Drug Applications (INDs) to the FDA permitting DCTD to act as a sponsor of investigational agents;

(2) It is responsible for the contracts, cooperative agreements and grants under which most clinical testing takes place.

In this handbook we shall refer to DCTD as the IND sponsor and the "proprietor" of the new agent development program. We shall refer to CTEP wherever the efforts of CTEP staff specifically come into play. We shall reserve the use of NCI for more general contexts, including overall support of clinical trials.

We welcome the reader's comments on the content of this handbook and how future updates can make this handbook more useful.

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Sponsors, Research Bases, and the Investigator

When investigators perform clinical trials, two organizations are crucial--the sponsor of the trial and the research base. The next two sections discuss the purposes and features of each. In particular, we describe the role of the DCTD as a sponsor of investigational agent trials; as a sponsor DCTD is responsible for the overall direction of the process of new agent development as well as its practical implementation. Of course, DCTD is not the only sponsor of trials involving new anticancer agents. The activity of private pharmaceutical companies has increased dramatically in recent years. We outline here the basis of the relationship among DCTD, pharmaceutical companies, and investigators supported by DCTD in the conduct of clinical trials. We also discuss the vital role of the research base in support of the investigator. As is the case with all types of research, clinical trials cannot take place without a substantial institutional commitment.

2. The Sponsor

The development of new anticancer agents is a long and complex process, but successes have been significant. The fact that some aggressive neoplasms are now curable with chemotherapy is the best possible evidence that agents with selectivity against cancer can be identified and used effectively. On the other hand, oncologists are well aware that for many common tumors, systemic treatment is unsatisfactory. The motivation to develop better therapy is therefore as powerful as ever. With the increased understanding of the malignant process due to recent and anticipated advances in molecular biology and biochemical pharmacology, there is every reason to expect that the development of new agents will proceed along increasingly rational lines in the future.

The process of new agent development is often divided into preclinical and clinical components. Although this division is operationally useful, it should be recognized that continual interplay and cross-feeding exist between the preclinical and clinical arenas. Evidence of synergy or the effectiveness of combined modality approaches in experimental models, for example, has provided the major motivation for a very large number of clinical trials. The converse is also true; clinical observations have from time to time given rise to new lines of basic investigation.

Historically, one of the most important effectors in the discovery and development of new anticancer agents has been the NCI. The prominence of NCI's role in new cancer agent development has no parallel elsewhere in developmental pharmacology. The justification for such intensive involvement of a Government agency in research and development is clear: Significant improvement of cancer treatment is in the public interest. Only more recently has there been substantial involvement on the part of the pharmaceutical companies. This is in contrast to the impressive role of the private sector in the development of many other classes of agents, such as antibiotics, anti-inflammatory agents, and endocrine agents. Current trends suggest an increasing interest by pharmaceutical companies in anticancer agents. Even so, NCI remains the largest sponsor of research with antineoplastic agents; currently, well over 150 compounds are in various stages of clinical testing; a far greater number are in preclinical development.

As part of this massive effort, NCI funds a clinical trials network that includes Cooperative Groups, new agent development contractors, and other investigators at Cancer Centers and University hospitals. More than 10,000 investigators from approximately 2,000 institutions participate in this effort.

In the United States, clinical research with experimental agents is carefully regulated. The ultimate authority for assuring the safety of the public in matters relating to investigational agents and medical devices rests with the Food and Drug Administration (FDA). FDA regulations, which are specific implementations of the Food, Drug, and Cosmetic Act, define the terms under which clinical work with experimental agents may proceed. Because these regulations have the force of law, they must be heeded by all those involved in clinical trials with investigational agents, including NCI, pharmaceutical companies, and investigators. An organization or individual that assumes legal responsibilities for supervising or

overseeing clinical trials with investigational agents is termed a sponsor. In the United States, the DCTD and private pharmaceutical companies most commonly sponsor such research in cancer. The designation obviously implies a substantial commitment of resources.

In addition, the Public Health Service Act mandates a number of safeguards for the rights and welfare of individuals who are involved as subjects of the research. Regulations of the Department of Health and Human Services (DHHS) administered by the Office for Human Research Protections (OHRP), DHHS, specify the requirements to ensure adequate protections for human subjects. Clinical investigators and institutions taking part in the clinical trials network are responsible for meeting the requirements of the HHS regulations.

As sponsor of an investigational agent, DCTD, and specifically CTEP, is responsible for seeing that clinical trials proceed safely and rationally from the initial dose-finding studies through to a definitive evaluation of the role of the new agent in the treatment of one or more specific cancer(s). Fulfillment of this goal obviously requires the active participation of CTEP staff throughout the entire process.

2.1 How NCI Funds Research

A full discussion of the means by which NCI funds research is beyond the scope of this handbook. Whether support comes from investigator-initiated grant, contract, or cooperative agreement, however, the process of peer review is central. Government officials can provide monies to investigators only in the context of mechanisms involving peer review; this process requires formal application by the investigator and (usually) multiple levels of evaluation. Once an application is approved, the NCI cannot provide more funding than is stipulated by the judgement of peer review and the Board of Scientific Advisors. Additional awards can, of course, be made after review and formal approval of a supplemental application. The provision of investigational agents for clinical studies is a separate issue and does not imply that NCI will provide funding for these same studies. However, for funded research proposals CTEP will make a good faith attempt to supply investigational agents required for that research.

2.2 Preclinical Development of New Agents

The DCTD could not effectively accomplish its overall aims in new agent development without a very extensive preclinical effort. The DCTD Developmental Therapeutics Program (DTP, http://dtp.nci.nih.gov) is heavily committed to the discovery and development of new anticancer agents. Readers are referred to a summary of the objectives, methods, and status of DCTD's preclinical agent discovery and development program in Boyd, MR: Status of the NCI Preclinical Antitumor Drug Discovery Screen, *Principles and Practice of Oncology Updates,* Vol. 3(10): 1-12 (1989), Appendix XVI.

2.3 Collaboration Between Sponsors: DCTD and the Pharmaceutical Companies

At present, most of the anticancer agents in clinical development by CTEP are also being developed by a pharmaceutical company. Although involvement of the pharmaceutical companies in research on antineoplastics is not new, the maturing of medical oncology as a specialty and the advent of agents for the successful treatment of many cancers have stimulated interest by industry in cancer treatment to an unprecedented degree.

Collaboration between DCTD and the pharmaceutical industry may occur at any step along the new agent development process. Private companies often submit compounds to DCTD for testing and joint development. Compounds may be submitted for antitumor screening, for preclinical toxicology, or for clinical testing. Conversely, if a compound is discovered by DCTD, the involvement of a collaborator is sought as early in development as possible, because DCTD does not market new agents. The early involvement of a pharmaceutical company permits substantial cost-sharing between public and private sectors, and can hasten by several years the availability of effective agents for all cancer patients.

Development plans for new agents, therefore, are usually a collaborative effort between DCTD and a pharmaceutical company. These plans are heavily influenced by the findings and opinions of the clinical investigators working with the agent. In this joint effort, DCTD and the private sector share the common goal of defining the contribution of a new agent to cancer treatment as precisely and expeditiously as possible. The timely approval of a New Drug Application (NDA) or Biologic License Application (BLA) by the FDA is in the public's interest. However, there may well be differences between these partners in sponsoring certain kinds of trials. The three-way relationship among clinical investigators, the DCTD, and private industry involves complex issues in coordination, in establishing priorities, and in the allocation of limited resources. To facilitate the necessary interactions, CTEP has developed a policy on the nature of the relationship between the participants. The policy, which formally recognizes the involvement of the private sector in the support of clinical trials, is articulated in a document entitled *"Policy Statement*: NCI-Cooperative Group-Industry Relationship Guidelines" (See Appendix I), http://ctep.cancer.gov/industry/industry.html.

2.4 Private Support of Trials Sponsored and Funded by NCI

As private support for clinical trials in cancer becomes more widespread, investigators holding grants, contracts, or cooperative agreements from NCI should carefully consider the allowable allocation of resources provided by a private sponsor for a trial already having NCI support. Investigators must make certain that Federal funds are not used to cover those costs of research that are also supported by private resources. Grants management personnel at NIH and auditors from DHHS are required to scrutinize such arrangements closely and may take steps to recover Federal funds if they have been used inappropriately.

In the specific case of the clinical Cooperative Groups, the Terms of Award of NCI's agreements with the groups permit them to accept industrial support, provided that industry funds are used for the support of additional costs generated as a direct result of the interest of a pharmaceutical company in a particular clinical trial. Such costs might include additional laboratory tests or special requirements for data collection.

In the case of trials funded under Phase 1 and Phase 2/3 cooperative agreements or contracts, the provision of resources for tasks not supported by Federal funds may or may not be appropriate; all such agreements should be submitted to the grant or contracting officer for prior approval.

2.5 Private Support of Trials Sponsored but Not Funded by NCI

Private support of a trial sponsored under an IND held by DCTD is appropriate under certain circumstances. However, there should be a written agreement between the protocol chair and the private firm; this agreement should also be sent to the Chief, Regulatory Affairs Branch (RAB), CTEP. In general, CTEP will favor the provision of data from trials of this kind to a pharmaceutical company. These arrangements may not be exclusive (i.e., may not serve to prohibit the supply of data to another party), however, unless CTEP has previously agreed with the pharmaceutical company that exclusivity is appropriate. In any case, the obligations of the investigator to DCTD as the sponsor, as detailed throughout this handbook, remain unchanged.

2.6 The Investigational New Drug Application (IND)

Any organization seeking to sponsor clinical trials with experimental agents must first submit an IND to the FDA (Note 1). The IND is the legal mechanism under which experimental agent research is performed in the United States (Note 2). No experimental agents may be administered to patients for research in the U.S. without an IND.

All IND sponsors have obligations which are specified in the regulations of the FDA. The DCTD, as a component of an agency in the DHHS, is just as accountable as a pharmaceutical company for meeting the IND regulations of the FDA.

The initial IND submission by the sponsor to FDA is a lengthy document that sets forth the experimental rationale for human testing, including results of animal toxicology studies, manufacturing data, purity and stability information, and an initial plan of clinical investigation.

The IND is the official record at the FDA of the sponsor's clinical research with the agent. Under FDA regulation, CTEP must maintain the IND as an accurate, timely repository of all information concerning clinical use of the agent, including all protocols, adverse events, and an annual report of the results of all clinical trials, plus any new relevant preclinical (particularly toxicologic) data. Obviously this means that there can be no use of the experimental agent without the knowledge and prior approval of the sponsor.

After a sponsor has submitted an IND, FDA has 30 days to complete its review. If FDA has safety concerns, it may place a hold on the initiation of any or all clinical trials with the agent. In certain circumstances, the sponsor may request a waiver of the 30-day waiting period. Please note that these are matters between the sponsor and the FDA. No investigator may initiate patient treatment on a protocol using DCTD agents until he or she has received written notice of approval from CTEP.

Note 1:
The use of the term sponsor is generally reserved for organizations assuming broad responsibilities for the development of a new agent. It is also possible for an individual investigator to hold an IND.

Note 2:
An IND must be submitted to perform clinical studies under the following conditions:

- When an investigational agent is manufactured in one state or country and transported to another state or country for clinical use.
- When the bulk material (or components of the agent) is manufactured in one state or country and transported to another state or country for further processing, formulation, or for final fill.

Although situations arise in which an agent is manufactured and tested within a state, technically, if any component of that clinical product (from the diluent to the vials and labels) is obtained from another state or country, the FDA could require an IND to be submitted and all the requirements to be adhered to.

2.7 The Marketing Application

After clinical trials have shown that the new agent is safe and effective, there is reason to make the agent generally available to patients and physicians. The formal process in the U.S. by which this occurs is the approval by FDA of a marketing application (New Drug Application for cytotoxic/cytostatic agents or a Biologic License Application for biological agents) submitted by a private firm; as noted previously, NCI does not submit NDAs or BLAs since it does not market products. The applicant seeks approval from FDA for one or more specific indication(s). Review and approval of an NDA or BLA are based on the demonstration of safety and efficacy assessed from detailed reports of the clinical trials; particularly randomized controlled studies. The contribution of a new agent in the treatment of a disease is demonstrated unambiguously if the agent is the only variable between the treatments.

The specific endpoints that constitute satisfactory evidence of efficacy (e.g., response rate, quality of life, survival) have been addressed in a published paper prepared by FDA and NCI entitled "Commentary Concerning Demonstration of Safety and Efficacy of Investigational Anticancer Agents in Clinical Trials." This paper was prepared with input and advice from the Oncologic Drugs Advisory Committee of FDA (a panel of outside experts in clinical oncology) and the Board of Scientific Counselors of the DCTD (a panel of outside experts in both preclinical and clinical oncology). A copy of this paper is included as Appendix II.
The approval of the NDA or BLA is a critical milestone not only for the pharmaceutical company but also for the clinical investigator, the practicing oncologist, NCI, and the general public. An affirmative decision by the FDA permits the pharmaceutical company to market and promote the agent for the approved

indication(s). Once an agent is marketed, no Federal regulation prevents any licensed physician from prescribing it for any indication he or she deems appropriate.

For the practicing oncologist, NDA or BLA approval means that the agent is readily available for routine treatment of patients. The practitioner no longer has to devise acceptable protocols with research intent, simply for the purpose of obtaining the agent for patient care. No longer must he or she use the cumbersome procedures for obtaining compassionate INDs from the FDA to treat individual patients.

For the clinical investigator, NDA or BLA approval means that it may be more difficult to recruit patients for further clinical trials with the agent, since use of the agent is no longer restricted to patients on research protocols.

For the NCI, NDA or BLA approval marks a step forward in the development of effective cancer therapies. Although the role of DCTD as a sponsor of clinical trials focusing on the approved agent usually decreases dramatically at that point, the NCI continues to sponsor further research with commercially available agents through its general support of clinical trials.

For the general public, NDA or BLA approval means that a new effective agent is now available on the widest possible basis. It is admittedly also true that an agent that was formerly available without cost for research purposes is no longer free to the patient after NDA or BLA approval. For financial reasons, the DCTD has found it necessary to discontinue the distribution of virtually all marketed agents, except for certain clinical trials of particularly high priority when the company continues to supply the agent to DCTD at no charge.

3. The Research Base and the Investigator
3.1 Definition and Purpose of a Research Base for Clinical Trials

A research base is an entity that assumes a broad range of responsibilities and functions for the support of clinical trials conducted under its name. Examples of research bases include Cancer Centers and Cooperative Groups. The research base supports the investigator in developing, organizing, implementing, and analyzing clinical trials. It assumes responsibility for the quality of the research, both in concept and execution, and has an important role in assuring patient safety.

An effective research base enhances the investigator's research in several specific ways. It provides assistance in developing protocols and obtaining approval by sponsoring agencies. It often offers centralized data management and statistical consultation. An effective research base should also provide the opportunity for internal peer review and quality assurance.

Obviously, the research base enhances its own scientific credibility by assuming responsibility for the quality of the scientific ideas and the care with which they are tested. These activities may also be an economical way of supporting multiple clinical investigations simultaneously.

In short, a research base provides an institutional source of support and assistance for the activities of protocol chairs and investigators. Clinical Cooperative Groups are examples of research bases whose functions are described in this section. Many of the same considerations about organization for support of clinical research apply to any Cancer Center or single institution.

3.2 Activities of the Research Base

The research base may assist the clinical investigator in many activities and may assume primary responsibility in several.

3.2.1 Protocol Development
3.2.1.1 Scientific Review

Many research bases have procedures for review of the science of a clinical trial, either at the concept stage or at the time a protocol is written. This review is distinct from the task of the Institutional Review Board (IRB) which may or may not view as part of its charge a critical scientific review. Ideally, a scientific review assists the investigator in focusing his or her ideas and perhaps in identifying other useful scientific resources within the research base. This process should facilitate research and assist in the testing of new ideas. Careful review may be particularly important for Phase 3 trials, because of the very substantial commitment of time, patients, and resources involved.

3.2.1.2 Biostatistical Consultation

The design of any clinical trial should be based on sound statistical principles. Issues such as sample size, stopping rules, endpoints, and the feasibility of relating endpoints to objectives are pivotal to a successful trial. Statistical expertise should be provided by a research base.

3.2.2 Protocol Administration

Since most protocols require multiple levels of approval, and since policies of the various sponsoring agencies may differ and change with time, a research base can provide valuable assistance to the investigator in obtaining these approvals. Establishment of a centralized mechanism for submitting and tracking a protocol through the necessary approvals, including the IRB, saves individual investigators a very large expenditure of time and effort that is much better directed elsewhere. A research base with multiple CTEP-sponsored protocols could efficiently assume the responsibility for communicating status changes, amendments, results reports, publications, and other pertinent protocol administration information to CTEP.

3.2.3 Establishment of an Affiliate Program

The participation of affiliate investigators often contributes to the success of cancer clinical trials. The research base must be as concerned about the quality of research performed by its affiliate investigators as that of its own staff.

CTEP has established a set of guidelines to assist research bases in developing a policy toward affiliate investigators (see Section 13). Each research base participating in investigational agent trials sponsored by DCTD should develop its own affiliate policy in accord with these guidelines.

The most important components of these guidelines are that the research base should, (a) define qualifications necessary for affiliate investigators and (b) periodically review their performance. Such review of performance should include site visits by investigators from the research base.

3.2.4 Agent Accountability and Storage

Although FDA regulation places the responsibility for maintaining accountability for the use of investigational agents with the investigator, an institution may assume these responsibilities for the investigators on its staff and assure itself of compliance with Federal requirements. (see Section 15).

3.2.5 Reporting of Results to CTEP

The results of trials involving IND agents must be reported to the sponsor. The Cooperative Groups, as research bases, inform CTEP directly of their results. In all other cases, such reporting is the responsibility of the protocol chair (see Section 10).

3.2.6 Data Management and Statistics

Since most cancer clinical trials involve professional staff other than the protocol chair, adequate collection of clinical data is a complex task that must be integrated into the medical practices of the institution. Furthermore, data collection is best done as data are generated; this practice promotes protocol compliance and permits the protocol chair to monitor the study's progress. For these reasons, data management organized and supported at the department or institution level is usually more efficient and reliable than that which is left to the individual investigator. Centralized data management is obviously not required of institutions performing NCI-supported trials, but its advantages seem clear. In the experience of CTEP's site visit monitoring program (see Section 16) the quality of execution of clinical trials is better in institutions that provide central support for data management.

3.2.7 Quality Assurance

This term, as discussed in detail in Section 16, applies to three features of the conduct of clinical trials.

- **Data Accuracy:**
  Are the data in the research record an accurate reflection of primary source documents?
- **Protocol Compliance:**
  To what extent was the protocol followed? Are the reported results based on the treatment set forth in the protocol? If not, was there good reason for departing from the protocol, and are these reasons fully documented in the research records and any resultant publications?
- **Procedural Requirements:**
  Were all necessary approvals obtained? Was the informed consent process adequate?

A quality assurance program permits the research base to satisfy itself that each participating investigator is fulfilling his/her responsibilities. It also provides the research base with data about the quality of execution of its clinical research, and it provides the investigator an opportunity to learn from an external evaluation of his/her performance. In its most constructive form, this process constitutes a peer review of performance and improves the quality of clinical research.

The implementation of these activities takes many forms. Section 16 describes the existing procedures of the Cooperative Groups and CTEP for quality assurance. Although CTEP does not require single institutions to establish internal quality assurance programs, inclusion of this subject in this section is intended to draw attention to the potential value of this activity for any research base. CTEP staff will assist any research base that desires assistance and advice in developing these programs.

The Development of a Clinical Trial

The following three sections explain CTEP policies for each phase of clinical investigation with experimental agents. For each phase we outline our scientific objectives as a sponsor of investigational agents. We also describe which physicians are eligible to study and administer investigational agents. These two aspects of agent use--study and administration--are formally quite separate issues. In general, eligibility to study NCI investigational agents has been restricted to institutions and physicians approved by peer review; these individuals may include grantees, contractors, Cooperative Group members, physicians affiliated with approved cancer centers, and recipients of investigator-initiated clinical research project grants (RO1, PO1). The application of this general rule to each phase of agent development is explained in detail. Except in certain explicitly defined circumstances outlined in the following sections, the administration of experimental agents is restricted to these investigators.

We also describe how investigators may obtain information about individual investigational agents and CTEP plans for their development.

4. Phase 1 Trials
4.1 Scientific Policies of CTEP
4.1.1 Planning of Phase 1 Trials

CTEP prospectively plans the Phase 1 development of each agent. Selection of schedules for clinical trials is based on experimental data (see Section 4.1.4 for details). Generally, each schedule is examined in not more than two studies. From the results of the Phase 1 and clinical pharmacology studies, CTEP and its collaborating investigators decide which schedule is to be taken into Phase 2. If the need exists, a second schedule may later be examined comparatively in selected tumors to define the therapeutic index better.

4.1.2 Objectives

Phase 1 trials determine a safe dose for Phase 2 trials and define acute effects on normal tissues. In addition, these trials examine the agent's pharmacology and may reveal evidence of antitumor activity. Therapeutic intent is always present in Phase 1 trials; indeed, anticancer agents are not tested in patients unless preclinical activity studies have already demonstrated evidence of significant activity in laboratory models.

Animal toxicology studies carried out prior to Phase 1 trials provide the investigator with

- estimates of a starting dose for clinical trials
- prediction of the likely effects of the agent on normal tissues.

These data provide the investigator with clues that help focus clinical observation of the patient. The dose is increased gradually by some defined procedure until a level is found that produces limiting but tolerable adverse events and/or clear signs of therapeutic activity. Phase I trials define acute effects that occur with a relatively high frequency on normal tissues.

Continued careful observation during Phase 2 and 3 trials is essential to identify less frequent acute adverse effects, as well as cumulative and chronic adverse events.

4.1.3 Patient Selection

Patients eligible for Phase 1 must have confirmed malignant disease that is not satisfactorily treated by conventional forms of therapy or for which there is no standard treatment. Initial patients should have normal organ function, in order that the investigator may reliably distinguish agent effects from disease effects. When there is impairment of a major organ, agent treatment may produce increased adverse effects because of decreased clearance or additive injury to the organ. Since most cancer agents will ultimately be used in some patients having impairment of major organ function (particularly cardiac, hepatic, and renal), it is reasonable to explore their use in such patients through Phase 1 trials explicitly designed to determine safe doses and pharmacology in these settings. CTEP will usually sponsor such trials selectively after the initial trials in patients with normal organ function. After successful completion of Phase 1 trials in adults with normal and abnormal physiology, other types of studies are initiated. These studies include those in pediatric populations, elderly patients, and (if hematotoxicity is dose-limiting) combination studies with hematopoietic growth factors. Such attempts are aimed at identifying a family of Maximally Tolerated Doses (MTDs) for each agent.

Typically, Phase 1 studies are performed in both women and men. If gender-specific pharmacologic differences exist, these differences must be characterized.

4.1.4 Schedule Selection

The number of separate schedules studied in Phase 1 is determined by several factors, including evidence of schedule dependence in experimental *in vivo* systems; pharmacokinetics, mechanism of action, if known;

and existing clinical data with similar compounds suggesting superiority of a particular schedule. Agents that are highly schedule-dependent in preclinical models are usually brought into Phase 1 on the putatively optimal schedule.

Because the correlation between schedule dependence in preclinical models and in the clinic is not firmly established, however, some agents may be candidates for a broader array of schedules. DCTD is prospectively evaluating the ability of experimental models to predict the schedule dependence of efficacy, adverse effects, and pharmacokinetics. For agents showing no particular schedule dependence in models, two extremes of schedules (e.g., single bolus dose per course and 5-day continuous infusion) are sometimes examined.

4.1.5 Starting Dose

The starting dose of a Phase 1 trial, as derived from preclinical toxicology, is 1/10 of the MTD in the most sensitive species tested.

4.1.6 Dose Escalation

Doses are generally escalated according to a scheme in which the initial increments are large and decrease rapidly as biologic effects become evident. Often, a modified Fibonacci plan is employed. However, when the goal is to escalate to a biologically effective dose as rapidly as possible, it may be justified to employ successive dose doubling until Grade 3 adverse events or two instances of a Grade 2 adverse event are seen. The exact schema may be affected by the steepness of the dose toxicity curve in animal models or, for trials of combinations of agents, the steepness of the single-agent dose toxicity curves. In all cases, the goal is to arrive at the recommended Phase 2 dose with the fewest number of escalations consistent with patient safety; this approach minimizes the number of patients receiving biologically inactive doses. The DCTD is actively evaluating other methods of dose escalation, based on the use of blood level data (see Section 4.1.7 below) and the accelerated titration designs for Phase 1 clinical trials at http://linus.nci.nih.gov/~brb/Methodologic.htm.

When there is sufficient concern about anticipated adverse events, a minimum of three patients not previously treated with the new agent should be entered at each dose level. In these cases, escalation to the next level should not occur until the safety of the current level has been established, which may require that at least three patients will have been observed for the entire course interval (e.g., 3 – 5 weeks). For many trials, however, escalation can proceed with one or two patients per level, provided no Grade 3 or repeated Grade 2 adverse events have yet been seen in the study. Intra-patient dose escalation should be considered for use wherever it is deemed safe. At least six patients should be treated at the recommended dose. The incidence of dose limiting toxicity acceptable for a recommended dose should be specified in the protocol (e.g., <33%).

4.1.7 Pharmacokinetics

The role of pharmacokinetics in Phase 1 is now receiving increasing emphasis, with specific focus on the possible use of such data to guide dose escalation. Human data on the pharmacokinetics of a parent compound and active metabolites, taken together with similar preclinical data *in vivo*, will be extensively analyzed over the next several years of Phase 1 trials to identify new approaches to dose escalations. This work is being coordinated by the Blood Level Working Group, composed of investigators from the DCTD and FDA. Investigators developing Phase I trials should consider pharmacokinetic determinations an integral part of a Phase 1 study. Because this may be limited by the availability of suitable methodologies, investigators should check with the Investigational Drug Branch (IDB) staff physician before writing a protocol.

4.2 Who Is Eligible to Study Phase 1 Agents

4.2.1 Contractors

Important resources for Phase 1 trials are institutions awarded cooperative agreement grants or contracts for these studies. Principal investigators are selected through competitive peer review in response to periodic solicitations from DCTD (Note 1). These contracts are usually awarded for 5 years.

Note 1:
When NCI seeks offerors for a contract, it issues a Request for Proposal (RFP). Notices of the availability of RFPs are published in the "NIH Guide to Grants and Contracts," which is widely distributed to universities in the U.S. They are also announced in the Commerce Business Daily, which announces all U.S. Government contract solicitations.

4.2.2 Other Phase 1 Investigators

Qualified investigators with peer-reviewed expertise in the conduct of early clinical trials are also eligible to conduct Phase 1 trials. Investigators are usually selected because of unique expertise or research experience relevant to the agent or the availability of certain patient populations or laboratory facilities to perform special studies. In all cases, such investigators must have demonstrated competence to conduct a Phase 1 study with anticancer agents.

Selection of Phase 1 investigators is a competitive process, with preference given to those with greatest expertise, ability to correlate clinical and laboratory biologic studies, and ability to complete a high-quality study as rapidly as possible. However, this competitive process is an open one, and all appropriate individuals are welcome.

Ad hoc Phase I investigators must fulfill all CTEP requirements for trials conduct, as defined in this section, and for reporting of data as described in Section 10.

4.3 Which Organizations Can Conduct Phase 1 Studies

Phase 1 trials will generally be conducted by single institutions. Multicenter trials with a new single agent whose adverse event profile is not yet known will not be approved, with the exception of pediatric Phase 1 studies (see Appendix III, Policy Statement: The Conduct of Phase 1 Trials in Children).

4.4 Who Is Eligible to Administer Phase 1 Agents

All Phase 1 agents will be administered only at the institutions listed on the cover page of the approved protocol and will be administered under the supervision of the protocol chair. These agents should *not* be sent to referring physicians, except with written permission of CTEP. Any part of the treatment that will be administered at a site other than the study center must be indicated in the protocol.

4.5 How to Obtain Information About Phase 1 Agents
4.5.1 Investigator's Brochure

This document contains all relevant information about the agent, including animal screening, preclinical toxicology, detailed pharmaceutical data, pharmacology and mechanism of action. CTEP has an Investigator's Brochure for each investigational agent it sponsors. These are routinely provided to investigators who are approved to conduct a clinical trial of the agent at the time the LOI is approved and when the Investigator's Brochure is updated. When necessary, investigators with approved LOIs or protocols may obtain the Investigator's Brochure from the address listed in Appendix IV.

4.5.2 IDB Physicians

Each DCTD investigational agent is assigned to an IDB staff physician, who coordinates its clinical development. Phase 1 investigators are advised to discuss a proposal with this physician before writing a formal protocol. IDB strongly encourages investigators to submit an LOI for Phase 1 trials (see Section 5.6 below). Relevant telephone numbers and addresses can be found in Appendix IV.

4.5.3 Other Information

Phase 1 investigators should carefully read the following sections that are relevant to issues arising with Phase 1 agents:

- Section 7 The Drafting of a Protocol
- Section 8 Protocol Review and Approval at CTEP
- Section 9 Ordering Investigational Agents from NCI
- Section 10 Responsibility for Reporting Results to CTEP
- Section 12 The Investigator and Protocol Chair: Roles and Responsibilities
- Section 15 Accountability and Storage of Investigational Agents
- Section 16 Monitoring and Quality Assurance

5. Phase 2 Trials

5.1 Scientific Policies of CTEP

5.1.1 New Agent Development Considerations

5.1.1.1 Planning and Coordination of Phase 2 Trials by CTEP

As a sponsor, DCTD must devise and implement a plan for Phase 2 trials of new agents. An adequate Phase 2 plan, while conceptually straight-forward, is often difficult to execute. A reasonable plan presupposes answers to the following questions:

- What doses and schedules that have emerged from Phase 1 ought to be carried forward into Phase 2?
- What diseases should be targeted for testing?
- How does the new agent fit into CTEP's priority list for various targeted disease studies? (For example, do we regard an analog of cisplatin as constituting a higher priority than a novel structure for testing in ovarian or head and neck cancer?)
- How does the new agent fit into the priorities of the clinical investigators who form the core of the NCI-supported clinical trials network?
- How can the CTEP assure that each agent receives an adequate test in each disease that is studied? How many studies should be mounted in each disease category? What kinds of patients are suitable for study entry? What are suitable stopping rules for Phase 2 trials?
- How to integrate full scientific investigation with NDA- or BLA-directed trials?
- How to perform Phase 2 studies if there are limited supplies of the new agent?
- What important laboratory correlates can be made within the context of a clinical trial?

The plan of Phase 2 development is prepared by CTEP staff working with the industrial sponsor during late Phase 1 and is announced in the solicitation of LOIs.

5.1.1.2 Single Agent Phase 2 Studies

A Phase 2 study:

1. Determines whether an agent has antitumor activity and
2. Estimates the response rate in a defined patient population.

In addition, well-designed Phase 2 trials do not permit the entry of more patients than necessary to ensure detection of a medically significant level of activity.

Phase 2 studies are disease-oriented. The various tumor types are tested in Phase 2 as distinct clinical entities, as each has differing prognostic factors, eligibility requirements, and patterns of responsiveness to a particular agent. As there may be many unknown or uncontrollable factors contributing to variability in outcome, CTEP attempts to sponsor two Phase 2 trials in each of the tumor types.

The goal of these initial Phase 2 trials is to determine whether the new agent has activity against particular cancers. These trials, therefore, serve as a screen for further study. For this reason, every effort should be made to avoid false results. Although false-positive results are certainly undesirable, false-negative Phase 2 results are especially misleading, as the discovery of a potentially useful antitumor agent may be significantly delayed or overlooked altogether.

CTEP has adopted guidelines concerning eligibility requirements based on patient characteristics that appear to have a particular impact on likelihood of response. Specifically, for initial Phase 2 studies, we currently seek trials that restrict patient eligibility to the minimum extent of prior therapy consistent with ethical medical practice. Protocols for the initial Phase 2 trials of an agent whose MTD has been well characterized should restrict patient entry in the following ways:

- For diseases that currently lack effective systemic therapy (e.g. liver and pancreas), trials should be limited to patients with no prior chemotherapy.
- For diseases in which systemic therapy may cause objective regression of tumors but with little or no impact on survival, entry of patients with no prior therapy will also be sought, whenever possible (e.g. carcinomas of the head and neck, cervix, esophagus, prostate, bladder, large bowel, kidney, stomach, non-small cell lung, and melanoma).
- For diseases that are potentially curable with systemic treatment (e.g. acute leukemias, diffuse non-Hodgkin's lymphomas, Hodgkin's disease, testicular cancer, limited small cell lung cancer, and ovarian cancer), patients having the minimum extent of prior treatment consistent with current ethical standards of care are selected.

This policy will have the following desirable consequences:

- Patients initially entered into Phase 2 trials will have the best chance of benefit from treatment and should be able to tolerate any adverse effects of therapy better than patients with poorer performance status, agent-resistant disease, and possible compromised major organ function from prior chemotherapy.
- Fewer patients are exposed to inactive agents.
- The chance of missing potentially active agents will be minimized.

Clearly, the population of patients defined in this way is highly selected, and the results of these initial trials will not necessarily be representative of the agent's activity in the general population of patients with the disease in question. Once a new agent shows significant activity in this initial, relatively favorable, subset of patients, eligibility criteria in subsequent studies will permit entry of patients with less favorable prognostic characteristics, so that such patients may have an opportunity to benefit from an active agent. In this second stage of the new agent's Phase 2 evaluation, a more accurate assessment of its activity in the general population of patients with cancer may be obtained.

5.1.1.3 Combining Agents

As a general rule, two or more agents should be combined when there is definite evidence of the activity of each alone against a particular cancer. We believe that the most rational approach to the development of a new cancer agent dictates that it should not be combined with another agent(s) until it has shown reproducible evidence of activity in at least two single-agent trials in a disease. Alternatively, or in addition, combinations may be proposed when there is a rationale firmly grounded on laboratory evidence that is relevant to the clinical circumstance.

In the past, much development of agent combinations occurred intuitively; oncologists combined two, three, or more putatively active agents in uncontrolled studies of antitumor effect and adverse effects. To be

sure, some very real therapeutic advances were achieved by this process, but the lack of a systematic and stepwise approach and the frequent absence of proper control groups have often left the oncology community in the uncertain position of not knowing whether results with a particular regimen represented progress or not. More particularly, the overall impact of a new agent on both efficacy and adverse events may remain unclear without a systematic approach. Finally, the process of NDA or BLA approval is impeded when available data do not elucidate the specific contribution of the new agent.

Clearly any intelligently designed and flexible new agent development program must provide room for both approaches. Well-conceived small pilot trials testing new hypotheses will always have an important place in the developmental therapy of cancer. We shall, however, continue to pay close attention to the rationale behind all proposed combinations and shall continue to ask whether certain proposals for therapeutic research might not be better approached by a Phase 3 design rather than Phase 2.

Although the activity of a single agent is the most common basis for its inclusion in a combination, CTEP will certainly consider other rationales. There may be substantial laboratory evidence of synergy between two cancer agents. Such evidence is particularly compelling if it is also based on a knowledge of mechanism of action. Alternatively, an agent inert against cancer might be added because of evidence that it alters the pharmacodynamics or pharmacokinetics of the cancer agent. For example, the modified porphyrins are being tested as both radio- and chemo-sensitizers, even though they themselves have little antitumor activity. In such cases, CTEP will carefully scrutinize the rationale and evidence offered in support of a proposal based on these kinds of considerations.

When combination studies are submitted to CTEP for review, therefore, it is particularly important to make clear the goals, background, and rationale of the proposal. If experimental results in the laboratory are the basis for the study, they should be relevant to the clinical circumstance and cited in adequate detail. If preliminary clinical results are the motivation, they should be similarly cited; unpublished results should be provided as part of the background or in an attachment to the protocol document. If the trial proposes a feasibility pilot, the protocol should state clearly what kinds of results the investigators would regard as medically significant and where they would propose to go next if a significant result is obtained. We are not requesting a detailed plan of a follow-up study or detailed speculations about likely outcomes. Rather, we are seeking an understanding of how the pilot proposal will fit into a strategy of development of the new therapeutic idea.

5.1.2 Individual Protocol Considerations

5.1.2.1 Single Disease Studies

Each tumor should be considered for Phase 2 study separately. With few exceptions, this means that there should be separate protocols for each tumor type. If there is a compelling reason for including several under one protocol, such as uncommon tumors, then there should be separate statements for each tumor type regarding: (a) eligibility requirements, including extent of prior treatment, (b) acceptable sites for measurable disease, (c) response criteria, and (d) accrual objectives.

5.1.2.2 Eligibility Requirements

- Tumor Types: For each proposed tumor type there should be separate statements on eligibility.
- Prior Therapy: Because it is clear that the extent of prior cytotoxic chemotherapy is an important determinant of probability of response, CTEP is seeking initial trials that restrict patient eligibility to the minimum extent of prior therapy consistent with ethical medial practice. (see Section 5.1.1.2)
- Measurability of Disease: To define quantitatively the antitumor activity of an agent, patients in Phase 2 trial must have measurable disease parameters.

In certain diseases, common sites of involvement are either not bidimensionally measurable or the techniques for assessment do not permit quantifiable measurement. Under these circumstances, tumor

response may be evaluated without quantification by an investigator; in such cases, it is particularly desirable that responses be assessed by more than one observer. Examples include bone metastases, lymphangitic pulmonary disease, and many parenchymal brain lesions.

Performance Status:

Under most circumstances, entry to initial Phase 2 studies should be confined to patients who are largely ambulatory (ECOG =<2). Patients should be expected to survive a sufficient period of time that adequate observations can be made.

Organ Function:

Evidence that the function of major organs is normal is required. This includes creatinine level of =< 1.5, cardiac function at least Grade 2, pulmonary function moderately compensated, and no neurologic, gastrointestinal or endocrine impairment that would compromise the safe use of the investigational agent.

Gender:

Where appropriate, both women and men should be studied. NIH policy requires that women and members of minority groups must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Please include a separate section regarding the "Inclusion of Women and Minorities" that describes the inclusion of women and members of minority groups appropriate to the scientific objectives of the study. In the protocol, the investigators must describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection of such subjects.

5.1.2.3 Accrual and Statistical Considerations

The accrual goals of a study should be specified in advance, with a maximum number of patients stated explicitly. Justification for the target sample size, in terms of precision of estimation or levels of type I and type II error, should be provided. Multistage designs for distinguishing an unacceptable level of response from a promising level are recommended {e.g., Fleming, *Biometrics* 38:143 (1982); Simon, *Controlled Clinical Trials* 10:1, (1989)}. The accrual rate of eligible patients that can be *realistically* anticipated should be given. Mechanisms should be in place for early stopping of negative trials.

Statistical considerations for Phase 2 trials of combinations should base unacceptable and promising levels of response on activity levels of the components or other combinations. References to those levels should be cited.

5.2 Who is Eligible to Study Phase 2 Agents

The following categories of physicians are eligible to serve as investigators in Phase 2 trials.

5.2.1 Cooperative Groups

All registered physicians of the Cooperative Group, including those at full member institutions, in Community Clinical Oncology Programs (CCOP), Cooperative Group Outreach Programs (CGOP), at cancer control, or at affiliate institutions may participate as investigators on CTEP's Phase 2 and Phase 3 trials.

Note: A Cooperative Group may have policies that place further restrictions on investigator eligibility.

5.2.2 Cancer Centers

Staff physicians at institutions designated as comprehensive or clinical Cancer Centers by the NCI may participate on CTEP's Phase 2 and Phase 3 trials. Such physicians may be:

- Staff physicians within the Center;
- Physician members of CCOPs for which that center is the research base; and
- Physicians affiliated with Cancer Centers (see Section 13 for further details on the affiliate policies of CTEP).

5.2.3 Affiliates

Physicians affiliated with a research base may participate as investigators on CTEP's Phase 2 and 3 clinical trials provided that:

- The affiliation is formalized and its terms are in writing based on the CTEP policies on affiliates. (see Section 13); and
- Each investigator is registered with CTEP by having submitted a signed FDA Form 1572, Supplemental Form for Investigator Registration, and Financial Disclosure Form (see Section 12 and Appendix V).

5.2.4 New Agent Development Contractors and Cooperative Agreement and Grant Awardees

This category includes those with Phase 1 or Phase 2/3 contracts or cooperative agreements awards and NCI-funded Consortiums including (a) Adult CNS Phase 1/2 Clinical Trials Consortium, (b) AIDS Malignancies Clinical Trials Consortium, (c) Pediatric Phase 1 Clinical Trials Consortiums and (d) Pediatric Brain Tumor Clinical Trials Consortium. This category also includes investigator-initiated grants to study new agents (e.g. R01, R03, R21 and P01).

5.2.5 Multicenter Phase 2 Trials

CTEP expects that Phase 2 trials will be performed only at the proposing research base. If a protocol chair wishes to collaborate with other institutions not formally affiliated with his or her research base, the protocol should include a description of the procedures by which the collaborating institutions will manage the conduct of the protocol and should list on the protocol face sheet each institution and the name of responsible investigator at each. The protocol should specifically address the issues described in Section 7.2.14.

5.3 Who is Eligible to Administer Phase 2 Agents

For a particular clinical protocol, physicians who may administer DCTD investigational agents are:

- Those registered with CTEP (see Section 14.1);
- Members of any research base or formally designated affiliate that is listed on the face sheet of the protocol; and
- any others who are individually named on the face sheet of the protocol.

5.4 Restriction on Participation in Phase 2 Studies

Please note that CTEP may restrict the testing of any investigational agent to a very limited number of locations. Although most new agents proceed to a Phase 2 program open to all eligible investigators, some are restricted to single centers or to specific centers until a safe, reliable Phase 2 dose has been defined and CTEP and the investigator community are confident that the agent is ready for general testing among all investigators. Limitation due to inadequate supply of the agent may also occur.

5.5 How to Obtain Information About Phase 2 Agents
5.5.1 Investigator's Brochure

This document contains all relevant information about the agent, including animal screening, preclinical toxicology, detailed pharmaceutical data, pharmacology and mechanism of action. The brochure also contains information about the clinical adverse events observed in clinical trials. CTEP has an Investigator's Brochure for each investigational agent it sponsors. These are routinely provided to

investigators who are approved to conduct a clinical trial of the agent at the time the LOI is approved and when the Investigator's Brochure is updated. When necessary, investigators with approved LOIs or protocols may obtain the Investigator's Brochure from the address listed in Appendix IV.

5.5.2 IDB Physicians

Each DCTD investigational agent is assigned to an IDB staff physician, who is responsible for coordinating the clinical development of the agent. When an investigator has important concerns about the design of a contemplated trial, he or she should contact that physician.

5.5.3 Clinical Research Pharmacists

The Pharmaceutical Management Branch has a staff of clinical research pharmacists that interact closely with IDB and Clinical Investigations Branch (CIB) staff physicians. Clinical research pharmacists are available to provide pharmaceutical and agent information data on DCTD investigational agents and are responsible for processing and approving all compassionate requests for DCTD agents. (See Appendix IV for addresses and telephone numbers).

5.6 The Letter of Intent

5.6.1 Definition

The Letter of Intent (LOI) is an investigator's declaration of interest in conducting a Phase 1 or 2 trial with a specific investigational agent in a particular disease. Approval of the LOI by CTEP reserves that "slot" for the investigator's protocol if it is submitted within a defined time frame (see Section 5.6.7) and signifies agreement that the investigator shall submit a protocol based on the terms stated in the LOI.

5.6.2 Purpose

CTEP has devised the LOI system to maximize the efficiency and fairness by which experimental agents are allocated to investigators for study. Proper use of the system ensure both CTEP and investigators of a steady flow of new agents into the clinical trials system. It enables CTEP to plan the development of several agents simultaneously. For the investigator, the LOI system also promotes much saving of time and effort, because its use should spare him or her the writing of a protocol that might not be approved. Protocols submitted subsequent to favorable review of an LOI are much more likely to be approved without request for major modification, because many of the crucial features of a Phase 2 proposal must be specified in the LOI itself. The LOI system also is used for the submission of combination pilot studies. In these cases, reviews typically focus on the rationale for combining the agents, the proposed sample size, and the adverse events of each agent when given alone. The system also provides the investigator with an opportunity to explore the proposal with CTEP staff at the concept stage.

5.6.3 Ground Rules for the LOI System

LOIs should be submitted for all Phase 1 or 2 trials that include a DCTD investigational agent. They should be submitted according to the following schedule:

- Agents Beginning Phase 1 - In advance of the IND filing, CTEP will announce the availability of an agent, issue a request for proposals for Phase 1 trials and provide a deadline for the submission of LOIs
- Agents Beginning Phase 2 - In late Phase 1, CTEP will issue a request for proposals for initial Phase 2 trials including a deadline for submission of LOIs.
- All Other Phase 2 Trials - After this deadline has passed, investigators may submit LOIs at any time.

Each Phase 1 or 2 protocol should be preceded by an approved LOI. Our experience demonstrates that protocols submitted without a previously approved LOI are more likely to be rejected as unnecessarily duplicative or needing major modification. If a Phase 1 or 2 protocol is submitted without a prior LOI having been submitted, the protocol will initially receive an "LOI-level" review before being reviewed as a protocol.

5.6.4 Submission of LOIs

In order to review the LOI properly, CTEP must have the following information:

- Principal Investigator;
- Lead Group/Institution;
- Other Participating Groups/Institutions;
- Requested NCI agents;
- Tumor type;
- Patient characteristics, including extent of prior therapy, performance status, and abnormal organ function permitted (if any);
- Phase of study;
- Treatment plan–Agents, doses and schedule of administration;
- Rationale/hypothesis;
- Laboratory correlate;
- Endpoints/statistical considerations;
- Proposed samples size;
- Estimated annual accrual;
- Accrual documented by prior (similar) trials; and
- List of competitive studies.

All of this information should be provided on the LOI Submission Form (Appendix VI) and submitted to the Protocol and Information Office, CTEP (address provided on the form).

Cooperative Group LOIs must be cosigned by the protocol chair and either the Group chair or the Group's executive officer.

Agent development contractor LOIs must be cosigned by the contract principal investigator.

We encourage protocol chairs to submit, where appropriate, a letter accompanying the LOI that explains in greater depth the rationale, where not obvious, or any unique features of the study. Such additional explanation is not usually necessary for single agent Phase 2 trials but may assist in the review of more complex proposals involving experimental agents.

5.6.5 Review of LOIs

On receipt of a LOI, CTEP sends an acknowledgment to the investigator. Letters of Intent are reviewed by the CTEP Protocol Review Committee (PRC). A consensus review will be sent to the Principal Investigator within approximately 30 days of submission.

5.6.6 CTEP LOI Review Criteria

At the time of LOI review, the PRC has available information on other studies in that agent/disease combination by other investigators, and other studies in the proposed disease by the investigator submitting the LOI. The committee considers the following in its deliberations:

- The rationale for the study (especially for combinations of agents);
- Study design, including dose, schedule, and comparison groups, if relevant;
- The characteristics of the patient population to be studied, particularly the extent of prior chemotherapy and performance status;

- The feasibility of the projected accrual, including an assessment of the past performance of the investigator in that tumor type;
- Competing studies of the investigator in that disease;
- All other protocols and LOIs for that agent/disease combination from other sources; and
- Any unique features to the proposal.

A letter of approval or disapproval, together with comments, is sent to the proposer.

5.6.7 After LOI Approval

Following approval of an LOI, the LOI Principal Investigator has 60 days in which to submit a protocol. It is expected that the protocol will conform to the plan agreed to at the LOI stage of development. At 45 days, a reminder letter is sent notifying him or her that the LOI will shortly expire. After the 60-day period has expired, CTEP will not be bound by previous approval of a LOI.

5.6.8 Information About the Status of an LOI

Further information about the status of a particular LOI may be obtained by calling the CTEP LOI Coordinator (see Appendix IV).

6. Phase 3 Trials
6.1 Scientific Policies of CTEP

If significant activity is observed in any disease during Phase 2, further clinical trials usually compare the efficacy of the experimental therapy with that of a standard or control therapy. If reasonable standard treatment can be defined for the disease in question, we generally wish to know whether the new agent or therapy constitutes a significant contribution in terms of patient benefit. A variety of trial designs may be suitable, according to the state of the art treatment in the particular disease. The most satisfactory ones are the controlled trial that compares the new agent to a standard single agent or a standard regimen plus the experimental agent to the standard regimen alone. Whatever design is selected, however, an appropriate control group must exist and relevant endpoints must be used to measure relative effects. Of greatest medical importance, of course, are relative survival and quality of life. Other measures, such as complete remission rate or disease-free survival, may also be of interest.

These studies, which attempt to isolate the role of a new agent in the treatment of a specific cancer, are of obvious importance to industrial sponsors, because the results are pivotal in applications to register the agent for commercial distribution. They are of no less importance to the oncology community, because such approval makes the agent generally available for patient care. The results of such trials may be of great medical importance as well. If the control group is properly selected and the experimental treatment is constructed as imaginatively as possible, such trials may yield valuable information for the care of cancer patients.

Every protocol must contain a section that discusses the study design and the plan for evaluation of the data. The major objectives of the study should be stated as hypotheses to be tested, and a target sample size should be clearly specified. Justification for the sample size goal, in terms of precision of estimation or of levels of type I and type II error, should be provided. In a Phase 3 study, it is insufficient simply to give the number of patients to be accrued on each arm. The protocol should specify the test to be used to compare the treatment groups, and the probabilities of drawing incorrect conclusions when performing this test with the proposed sample size should be given. The magnitude of improvement in outcome that can be reliably detected using the planned sample size should also be specified. The accrual rate of eligible patients per year that can be realistically anticipated should be stated and documented. The protocol should describe specific statistical plans for interim analysis of accumulating data.

The committee for monitoring interim results should also be indicated.

If evaluation of treatment effect will require use of nonrandomized controls, a thorough description of the control group to be employed should be part of the protocol. This description should include a detailed discussion of comparability issues and analytic techniques.

6.2 Who Is Eligible to Conduct Phase 3 Trials

Phase 3 trials may be submitted from any source eligible to submit a Phase 2 trial (see Section 5.2) Because the sample sizes required for such studies are usually quite large, however, a multicenter approach is frequently the only feasible one. It is expected, therefore, that the clinical Cooperative Groups will be the major research bases for such trials. Proposals for Phase 3 studies from single institutions should be very specific in documenting adequate accrual potential.
Furthermore, if the proposal includes collaboration with institutions not formally affiliated with the research base, the protocol should include a description of the procedures by which the collaborating institutions will manage the conduct of the protocol (see Section 7.2.14).

6.3 Eligibility Requirements

Phase 3 clinical trials must include a review of the available evidence to show whether or not clinically important gender or race/ethnicity differences in the response to the intervention are to be expected. The design of such trials must reflect the current state of knowledge about any such expected differences. Phase 3 clinical trials are, in addition, required to provide valid analysis to measure differences of clinical or public health importance in intervention effects based on gender or racial/ethnic subgroups where there is evidence supporting differences.

Investigators should consider the following circumstance when planning a Phase 3 clinical trial:

- Prior data strongly indicate that the intervention will show significant clinical or public health differences among gender, racial, and/or ethnic subgroups. In this case, the primary question(s) to be addressed and the design of that proposed Phase 3 trial must specifically accommodate these differences. For example, if men and women are thought to respond differently to an intervention, the Phase 3 trials must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for both.
- Prior data strongly support no significant clinical or public health differences among subgroups from the intervention. In this case, gender, race, and/or ethnicity will not be required as subject selection criteria. However, the inclusion of gender, racial, and/or ethnic subgroups is still strongly encouraged.
- Prior data neither strongly support nor negate the existence of significant clinical or public health differences among groups. In such cases, the Phase 3 trial must include sufficient and appropriate gender, racial, and/or ethnic subgroups, so that valid analysis of the intervention effects on subgroups can be performed. However, the trial will not be required to provide high statistical power for each subgroup.

<u>Cooperative Group Phase 3 studies:</u>

Effective October 1, 1995, all Phase 3 protocols must include accrual targets for males, females, and minorities (protocol specific accrual targets for Phase 1 and 2 studies are NOT required). The accrual targets should reflect the expected accrual over the life of the study. The NCI suggests the accrual targets be based on data from similar trials completed by the Cooperative Group during the previous 5 years. It is hoped that the accrual targets will resemble the gender, racial, and ethnic composition of the U.S. population as closely as possible. A worksheet, including a description of the currently recognized HHS racial and ethnic categories, is attached for your reference.

Protocols that do not address the above gender and minority issues will be returned without Protocol Reviewed Committee (PRC) review.

Planned Gender and Minority Inclusion:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female							
Male							
Unknown							
Total							

HHS Racial and Ethnic Categories

I. American Indian or Alaskan Native: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.
II. Asian or Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes China, India, Japan, Korea, the Philippine Islands, and Samoa.
III. Black, not of Hispanic Origin: A person having origins in any of the black racial groups of Africa.
IV. Hispanic: A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race.
V. White, not of Hispanic Origin: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

Special Populations:
Individuals from special populations (minorities, cancer survivors, HIV+ individuals, pregnant and breast-feeding women) can NOT be arbitrarily excluded from participation on a study. All exclusions must be justified based on establishment that inclusion is inappropriate with respect to the health of the research subjects or the purpose of the research.

6.4 Coordination of Planning With CTEP Staff

Large clinical trials involve years of effort and a substantial expenditure of resources. Accordingly, a certain amount of coordination is necessary for the optimal planning of specific studies of this type. Staff members of CTEP are in an excellent position to advise investigators on the existence of other proposed or ongoing studies that are closely related or even identical to ones being planned. In addition, CTEP staff can advise investigators contemplating large-scale trials concerning the concordance of the proposed trial with CTEP program goals.

We have therefore adopted procedures by which ideas for clinical trials can be evaluated by CTEP staff before the investment of time and energy in development of a complete protocol. For Phase 1 and Phase 2 studies using CTEP resources, investigators are required to submit a Letter of Intent (LOI); for Phase 3 studies, investigators are required to submit a written concept for the proposed trial.

In general, these provide a sketch of the proposed study, including the hypothesis to be investigated, its rationale, and relevant design considerations. CTEP can then formally review and provide a written Program Concept Review commenting on study originality and programmatic interest.

The Planning and Execution of a Clinical Trial

The following five sections provide a detailed description of the responsibilities of the investigator for the implementation of a clinical trial, from the drafting of the protocol to completion of the study. They are

intended to guide both the protocol chair and the participating investigator and outline NCI policies on the responsibilities of each in the execution of a clinical trial.

7. The Drafting of a Protocol

A protocol is the detailed written plan of a clinical experiment. This section details the essential features of a protocol. Careful attention to the following material will expedite the review of your protocol by CTEP.

7.1 Title Page

The face sheet of the protocol is the primary source of identifying information for the Protocol and Information Office (PIO) of CTEP, for the agent distribution system, for the IND file at the FDA, and for the listing of the protocol in the Physician Data Query (PDQ) system. Each protocol submitted to CTEP, therefore, must have a title page or face sheet that contains the following items:

- Date of document
- Local protocol number (i.e., institution or group number)
- Title of study
- A single protocol chair who will be responsible for the study, including his or her name, institution/Cooperative Group, address, phone and fax numbers, and e-mail address (*A trainee may not be protocol chair-see Section 12.2.2*)
- Full name of institution/Group submitting the study
- List of each participating institution/Group, and
- For DCTD-supplied IND agents, a listing of each agent by name and NSC number.
- Cooperative Groups may summarize by specifying "all Group members" or "restricted to…" and list institutions.
- Protocols from sources other than the Cooperative Groups should specify each institution or site participating in the study, together with a responsible physician, telephone and fax numbers, and e-mail address at each site.

7.2.1 Schema

All treatment studies should include a brief schema depicting the treatment regimen(s).

7.2.2 Objective(s)

The objectives should be stated clearly. They generally should be stated as hypotheses to be tested. The study design should be capable of answering the questions posed by the objectives. The statistical section should clearly state how the data will be analyzed in relation to each of the objectives. The hypotheses to be tested in ancillary studies also must be clearly stated, and the statistical section should address analyses of the data in relation to these hypotheses.

7.2.3 Background and Rationale

Sufficient background information should be included so that the rationale for the study is clear. Any unpublished data relevant to the rationale should be included in either this section, or, if extensive, as an appendix to the protocol submission. In addition to the background and rationale included for therapeutic aspects of a study, information should be provided to support ancillary studies to be performed. The rationale should be clearly stated for studying particular correlations between tumor characteristics and outcome measurements (response to therapy, disease-free survival, overall survival, etc.). The choice of the particular techniques to be used should also be justified.

7.2.4 Patient Eligibility Criteria

The issues here have been discussed previously (Sections 4.1.3 and 5.1.2.2). Studies with objective response as an endpoint should include clear statements specifying whether tumor sites to be followed for response must be measurable, what criteria must be fulfilled to consider disease measurable, whether evaluable disease is permitted, and if so, at what sites. For ancillary studies, this section should include information regarding the choice of tumor sampling technique. For example, will aspiration biopsies be sufficient, or will surgical samples be required? How much tissue will be needed? What measures will be imposed to assure that the histopathologic diagnosis is not compromised? How will issues of tumor heterogeneity be addressed? What biases may be introduced by the sampling techniques and the amount of tissue required for the studies proposed?

7.2.5 Pharmaceutical Information

A separate pharmaceutical section is required for each agent. The content of the pharmaceutical section is dependent on whether the agent is investigational or commercial.

7.2.5.1 Investigational Agent Pharmaceutical Section

This section should include the following:

- Product Description-Include the available dosage forms, ingredients, and packaging as appropriate. Also state the agent's supplier. For investigational agents sponsored by the Division of Cancer Treatment and Diagnosis, NCI, the supplier will be NCI.
- Solution Preparation (how the dose is to be prepared)-Include reconstitution directions and directions for further dilution if appropriate.
- Storage Requirements-Include the requirements for the original dosage form, reconstituted solution and final diluted product, as applicable.
- Stability-Include the stability of the original dosage form, reconstituted solution and final diluted product, as applicable.
- Route of Administration-Include a description of the method to be used and the rate of administration if applicable. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30 to 60 minutes, intravenous bolus, etc. Describe any precautions required for safe administration.
- Adverse Events - Include a description of the Reported Adverse Events and Potential Risks. For investigational agents the investigator should refer to the pharmaceutical data sheet for the agent or the appropriate Investigator's Brochure.

7.2.5.2 Commercial Agent Pharmaceutical Section

This section should include the following:

- **Product description:** State the agent's supplier, i.e., commercially available.
- **Preparation (how the dose is to be prepared):** Investigators may refer the reader to the package insert for 'standard' preparation instructions. If the agent is to be prepared by 'non-standard' or protocol-specific fashion, the reconstitution directions and instructions for further dilution must be included. Appropriate storage and stability information should be included to support the method of preparation.
- **Route of administration:** Briefly describe how the agent will be administered. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30 to 60 minutes, intravenous bolus, etc.
- **Adverse Events:** The investigator may refer the reader to the agent's package insert. Note: The Informed Consent document should contain a list of all expected adverse events that the patient is likely to experience. All adverse events should be written in laymen's terms.

7.2.6 Treatment Plan

Describe the protocol treatment clearly so it can be followed by all staff involved in the treatment of patients and in the conduct of the study. See Appendix XVI, Guidelines for Treatment Regimens: Expression and Nomenclature.

7.2.7 Procedures for Patient Entry on Study

Procedures for patient entry, whether randomized or nonrandomized, should be specified. Required information includes a description of the randomization process and the patient characteristics and stratification factors (if any) to be provided at the time of entry. Patients should be registered on study prior to beginning treatment.

7.2.8 Dose Modification for Adverse Events

The plan of dose change for adverse events should be stated for *each* study agent. Dose modification criteria should be described in terms of NCI Common Toxicity Criteria.

Protocol Authors should carefully review the Investigator's Brochure for all investigational agents to be sure that they have included all reasonable measures to monitor expected adverse events.

Instructions for reporting adverse events should be included in the protocol text.

7.2.9 Criteria for Response Assessment

The criteria for scoring responses should be included. These should be specific for both measurable and evaluable disease. Disease-specific criteria are often required and should clearly indicate acceptable means of measurement, i.e., CAT scans, radio-nuclide scans, ultrasound, etc.

7.2.10 Monitoring of Patients

Specify how patients will be followed for assessment of treatment adverse events and therapeutic effect. A table of follow-up parameters that incorporates the schedule is particularly useful. The DCTD Common Toxicity Criteria should be used for all DCTD-sponsored trials.

7.2.11 "Off-Study" Criteria

Criteria for terminating protocol treatment and/or removing a patient from treatment or from study should be specified.

7.2.12 Statistical Considerations

An adequate statistical section discusses the study design in relation to the objectives of the study and the plan for the evaluation of the data, specifically:

- Method of randomization and stratification
- Total sample size justified for adequate testing of primary and secondary hypotheses
- Error levels (alpha and beta) in Phase 3 studies
- Differences to be detected for comparative studies
- Size of the confidence interval to be constructed around the estimated outcome
- Estimated accrual rate and/or study duration, with supporting documentation
- Stopping guidelines, including statistical and administrative procedures for monitoring the progress of the trial to implement early termination for very positive results, or for results sufficiently negative to preclude the eventual achievement of statistically significant positive results

- Expected outcome parameters as appropriate (response rate, time to progression, survival times, etc.)
- Primary endpoint for interim and final analysis
- Clear specification of primary and secondary (e.g. subset) hypotheses
- Maximum number of patients, and
- Plan for analysis.

7.2.13 Records to be Kept

Specify the document on which each of the following is to be recorded, where it is to be sent, and on what schedule.

- On-study information, including patient eligibility data and patient history
- Flow sheets, or other forms for interim monitoring
- Specialty forms for pathology, radiation, or surgery when required, and
- Off-study summary sheet, including a final assessment by the treating physician.

7.2.14 Participation

All protocol treatments and observations will be made by investigator-physicians affiliated with a research base (refer to Section 3), and registered with CTEP. Under certain defined circumstances, it may be appropriate for interim treatments to be administered by certain physicians not registered with CTEP (other than trainees, who are assumed to be under the supervision of a registered investigator). In such cases, the protocol should state:

- Precisely what responsibilities those physicians will assume, including response assessment, and adverse event reporting
- How dose modifications will be decided and reported, and the mechanism by which data needed for evaluating adverse events and response will be transmitted to the registered investigator responsible for the patient, and
- The intervals at which a patient should be evaluated by a physician-investigator at the research base.

See Section 14 for further details concerning which physicians may actively participate in a clinical trial involving DCTD investigational agents.

7.2.15 Multicenter Trials

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the following guidelines must be followed:

Responsibility of the Protocol Chair:

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of adverse events to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office of Human Research Protections (OHRP), DHHS. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals for each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of adverse event reports. There are two options for adverse event reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center; or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit adverse event reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit; or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Agent Accountability Record forms, patient registration lists, responsible assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol
The protocol must include the following minimum information:
- The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
- The Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
- Describe how adverse events will be reported from the participating institutions, either directly or indirectly to CTEP or through the Coordinating Center.

Agent Ordering

Except in very unusual circumstances, each participating institution will order DCTD-sponsored investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

7.2.16 Laboratory Approaches to be Used for Ancillary Studies

This section should include a description of the technical approaches to be used for ancillary studies. The description does not need to be extremely detailed, but it should provide sufficient information for the reviewers to determine whether the approach is appropriate and the proper controls are included. For example, if flow cytometry is to be used for analysis of ploidy or S-phase fraction, the methods section should indicate whether frozen tissue or paraffin-embedded tissue will be used, the number of cells to be counted per sample, the control cells to be used, etc. Details are not required regarding reagents to be used for standard techniques; reference can be made to the technique. Some evidence should be presented regarding the investigator's experience with the techniques to be used.

7.3 Informed Consent

Each informed consent document must be protocol-specific and contain the elements required by Federal regulation. These regulations do not specify the language of the document but provide a list of elements that must be addressed in the text of the consent form. A checklist of these elements can be found in Appendix VII. CTEP will not approve a protocol if its informed consent form fails to address each of these elements adequately.

The use of a model informed consent by a research base can assure inclusion of the essential elements and permits tailoring of the protocol-specific elements to the needs of individual studies. Minor changes to the model informed consent form may be made by the individual institutions. However, any changes in risks or alternative procedures should be approved by the originator of the informed consent document. CTEP will not approve a protocol if its consent form fails to address each of these elements adequately.

Protocol authors should be certain that the description of expected adverse events is complete and balanced and reflective of the treatment plan to be used. Consult the Investigator's Brochure for information about expected adverse events for investigational agents and the package insert for commercially available agents. Adverse events of other modalities used in the study (e.g., radiotherapy, surgery) must also be described.

In response to concerns that many informed consent documents for cancer clinical trials have become complex, lengthy, and difficult to understand, NCI convened a working group of medical, ethical, communication, and consumer experts along with officials from OHRP and FDA. The result of this initiative is the development of guidelines for writing consent documents that are more understandable to prospective research participants. They are called the *Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials*, which include a fill-in-the-blank consent form template and four sample consent forms. The Recommendations have the potential to improve the quality of informed consent in cancer clinical trials. We strongly urge you to use them as you write informed consent documents for cooperative group protocols. Also, you are encouraged to share the Recommendations with your IRBs. The templates are available as a working document on the CTEP website.

7.4 Protocol Templates

NCI staff have developed several model protocol templates. To facilitate rapid review, you are encouraged to utilize the NCI protocol templates.

Many clinical trials organizations have also devised model protocols and consents because the essential elements of a protocol are standard for a given class of studies, the elements of which can be altered to suit the needs of a particular study. The use of model documents is an effective way of ensuring a complete protocol. Those who use such models, however, should make certain that inappropriate "boilerplate" text does not get carried over to protocols where it makes little or no sense. Our experience is that disease-oriented background information and statistical sections (sample size estimates and stopping rules) are at greatest risk for the "word processor syndrome."

7.5 Protocol Checklist

A protocol checklist is available (Appendix VII, also consult NCI web site, http://www.cancer.gov/, under Conducting Clinical Trials, Guide to Understanding Informed Consent, Safeguards-Simplification of Informed Consent Documents: Templates) to assess if your protocol document is complete. The protocol checklist also includes NCI-approved boiler plate language for administrative and agent-specific issues.

8. Protocol Review and Approval at CTEP

8.1 The Protocol and Information Office (PIO)

Within CTEP, the PIO manages the review process and maintains the official record of all CTEP-sponsored protocols, amendments, results, publications, and protocol-related communications as well as all protocol

submissions for PDQ, http://www.cancer.gov/search/clinical_trials/, and FDA. More than 10,000 protocols are maintained in the PIO.

All protocols and related correspondence should be addressed directly to the Head, PIO, Executive Plaza North, Room 7000, 6130 Executive Boulevard, Bethesda, Maryland, 20892. *The PIO will distribute all mail to the appropriate CTEP physician staff.* Please do not direct protocol-related materials to any other CTEP staff member. Doing otherwise will lengthen the time required for resolution or review. The fax number for the PIO is 301-496-9384.

In the submission of each new protocol, please also include a Protocol Submission Worksheet, http://ctep.cancer.gov/forms/index.html. All telephone calls regarding status of protocol and amendment reviews should be directed to the PIO at 301-496-1367.

8.2 How to Submit a Protocol

Each new protocol should be sent directly to the PIO. You must include in the submission:

- The Protocol Submission Worksheet, http://ctep.cancer.gov/forms/index.html.
- Two copies of a paginated, legible protocol, including a local protocol number. Please be certain the protocol document contains information about *each* of the topics listed in Section 7.1 and Section 7.2.
- An informed consent document which addresses the elements required by FDA regulation (Appendix VII).

If these items are missing or incomplete, the submission will be returned to the protocol source without review.

Upon receipt by the PIO, each protocol is assigned an NCI protocol number. You will receive an acknowledgment of your protocol submission with the NCI-assigned protocol number. *This NCI protocol number must be referenced in all subsequent communications with CTEP regarding this study.* The assignment of this number does not imply approval; only the final approval letter signifies approval and the authorization to order investigational agents.

8.3 IRB Approval

Each investigator must meet the requirements of the Federal regulations for human subjects assurances and informed consent and for IRB review and approval (45 CFR 46: http://www.access.gpo.gov/nara/cfr/waisidx_01/45cfr46_01.html and 21 CFR 50 and 56: http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html. Also see Section 12.1.1 and Section 12.1.2).

Except for Cooperative Group protocols, each protocol must have documentation of IRB approval prior to CTEP approval. Evidence of IRB approval may be submitted to CTEP at any time in the review process. If multiple institutional IRBs are involved, only the approval from the coordinating research base need be submitted for CTEP records; of course, each investigator must meet Federal regulations for informed consent and IRB review (45 CFR 46 and 21 CFR 50 and 56).

Failure of investigators to submit evidence of IRB approval is a major cause of delay in protocol approval. The documentation requirements are satisfied by completion of Form 310, or by a letter specifying:

- The study title
- The protocol chair and the institution's assurance number; i.e., the assurance number issued by the OHRP, DHHS
- Date of IRB review
- The dated signature of an institutional official, usually the IRB chair.

8.4 Protocol Review

CTEP must review and approve every protocol involving DCTD investigational agents or studies that have any NCI support (funding). Each protocol is reviewed for completeness, scientific merit, duplication of existing studies, patient safety, and adequacy of regulatory and human subjects protective aspects.

Protocol Submission Requirements and Review Type

Group Trials

Protocol Description

Study Type	Treatment	DCTD agent	# of pts. accrued	Submission Required?	Review
Phase 1, 2, or 3	Yes	Yes	>1	Yes	Full
Phase 1, 2, or 3	Yes	No	>100	Yes	Full
Phase 2, 3	Yes	No	<100	Yes	Developmental Strategy
Phase 1	Yes	No	<100	Yes	Developmental Strategy
Correlative study	No	No	>100	Yes	Developmental Strategy
Correlative study	No	No	<100	No (Describe in Type 5 report)	N/A
*CTEP Lead Reviewer Discretion					

Non-Group Trials					
Protocol Description					
Study Type	**Treatment**	**DCTD agent**	**# of pts. accrued**	**Submission Required?**	**Review**
Phase 1, 2, or 3	Yes	Yes	>1	Yes	Full
Phase 1, 2, or 3	Yes	No	>100	No	N/A
Phase 2, 3	Yes	No	<100	No	N/A
Phase 1	Yes	No	<100	No	N/A
Correlative study	No	No	>100	No	N/A
Correlative study	No	No	<100	No	N/A

Full Review

- Types of studies
- Phase 1 to 3 treatment studies that utilize a DCTD-supplied agent
  or
- Phase 1 to 3 treatment studies with accrual >100 patients
- Full CTEP review for scientific, safety, regulatory, and administrative issues
- Consensus review may include comments that require a response or recommendations
- CDUS reporting
- Complete – Phase 1 and 2 studies that utilize a DCTD-supplied agent
- Abbreviated – all other studies
- CTC version 2.0
- Must comply with DHHS guidelines regarding special population accrual
- Amendments are processed in standard fashion

Developmental Strategy

- Types of studies
- Phase 2 to 3 treatment studies that do NOT utilize a DCTD-supplied agent and that have expected accrual <100 patients
- *CTEP lead reviewer option* – Phase 1 treatment studies that do NOT utilize a DCTD-supplied agent and that have expected accrual <100 patients
- Phase 1 to 3 non-treatment studies with expected accrual >100 patients
- CTEP review for safety and administrative issues
- Consensus review typically limited to recommendations
- CDUS reporting – abbreviated
- CTC version 2.0
- Must comply with DHHS guidelines regarding special population accrual
- Amendments are processed in standard fashion

8.4.1 Receipt of the Protocol by CTEP

Upon receipt, the protocol is checked for completeness (including legibility, complete pages, presence of required sections, and the informed consent). All protocols submitted to the NCI must also include the Protocol Submission Worksheet (Section 8.2). Each protocol is also examined to verify that the investigator/institution is eligible to conduct a DCTD-sponsored study; i.e., has an approved mechanism of sponsorship by NCI (Cooperative Group, Cancer Center, contract, R01/P01, etc.). Investigator eligibility is

explained more fully in Sections 4.2, 4.3, 4.4, 5.2, 5.3, and 6.2. If the protocol is incomplete, or the investigator/institution is not eligible under the proposed category of sponsorship, then the protocol source is so informed and the study is not reviewed for scientific content. CTEP sends the protocol source an acknowledgment of studies that are complete and eligible at submission.

8.4.2 Scheduling the Protocol for Review

The PIO schedules the protocol for review by the Protocol Review Committee (PRC) within approximately 2 weeks of receipt. The cutoff date for protocol receipt is Thursday at noon. Protocols that are complete and eligible are registered and scheduled for review the second Thursday after receipt.

Therefore, a protocol arriving Thursday morning will be scheduled for review in 14 days; if that same protocol arrives Friday, it will wait another week for registration and distribution, and require 20 days to reach the review committee.

8.4.3 Review by the CTEP Protocol Review Committee

All protocols are reviewed by the CTEP PRC. This committee, composed of the professional staff of CTEP, additional consultants from other NCI divisions, and chaired by the Associate Director, CTEP, meets weekly and usually reviews 10 to 20 protocols, LOIs and concepts at each session.

Each protocol is assigned a minimum of five reviewers; as many as six to seven may be required for complex multimodality protocols. The protocol and informed consent form are reviewed by an oncologist(s), biostatistician, pharmacist and regulatory affairs professional(s) with expertise in informed consent issues.

8.4.3.1 The Review of the Protocol

The PRC discusses the protocol after hearing the reviews of each assigned reviewer and makes a decision that the science and safety of the study are:

- *Accepted as written;*
- *Accepted with recommendations* - The investigator is requested to consider the points raised in the consensus review but is not obligated to amend the study. If changes are made prior to activation of the study, the investigator must send CTEP an activation amendment that details any changes in the CTEP-approved document;
- *Acceptance deferred pending revisions* - The PRC has significant questions about the proposed study. It cannot be accepted unless the investigators satisfactorily address the concerns of the written consensus review. The investigator should submit a revised protocol within 30 days of receipt of the consensus review (Section 8.4.3.5); or
- *Disapproved* - In the judgment of the PRC, the protocol cannot be approved even with major revisions.

The PRC disapproves relatively few submitted studies and only does so when it feels that a proposal is unnecessarily duplicative or irretrievably flawed in concept, design, safety, or feasibility.

8.4.3.2 The Review of the Informed Consent

The PRC also reviews the informed consent document to be certain that:

- The document includes all required elements of informed consent as mandated by Federal regulation (see Appendix VII); and
- The description of potential benefits and adverse events is complete and accurate.

Any changes made to the consent document resulting from a CTEP review should be made known to the IRB.

It is not the intent of the CTEP informed consent review to supplant the review of the IRB. Provided the consent document meets the requirements of regulation and law and contains sufficient information to enable an individual to make an informed choice, the local IRB approval of the contents of an informed consent document is generally to be regarded as definitive.

Minor changes to the CTEP-reviewed informed consent form may be made by the individual institutions. However, any changes in risks or alternative procedures should be approved by the originator of the informed consent document.

8.4.3.3 The Review of Regulatory and Administrative Concerns

The PRC also reviews each protocol to assure proper instructions for reporting adverse events are included, an accurate and up-to-date pharmaceutical section is provided, and necessary instructions for multicenter trials are given, if appropriate. Please refer to the protocol checklist for a complete list of all regulatory and administrative issues (Section 7.5).

8.4.3.4 The Consensus Review

After the PRC meeting, the primary reviewer generates a consensus review, which states the collective concerns of the PRC. This consensus review, together with a cover letter stating the summary PRC decision, is sent to the protocol source within approximately 30 days of receipt of a complete protocol.

8.4.3.5 Responding to CTEP Consensus Review

If revisions are required in the protocol or the informed consent, the investigator should send a revised protocol and/or informed consent document to the PIO. The revised documents should be accompanied by a cover letter that details the responses to the points raised in the consensus review. If the reviewers find the response satisfactory, then the protocol goes forward for final approval.

The consensus reviewer may choose to send the revised protocol back to the full PRC for further consideration. In any case, if the protocol is still not accepted, then a letter is sent to the investigator detailing any remaining CTEP concerns. The investigator should respond to this re-review in the same way as described for the initial consensus review. This process continues until the science, regulatory, and administrative aspects, and informed consent are each accepted or the study is withdrawn or disapproved. Each evaluation of a revised study requires 10 - 30 days on average.

8.5 Protocol Approval

Upon final acceptance of the protocol and the informed consent, as indicated by the concurrence of the consensus reviewer and appropriate CTEP staff, a letter of protocol approval is sent to the protocol source.

Please note that protocol approval will not be given by telephone. Although CTEP staff may discuss the study with the protocol chair, he or she should consider nothing official until written notice is received. Approval letters are sent via fax if the protocol source has provided a fax number. After written approval is sent, orders for investigational agents will be honored. All approved protocols using DCTD-sponsored agents are submitted to the FDA as part of the IND file.

8.6 Amendments

Any change to the approved protocol document must be documented point by point in a cover letter, and a replacement page(s) or a revised protocol document submitted to the PIO (See Protocol Submission Worksheet, http://ctep.cancer.gov/forms/index.html, Appendix VIII). Please reference the NCI protocol number, date each amendment, and number sequentially for each study. Upon receipt, each amendment is reviewed by CTEP staff.

8.6.1 Editorial Amendments

To reduce unnecessary workload for all parties involved, amendments that only include editorial and administrative (except as outlined below) changes do NOT require prior CTEP approval. CTEP will send the Principal Investigator an approval letter for their records.

CTEP would recommend that all editorial and administrative amendments for a given protocol be batched and submitted at one time. CTEP would recommend that the editorial comments be submitted on an annual basis or incorporated into an amendment that relates to scientific, safety, or other issues.

What qualifies as an editorial or administrative change?

Examples of editorial changes would include:

- Typographical correction (except if patient safety is involved, e.g., dose regimen).
- Rephrasing a section to add clarity
- Reformatting

Administrative changes that do NOT require CTEP approval would include:

- Address, telephone, E-mail changes
- Addition/deletion of physician co-investigators to studies that do NOT utilize a DCTD-supplied investigational agent
- Addition/deletion of non-physician co-investigators to any trial
- Addition/deletion of an institution to a 'Group-wide' study

Examples of administrative changes that either require approval and/or require prompt CTEP notification include:

- Addition/deletion of an institution to a 'limited-institution' study
- Addition/deletion of physician co-investigators to studies that utilize a DCTD-supplied investigational agent
- Change of Protocol Chair or Principal Investigator
- Change in protocol status
- Addition/deletion of a Group to an InterGroup study

8.6.2 Activation Amendment

Any change in the protocol that occurs between CTEP approval and activation by the research base should be submitted to CTEP as an "Activation Amendment." Such amendments are often used when the CTEP approval letter conveys recommendations that the investigator wishes to implement.

8.6.3 Scientific and Participant Amendments

- Each amendment that modifies the protocol document, the informed consent or the participants in the approved protocol must be submitted to CTEP for approval prior to implementation.
- For those rare studies where an immediate change is imperative for patient safety, the IDB staff physician for that agent may be contacted by telephone, and the written amendment must be sent to the PIO within 3 working days.

Each amendment is recorded in the official PIO protocol file, the agent distribution file, the IND file, PDQ, and by the CTEP Clinical Trials Monitoring Service (CTMS), where applicable.

8.7 Study Status

Changes in study status should be communicated immediately to the CTEP PIO. Changes can be easily reported via amendment (See Appendix VIII). The following list shows the categories of study status recognized by CTEP and PDQ (also see Appendix IX):

- AP (Approved) – Trial is active but no patients have been accrued.
- AC (Active) – Trial is open and accruing.
- TC (Temporarily Closed to Accrual) – Trial is temporarily not accruing.
- TB (Temporarily Closed to Accrual and Treatment) – Trial is temporarily not accruing and patients are not receiving therapy.
- CA (Closed to Accrual, Patients still on Treatment) – The protocol has been closed to patient accrual. Patients are still receiving therapy.
- CB (Closed to Accrual, All Patients have Completed Treatment) – The protocol has been closed to patient accrual. All patients have completed therapy, but patients are still being followed according to the primary objectives of the study. No additional investigational agents are needed for this study.
- CP (Completed) – The protocol has been closed to accrual, all patients have completed therapy, and the study has met its primary objectives. A final study report/publication is attached or has been submitted to CTEP.
- AD (Administratively Completed) – The protocol has been completed prematurely (e.g., due to poor accrual, insufficient agent supply, IND closure). The trial is closed to further accrual, and all patients have completed protocol treatment. A final study report (see below) is not anticipated.

8.8 Reactivation of Studies

Protocols that are temporarily closed require written CTEP approval prior to reactivating if they are:

- Temporarily closed for reasons of patient safety or regulatory issues; or
- Closed for reasons of peer review, site visit, or other NCI-initiated reasons.

Protocols that are temporarily closed to accrual by the research base based on early stopping rules do not require CTEP approval to be reactivated.

9. Ordering Investigational Agents from NCI

The DCTD will provide investigational agents for use in CTEP-approved protocols as well as for Special Exception and Group C guideline requests (see Section 17 and Section 18) to registered investigators with a current FDA Form 1572, Supplemental Investigator Data Form, Financial Disclosure Form, http://ctep.cancer.gov/forms/index.html, and CV on file with PMB (see Section 12.1). Except for NCI Cooperative Groups, agents will not be sent to assistant investigators who are not named on the protocol or who have not filed a FDA Form 1572.

Investigational agents supplied by DCTD will be used only for treatment of patients entered onto CTEP - approved protocols.

9.1 How to Place Agent Orders

Complete the Clinical Agent Request Form NIH-986, http://ctep.cancer.gov/forms/index.html, which provides the following information:

- Investigator name and NCI-assigned investigator number
- Telephone and fax numbers of investigator and/or individual preparing form
- NCI-assigned protocol number
- NSC number, current inventory as indicated on Agent Accountability Record, agent name, strength and dose form, and quantity

- The investigator or designee must date and sign the agent request form. *No matter who may be delegated to sign this form (e.g. the pharmacist), the investigator is responsible for the disposition of all investigational agent shipped under his or her name*
- Only one agent may be entered on each line on the form
- If there is more than one protocol per agent, use a separate line for each protocol
- Indicate the one official shipping address to which the agent is to be sent
- Orders should be submitted to the Pharmaceutical Management Branch (PMB) by fax at 301-480-4612 or mailed. The mailing address is listed in Appendix IV (see section 9.4).

9.2 Particular Points to Note

- The clinical agent request form should be completed in full and typed. If it is not complete, the form will be returned.
- All clinical agent requests should use this form, including those for Special Exception and Group C use.
- Normal PMB processing time is two (2) working days. Orders will be shipped within two working days, based on the agent's availability and provided there are no shipping restrictions (e.g. holidays or in the case of thermolabile agents which are generally shipped Monday through Thursday, unless special arrangements are made for weekend delivery (must fax the order and call PMB to confirm receipt of the order).
- Generally allow one week for delivery of faxed orders.
- Do not order more than a 2-month supply at a time.
- Avoid ordering excessive quantities. CTEP will reduce the quantity shipped if the order is excessive in relation to protocol requirements, or if the inventory at CTEP is insufficient at that time.
- Requests for next day delivery must be received by PMB by 2:00 PM Eastern Time. Next day delivery must be stated on the order and an express courier account number must be provided. Please telephone PMB (301-496-5725) to confirm receipt of orders requesting next day delivery.

9.3 Routing of Agent Requests

Investigators should submit agent requests directly to the Pharmaceutical Management Branch (See Appendix IV).

Cooperative Groups: Some Cooperative Groups require that agent requests be routed through the operations office. Check with your Cooperative Group operations office to determine its policies.

9.4 Affiliates and Agent Orders

Investigators at affiliated institutions or clinics of a research base should order CTEP-supplied investigational agents directly from PMB. The PMB policy of shipping investigational agents to the investigator's institution or practice site assures that all investigators receiving investigational agents are registered with PMB, simplifies agent tracking and accountability, minimizes delays in correspondence in emergencies, assures agent integrity, reduces administrative workload and eliminates secondary shipping expenses.

PMB policy does allow for investigational agents to be received by a centralized pharmacy for re-distribution to local satellite institutions and affiliated investigators who are registered with PMB and have designated the "central pharmacy" as their shipping address. Such arrangements should be arranged with the PMB. The central pharmacy must ensure that all investigators receiving investigational agents have a current FDA Form 1572 on file with PMB and satellite dispensing records must be maintained. Local satellite institutions or affiliates must be serviced by couriers or the central pharmacy staff. CTEP-supplied investigational agents must not be repackaged or forwarded by mail or express courier. Institutions that are separated geographically, requiring mailing of investigational agents are not considered satellites for agent

accountability purposes and should receive investigational agents directly from PMB. These sites may order directly or in some situations, the central pharmacy may fax the orders to PMB for delivery to the participating investigators.

CTEP policy does not permit secondary distribution of investigational agents to other physicians or the transfer of investigational agents between institutions. CTEP intends that IND agents be distributed directly to investigators. If under exceptional circumstances emergency transfer seems justified, explicit pre-approval by the Pharmaceutical Management Branch is required.

If investigators wish to incorporate the potential of having a local oncologist administer some of the treatments for late Phase 2 or Phase 3 trials, the procedures for handling such situations must be incorporated in the protocol. Investigators should contact the Pharmaceutical Management Branch for assistance in developing the procedures. In such situations, the local oncologist(s) must register with PMB, they must be covered by an appropriate IRB, and PMB will ship the agents directly to the local investigator.

Finally, CTEP may approve a special distribution arrangement for certain unusual circumstances.

9.5 Requests for Nonresearch (Treatment) Use of Investigational Agents

Requests for use of DCTD investigational agents under Group C or Special Exception categories must satisfy certain requirements. These considerations are detailed in Section 17 and Section 18 of this handbook.

9.6 Requests for Nonclinical (Laboratory) Use of Investigational Agents

Investigational agents for non-clinical or laboratory use cannot be taken from supplies received for CTEP sponsored clinical trials. Requests for nonclinical use of investigational agents for preclinical or laboratory experiments should be directed to the Pharmaceutical Management Branch. (See Appendix IV for the address). A signed Material Transfer Agreement is required prior to sending the agent.

9.7 Status of Investigational Agents Following FDA Marketing Approval

In many instances, the DCTD continues to evaluate antineoplastic agents in ongoing clinical trials after they have received FDA marketing approval, in an attempt to identify more effective therapeutic regimens. In addition, physicians who have initially registered a patient to receive an agent under a Group C, TRC, or Special Exception protocol before an agent is approved by FDA may continue to receive the agent at no cost from CTEP for the registered patient. This is not a firm policy; it depends on the cooperation of the manufacturer (sponsor) supplying the agent.

Commercially-available agents supplied to investigators or physicians under an NCI protocol, including a Group C, TRC, or Special Exception protocol, are still considered investigational. Therefore, the same accountability requirements for investigational agents in place prior to the agent's approval continue to apply.

10. Responsibility for Reporting Results to CTEP

10.1 Introduction

The timely and accurate reporting of data from investigational agent trials to the sponsor is an important responsibility of investigators testing IND agents. The receipt of these reports in a timely fashion is not an arbitrary requirement. The information contained in them is the material that informs CTEP of the progress of the development of the agent and suggests promising new directions. In addition, the investigator is

required by CTEP to meet his/her obligations under FDA regulations to (a) monitor the study and (b) submit reports of current findings to that agency. Failure to comply with these reporting requirements is a serious breach of the agreement that each investigator makes in signing the FDA Form 1572, http://ctep.cancer.gov/forms/index.html, and may result in suspension or termination of investigator privileges.

For all trials, it is important to report two types of data: individual patient data and study summaries. Each is briefly discussed in the following paragraphs. Following that, specific reporting requirements for Phase 1 trials are detailed in Section 10.2.1; and for Phase 2 and 3 trials, in Section 10.2.2.

- **Case Report Forms -** Information about patients is recorded on case report forms (or in a computerized clinical trials database) that incorporate all patient data stipulated in the protocol.

The case report document should not be the same as the patient's primary medical record. The former ultimately serves as the formal and fixed data base on which the study is reported. A well-designed case report form will assist the investigator and assistants in collecting and recording all data called for in the protocol. The patient's chart, although the primary medical record, is generally not organized for purposes of research and does not reliably contain the judgments of the treating physician on the effects of the protocol treatment. For these reasons, a separate research record (i.e., case report form or well-designed clinical trials database) should be maintained on each protocol patient. Case research records are best maintained concurrently with the medical record.

A research record should include not only the actual data, but the responsible physician's assessment of the treatment effect (e.g., response category) and judgment as to whether any medical events in the patient's course were treatment-induced (i.e., agent-related adverse events). Unfortunately, adverse events are probably often underreported, particularly if the effect is well described.

- **Study Summary Forms -** The study summary is a tabulation and analysis of the collated individual patient data. It includes not only objective tabulations of data, but the assessment of the protocol chair concerning each case, with particular attention to eligibility, evaluability, and interpretation of the observations.

In addition to data recording and reporting, investigators and protocol chairs have several other responsibilities for the reporting of pertinent protocol information to CTEP. Procedures for reporting study data vary according to the type of study and category of sponsorship. They are outlined below for the three phases of clinical agent development.

10.2 Report Requirements of Phase 1, 2 and 3 Trials

10.2.1 Clinical Trials Monitoring Service (CTMS)

CTMS reporting is required for all early Phase 1 studies. NCI staff determine if a study is early Phase 1. The criteria to determine if a study is early Phase 1 include the first time the agent is utilized in human studies or the first time a new agent combination is used in humans or the first time an agent or combination is utilized in a specific patient group (e.g., children).

For each patient on trial, data are recorded on a DCTD Case Report Form or its electronic counterpart, ACES software (described below). This form is specific for early Phase 1 pharmacokinetic trials. All information specified in the protocol should be recorded. It must be maintained prospectively. These forms are submitted biweekly (via mail or electronically) to CTMS of CTEP. The biweekly submission should include case report updates on patients actively on study and data on all new patients entered since the last submission. At the end of each course, the investigator should indicate which medical events in the patient's course were in his/her judgment agent-induced.

All evaluations regarding adverse events should be reported using the DCTD Common Toxicity Criteria.

These reporting requirements apply to *all* Phase 1 trials of agents newly entering clinical trial, including both adult and pediatric studies. The protocol chair will periodically receive a full report of his or her study from the CTMS and should review the printout for accuracy and report any discrepancies to CTMS. The CTMS provides CTEP with summary information on all trials in the database for each agent. The CTMS analyzes the data from Phase 1 trials for timeliness of submission and completeness and provides monthly reports of this analysis to CTEP investigators.

A computer-based software package (ACES), available from CTMS, emulates the case report form. Data from Phase 1 trials may be entered directly in a PC; the software contains a facility for direct transmission via telephone to CTMS.

10.2.2 Clinical Data Update System

The CDUS is the primary clinical trial data resource for DCTD and the Division of Cancer Prevention (DCP). A CDU should be submitted for all DCTD- and DCP-sponsored trials (Phase 1, 2, and 3). This includes all DCTD-sponsored Cooperative Group and CCOP Research Base treatment trials utilizing DCTD-supplied investigational agents; all DCTD-sponsored Cooperative Group and CCOP Research Base treatment trials utilizing non-NCI agents (commercial or investigational); all DCTD-grant funded non-Cooperative Group (Cancer Center or other institution) trials (if CDUS reporting is a grant requirement) utilizing non-NCI agents; all DCTD-sponsored Cooperative Group and CCOP Research Base non-treatment trials (accrual >100 pts.); and all DCP-sponsored CCOP Research Base cancer prevention and control trials.

CTEP staff, in conjunction with external participants (e.g., Cooperative Groups, Cancer Centers, FDA, manufacturers), have made every attempt to define the minimum number of data elements needed to fulfill the regulatory, scientific, and administrative needs of the NCI. The type and amount of data required from an investigator depends upon the following:

- The trial source (Cooperative Group and CCOP Research Base vs. non-Cooperative Group),
- Whether the trial utilizes a DCTD-supplied investigational agent,
- The phase of the trial, and
- If the trial is sponsored by DCTD or DCP.

Abbreviated CDUS

The abbreviated CDUS requires quarterly submission of protocol administrative information (e.g., status) and patient-specific demographic data (e.g., gender, date of birth, race, etc.)

Complete CDUS

The complete CDUS data set includes information obtained in the abbreviated CDUS data set as well as patient administrative information (e.g., registering institution code, patient treatment status), treatment information (e.g., agent administered, total dose per course), adverse event (AE type and grade as determined by CTC), and response information (e.g., response observed, date response observed).

Summary of the CDUS reporting requirements:

Cooperative Groups and CCOP Research-Based Trials:

Study Type	DCP	DCTD-Non-Treatment	DCTD Treatment-NCI Agent*	DCTD Treatment-Non-NCI Agent**
Phase 1	Abbreviated	Abbreviated	Complete	Abbreviated
Phase 2	Abbreviated	Abbreviated	Complete	Abbreviated
Phase 3	Abbreviated	Abbreviated	Abbreviated	Abbreviated

*CTMS-monitored Phase 1 trials should continue to be reported to CTEP using the CTMS system; these trials will not require CDUS reporting.

**Please note that the NCI may choose to "upgrade" a Phase 1 or 2 treatment study from abbreviated to complete CDUS reporting based on the priority of a trial. Investigators will be notified in writing during the consensus review and protocol approval process regarding the reporting requirements for a given study.

Non-Cooperative Groups (Cancer Centers and Other Institution) Trials Utilizing DCTD Agents or Grant Funding (If CDUS reporting is a grant requirement):

Study Type	DCTD-Non-Treatment	DCTD Treatment-NCI Agent*	DCTD Treatment-Non-NCI Agent**
Phase 1	None	Complete	Abbreviated
Phase 2	None	Complete	Abbreviated
Phase 3	None	Abbreviated	Abbreviated

*CTMS-monitored Phase 1 trials should continue to be reported to CTEP using the CTMS system; these trials will not require CDUS reporting.

**Please note that the NCI may choose to "upgrade" a Phase 1 or 2 treatment study from abbreviated to complete CDUS reporting based on the priority of a trial. Investigators will be notified in writing during the consensus review and protocol approval process regarding the reporting requirements for a given study.

Additional information regarding the CDUS is available on the CTEP web site, http://ctep.cancer.gov/reporting/cdus.html.

10.2.3 Adverse Events

The importance of reporting adverse events (AE) cannot be overstated. Section 11 discusses these requirements in detail. You are reminded that *some types of events must be telephoned immediately.* IDB maintains a 24-hour line at 301-230-2330 to record these messages. You are urged to call if in doubt concerning the need to report any particular reaction.

10.2.4 Study Status

Changes in study status must be promptly communicated in writing to the CTEP PIO (See Section 8.7). Telephone discussions with CTEP physician staff are not considered formal notice of status changes.

10.2.5 Amendments

All amendments to a Phase 1 protocol must be submitted and approved by CTEP prior to implementation (see Section 8.6).

10.2.6 Presentations

A progress report of the study may be presented by the protocol chair at meetings of the Phase 1 Working Group held at NCI, usually twice a year. Minutes of the meeting are circulated to Phase 1 investigators and other interested parties.

10.2.7 Publications

Any publication resulting from a DCTD-sponsored study should be sent to the Protocol and Information Office, CTEP, identifying the protocol by the NCI protocol number.

10.3 Retention of Records

FDA regulations require that all research records (including patient charts, case report forms, x-rays and scans that document response, IRB approvals, signed informed consent documents and all agent accountability records) must be kept by the investigator for at least 2 years after an NDA or BLA has been approved for that indication or the CTEP IND has been closed. CTEP will notify investigators when these events occur. This requirement is an explicit part of the FDA Form 1572, http://ctep.cancer.gov/forms/index.html (see Appendix V).

10.4 Reporting to IRBs

Each investigator must report to his or her IRB any problems, serious adverse events, or proposed changes in the protocol that may affect the status of the investigation and the willingness of patients to participate in it. The investigator must also give a report to the IRB at intervals appropriate to the degree of risk in the study, but no less frequently than once a year, or at study closure.

11. Adverse Events

Because most antineoplastic agents have a very narrow therapeutic index, adverse events commonly accompany treatment. Since cancer patients often exhibit signs and symptoms referable to cancer or its complications, both the definition and identification of a medical event as an adverse event to a cancer agent present special problems for the investigator and sponsor. We have developed operational definitions and guidelines for reporting adverse events (AEs) that apply to anticancer agent trials (see http://ctep.cancer.gov/reporting/adeers.html, Appendix XI). The prompt reporting of AEs to the CTEP is the responsibility of each investigator engaged in clinical research with investigational agents supplied by the DCTD. *Investigators are encouraged to submit reports even if there is only a suspicion of an agent effect.* Timely and accurate reporting of AEs is necessary because only the sponsor can collate information from diverse sources and quickly disseminate the information to investigators working with the agent. The centralization of information on real or suspected AEs makes possible a much more accurate determination of the degree to which a suspected event is in fact agent-induced. Finally, regulations require DCTD to report to FDA all findings regarding AEs occurring in trials under its sponsorship.

The DCTD Common Toxicity Criteria should be used in reporting adverse events on all DCTD-sponsored trials.

A section giving detailed instructions for reporting adverse events should be included in each protocol document for DCTD sponsored trials.

11.1 Adverse Events with Commercially Available (Non-Investigational) Agents

For studies sponsored or funded by NCI involving commercially available agents not provided under an IND, AEs should be reported in writing using the standard FDA adverse event reporting form (Form 3500, MedWatch) for unexpected life-threatening (Grade 4) or fatal (Grade 5) events. The specific reporting guidelines are available in Attachment B of the NCI Expedited Adverse Event Reporting Guidelines (See Appendix XI).

11.2 Adverse Events and Routine Reporting of Adverse Events

The reporting of AEs is in addition to and does not supplant the reporting of adverse events as part of the regular scientific report of the results of the research protocol. Reporting of adverse events should be in accord with the procedures for reporting results described in Section 10.

11.3 Actions Taken by CTEP on AE Reports

CTEP physicians review each submitted report, including the investigator's assessment. This review may result in a request for further information from the investigator.

Each submitted AE report is classified according to its likely relation to the agent, and to the patient's underlying disease. Based on this assessment, a decision is made concerning the need for further action.

The prime consideration is whether the new findings affect the safety of patients enrolled in ongoing trials. If so, CTEP takes immediate steps to notify the investigator community, the FDA and the collaborating pharmaceutical firm simultaneously.

In addition, other measures may be taken, including:

- Communicating the new information by sending written notice directly to investigators
- Altering existing research by modification of protocols or discontinuing or suspending one or more trials
- Investigating the reaction by initiating special clinical or preclinical studies
- Altering the process of informed consent by modifying existing informed consent forms or informing patients of new findings.

The Organization of a Clinical Trial

The following five sections provide a detailed description of NCI policies and procedures for individuals and institutions, including the research base. It includes a discussion of affiliates, accountability and storage of investigational agents, and monitoring and quality assurance.

12. The Investigator and Protocol Chair: Roles and Responsibilities

An investigator is any physician who assumes full responsibility for the treatment and evaluation of patients on research protocols, as well as the integrity of the research data. The term distinguishes physicians acting as investigators from those who assume the more limited role of simply administering investigational agents. The investigator is responsible to see that the protocol is followed and the data are collected promptly and accurately, even if he or she delegates the administration of the agent to another physician. Most cancer trials involve collaboration among many investigators, one or more of whom is designated a protocol chair.

12.1 The Investigator

There are over ten thousand physicians eligible to receive DCTD-sponsored investigational cancer agents. Most are eligible because they are investigators supported by a peer-reviewed NCI-funded grant, contract, or cooperative agreement. Each investigator agrees to certain essential principles of participation in clinical trials with investigational agents. These principles are contained in an agreement, the FDA Form 1572, http://ctep.cancer.gov/forms/index.html, which is defined by FDA regulation (see Appendix V).

12.1.1 The FDA Form 1572

In signing the FDA Form 1572, the investigator assures CTEP that the clinical trial will be conducted according to ethically and scientifically sound principles. More specifically, a signed FDA Form 1572 commits the investigator to the following obligations or tasks:

- The investigator provides on the FDA Form 1572 a *statement of the education and experience* which qualify him or her to perform the study.
- The investigator assures that a properly constituted *IRB will be responsible for the initial and continuing review and approval of the study.* Any changes in the research protocol will require IRB approval, and all unanticipated problems involving risks to human subjects must be reported to the IRB. Such changes must also be approved by CTEP (Section 8.6).
- The investigator is responsible for the proper and secure storage of the investigational agents and is required to *maintain adequate agent accountability records* (Section 15).
- The investigator is required to *prepare and maintain adequate and accurate case histories* designed to record all observations and other data pertinent to each patient (Section 10).
- The investigator is required to *furnish reports to the CTEP as the investigational agent sponsor* (Section 10). In the case of multicenter studies, it is actually the coordinating center and the protocol chair who are responsible for the generation of these reports. The investigator is responsible for submitting data to the coordinating center.
- *The investigator is responsible for promptly reporting any AE reasonably regarded as caused by or probably caused by the agent, and, if the AE is alarming, it shall be reported immediately (according to protocol guidelines).*

CTEP devised a detailed policy statement that adapts this necessarily ambiguous language to the setting of cancer clinical trials, so that an investigation may more easily determine when a medical event needs to be reported to CTEP (Section 11).

- The investigator shall *maintain agent accountability records and case histories for 2 years* following the date an NDA or BLA is approved for that indication or, for at least 2 years after the IND is closed, whichever is longer. CTEP will notify investigators when an IND has been closed.
- Upon the request of a scientifically trained and properly authorized employee of the DHHS (either FDA or NCI), the *investigator will make records available for inspection and copying.*
- The investigator certifies that *he or she will personally conduct or supervise the clinical trials. If other physicians administer investigational agents, they will do so only under the direct supervision of the investigator.* Each attending physician who meets the DCTD investigator definition is required to be registered with CTEP by submitting a completed FDA Form 1572 to PMB.
- The investigator certifies that *he or she will inform subjects or their representatives that agents are being used for investigational purposes* and *will obtain the written consent of the subjects or their locally authorized representatives.*
- The investigator *assures CTEP that the study will not be initiated until the IRB has reviewed and approved the study.*

12.1.2 Responsibilities of an Investigator for Human Subjects Protection

The responsibilities of an investigator for IRB review deserve special mention. Each investigator who participates in NCI-sponsored clinical research must have the research approved by an IRB. The procedures followed by the investigator and his or her institution for the protection of human subjects, including IRB composition and function, as well as the basic elements of the informed consent document, are specified in regulations of the DHHS. All clinical research sponsored by DHHS must be in compliance with these regulations (Title 45, Code of Federal Regulations, Part 46 http://www.access.gpo.gov/nara/cfr/waisidx_01/45cfr46_01.html and Title 21, Parts 50 and 56, http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html, and http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html. Within DHHS, the Office for Human Research Protections (OHRP), http://ohrp.osophs.dhhs.gov/index.html, administers these regulations with each institution. The OHRP negotiates assurances of compliance with DHHS regulations for the protection of human subjects. Under an assurance, the IRB is authorized to review and approve research. Each investigator who participates in NCI-sponsored research must conduct the research at an institution with an OHRP-approved assurance.

12.2 The Protocol Chair

12.2.1 Responsibilities

The chair of a clinical trial assumes certain responsibilities in addition to those of the participating investigator. Specifically, these include:

- Writing the protocol document
- Assuring that necessary approvals are obtained, including those of the IRB, the sponsor (DCTD), and any others for the protocol and subsequent amendments
- Monitoring the study during its execution, which includes:
    - Reviewing each case record to confirm eligibility
    - Reviewing each case record to determine compliance with the protocol
    - Reporting adverse events
    - Determining any necessary changes in the protocol and the informed consent documents and submitting them as protocol amendments to the research base and to CTEP
    - Monitoring accrual to the study and stopping the study when the requirements of the study design have been fulfilled
    - Reporting study status changes to CTEP (see Section 8.7).
- Analyzing Results: By assessing each case to determine eligibility, evaluability, adverse events, protocol compliance, and outcome (this assessment should be independent of that of the treating investigator)
- Reporting Results to CTEP: Results should be presented in fully analyzed and tabulated form. The protocol chair bears the primary responsibility for this task. In Cooperative Group trials, of course, the statistical center is the protocol chair's most important collaborator in fulfillment of reporting requirements.

12.2.2 Who May Serve as a Protocol Chair

Since the protocol chair is responsible for meeting all NCI requirements for IND agent research, as stated in this manual, the protocol chair must be a fully qualified investigator. Trainees may not serve as protocol chairs.

13. Affiliate Investigators

The participation of physicians who collaborate with major institutions in clinical trials is an important component of the NCI program. The contributions of these participants is recognized by NCI, the clinical Cooperative Groups, and many Cancer Centers. To assure and maintain the high quality of clinical research conducted by the clinical trials organizations, it is important to maintain a strong relationship between these affiliate investigators and the research base.

To accomplish this objective, research base administrative policies and procedures are needed that permit all participating investigators to have easy access to accurate and timely information on matters of scientific importance and to conduct treatment research in compliance with Federal regulations. The following guidelines have been provided to assist research bases in formulating specific policies for strengthening the relationship between affiliate investigators consistent with these goals. The content of the following guidelines applies to affiliates of any research base.

We recommend that each research base develop a formal affiliate policy consistent with these guidelines.

13.1 Affiliate Investigators Definition

An affiliate investigator of a research base is a physician who:

- Participates in research clinical trials organized by the research base, and
- Has satisfied all criteria for affiliate membership as defined by the research base.

13.2 Requirements of an Affiliate Investigator

All affiliate investigators:

- Must have demonstrated competence in the treatment of cancer patients as defined by the research base
- Must have the ability to accrue a minimum number of patients as set by the research base
- Must have established a close cooperative professional relationship with the research base through regular participation in group meetings and/or educational sessions sponsored by the research base
- Must have successfully passed a *probation period* during which time the affiliate investigator has demonstrated:
    - Ability to enter patients on protocol
    - Ability to comply with the protocol
    - Ability to provide accurate and sufficient data to the research base
    - Ability to adhere to the procedures and standards of the research base and the CTEP
- Must have an appropriate OHRP assurance for the protection of human subjects (Section 12.1.2).

13.3 Responsibilities of Affiliate Investigators

The affiliate investigator must adhere to the procedures of the research base and CTEP for the conduct of clinical research by:

- Meeting the record keeping policies of the research base
- Making certain that each protocol has the full approval of an authorized IRB prior to involvement of human subjects
- Making certain that each patient signs and is given a copy of the IRB-approved consent form. The consent forms should be maintained on file by the affiliate investigator
- Complying with the policies of CTEP and FDA concerning the use of investigational agents, which include as a minimum:
    - Filing a signed FDA Form 1572, http://ctep.cancer.gov/forms/index.html, with CTEP
    - Observing DCTD policy and procedures for the proper and secure storage of investigational agents, including maintaining NCI Agent Accountability Records, http://ctep.cancer.gov/forms/index.html (Appendix XII).
    - Agreeing that primary medical records of patients may be audited in accordance with the policies of the research base, CTEP, and FDA (Section 16).

13.4 Responsibilities of Research Bases for Affiliates

13.4.1 The Cooperative Groups

The Cooperative Groups have the following responsibilities for their affiliate investigators:

- Maintaining an accurate and up-to-date list of all member institutions and affiliate investigators
- Informing CTEP of important actions regarding membership status of its member institutions and affiliate investigators
- Reviewing performance of all members in periodic and timely fashion (including on-site data audits)
- Assuring that all members, full and affiliate, are in compliance with CTEP policies and DHHS regulations
- Ensuring that each affiliate institution/investigator has registered an appropriate assurance with the OHRP, http://ohrp.osophs.dhhs.gov/index.html.
- Ensuring that full local IRB approval has been obtained prior to allowing registration of patients on any protocol and on a continuing basis

13.4.2 The Principal Investigator Responsibilities for Affiliate Investigators in Cooperative Group Protocols

The principal investigator in Cooperative Groups has the following responsibilities for affiliate investigators:

- Assuring the Cooperative Group that the affiliate member's performance meets the procedures and standards of the research base
- Informing the Cooperative Group of important changes in affiliate member relationships
- Agreeing to site-visit the affiliate as deemed necessary by the Cooperative Group
- Providing the affiliate with accurate and timely information on matters of scientific importance
- Communicating to affiliates in a timely manner all policies (and any changes in policy) on the conduct of clinical research.

13.4.3 Cancer Centers

The Cancer Centers have the following responsibilities for their physician members and for their affiliate institutions:

- Maintaining an accurate and up-to-date list of all members and affiliates
- Informing CTEP of important actions taken regarding membership status of its members and affiliate investigators
- Conducting periodic and timely review of the performance of all members and affiliate investigators (including audits of affiliate data)
- Agreeing to site-visit the affiliate investigator in accord with CTEP policies
- Assuring that all members and affiliate investigators are in compliance with CTEP policies and FDA regulations
- Ensuring that each affiliate institution/investigator has registered an appropriate assurance with the OHRP, http://ohrp.osophs.dhhs.gov/index.html
- Ensuring that full local IRB approval has been obtained prior to allowing registration of patients on any protocol and on a continuing basis
- Communicating to affiliate investigators in a timely manner all policies and changes in policy on the conduct of clinical research.

14. Who May Administer Investigational Agents

14.1 Restrictions to Physicians Registered as Investigators with CTEP

The distribution of investigational agents is restricted to physicians who are registered as investigators with CTEP. Specifically, *the secondary distribution of investigational agents from registered investigators to unregistered physicians is prohibited.* All patients on clinical trials involving the use of investigational agents must receive all treatments with these agents from a registered investigator.

The reason for this policy is clear. Physicians who treat patients as part of a clinical trial must have a commitment to the goals of the trial and to the methodologic requirements of clinical research. They must be experienced in the evaluation of therapeutic results and of the adverse event manifestations of anticancer therapy. The major issue, therefore, in the conduct of a clinical trial is: Who is making the observations and the decisions? For example, who is deciding on the dose modifications and the laboratory tests to be obtained? Who is observing the patient for adverse events of the investigational agents? A physician performing these tasks with investigational agents must have the training and experience to function effectively as a clinical investigator, and acknowledge his or her commitment to those principles.

All investigators participating in trials sponsored by CTEP must be formally registered with their research base (i.e., Cooperative Group or Cancer Center) and with CTEP. Such registration signifies that the physician-investigator meets certain requirements for participation in clinical trials. Investigators register with CTEP by completing a FDA Form 1572, a Supplemental Investigator Data Form, and a Financial Disclosure Form, http://ctep.cancer.gov/forms/index.html, (Appendix V).

Physicians in training may administer investigational agents under the direct supervision of a registered investigator holding a current FDA Form 1572. They need not submit a FDA Form 1572 under their own signature. In such cases, the registered investigator assumes complete responsibility for the use of these agents.

CTEP recognizes that it is often convenient for a Cooperative Group member or Cancer Center physician to ask a local physician to administer protocol treatment to a patient who may have traveled long distances to the research base for initial consultation. We believe that this approach is ultimately detrimental to the clinical research effort unless very careful surveillance is maintained by the investigator. If close monitoring is impossible, it seems much more sensible to require that all treatments be administered by registered investigators. Physicians will have to carefully consider whether a patient being evaluated for study will be able to receive each treatment at the hands of a registered physician. We are confident, however, that the benefits of this policy, in terms of both patient safety and integrity of the research data, far outweigh the disadvantages and are in the long term best interests of both patients on clinical trials and the agent development program of the DCTD.

15. Accountability and Storage of Investigational Agents

The investigator is responsible for the proper and secure physical storage and record keeping of investigational agents received from CTEP. Specifically, the investigator must:
Maintain a careful record of the receipt, use and final disposition of all investigational agents received from CTEP, using the NCI Agent Accountability Record Form (DARF), http://ctep.cancer.gov/forms/index.html.

- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent
- Return any unused investigational agents to PMB at the completion of the study or upon notification that an agent is being withdrawn

The intent of the agent accountability procedures described in this section is to assist the investigator in making certain that agents received from DCTD are used only for patients entered onto an approved protocol. The record keeping described in this section is required under FDA regulation. Investigators are responsible for the use of investigational agents shipped in their name. Even if a pharmacist or chemotherapy nurse has the actual task of handling these agents upon receipt, the investigator is the responsible individual and has agreed to accept this responsibility by signing the FDA 1572, http://ctep.cancer.gov/forms/index.html.

15.1 Procedures for Agent Accountability and Storage

- Each investigational agent should be stored separately by protocol. If an agent is used for more than one protocol, there should be separate physical storage for each protocol. Remember that CTEP provides and accounts for agents on a protocol-by-protocol basis.
- Each agent should be accounted for separately by protocol. If an agent is used for more than one protocol, there should be a separate Agent Accountability Record Form (DARF) for each protocol, http://ctep.cancer.gov/forms/index.html. There should be a separate DARF for each agent in a multi-agent protocol.
- Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (e.g., an agent with a 1-mg vial and a 5-mg vial would require a different DARF for the 1-mg vial than for the 5-mg vial).
- The DARF has been designed for use at each location where agents are stored, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas.
- The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (e.g., receipt of agent, returns, broken vials, etc.). A copy of the DARF may be found at http://ctep.cancer.gov/forms/index.html.
- DCTD-supplied investigational agents may be transferred, with an institutional (intra-institutional transfer) from a completed DCTD protocol to another DCTD-approved protocol that utilizes the same agent and formulation. An NCI Investigational Agent Transfer form must be completed and submitted by fax (301-402-0429) to the Pharmaceutical Management Branch (PMB) for each agent transfer. Transfer forms should be submitted within 72 hours of the actual transfer. Transfer of DCTD-supplied investigational agents from an active protocol requires prior PMB approval (telephone 301-496-5725). (See PMB Policy and Guideline on the CTEP Home Page.)
- Inter-institutional transfer of DCTD investigational agents is not permitted unless specifically pre-approved or authorized by the Pharmaceutical Management Branch.

15.2 Investigational Agent Returns

Many investigators are not aware that investigational agents must be returned to the IND sponsor. DCTD, as the investigational agent sponsor, is responsible for investigational agent accountability, which includes receipt, distribution, and final disposition of all investigational agents. Investigators are required to return agents if:

- The study is completed or discontinued
- The agent is expired
- The agent is damaged or unfit for use (e.g., loss of refrigeration)

In situations where a DCTD agent is no longer required for a completed or discontinued protocol, DCTD procedures permit the transfer to another DCTD-sponsored protocol that is using the identical agent and formulation through completion of the NCI Transfer Investigational Agent Form, NIH-2564-1, http://ctep.cancer.gov/forms/index.html, see Section 15.1.

In situations where there is an obvious excess inventory, or the agent will not be used before the expiration date and you have another DCTD protocol(s) using the identical agent, please contact the Pharmaceutical Management Branch (301-496-5725) for assistance in transferring the agent to another DCTD-sponsored study. Otherwise, return the agents as stated in the steps below.

To return investigational agents to DCTD:

1. Package the agents securely to prevent breakage (enclose within a zip-lock bag)
2. Complete the Return Drug List Form, NIH-986 (Appendix X). Save a copy for your records.
3. Send to the NCI Clinical Repository at the address indicated on the Return Drug Form. Since agents are not re-used upon return, rush delivery is not necessary.

15.3 Verification of Compliance

Investigators are reminded that compliance with procedures to ensure proper agent usage will be reviewed during site visits conducted under the monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained, and will spot-check the agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol.

15.4 Handling of Antineoplastic Agents

There has been considerable concern about the potential risk of chronic exposure to low-level concentrations of antineoplastic agents among health care workers routinely handling these agents. The potential mutagenic activity of antineoplastic agents has been examined *in vitro* and *in vivo*. Urinary alkylating and anthracycline agents have shown mutagenic activity in experimental systems, whereas this has not been demonstrated for most of the antimetabolites and vinca alkaloids. Recent reports indicate that antineoplastic agents may be absorbed by workers who are handling them. In addition, some of the compounds are carcinogenic in animals and are suspected of being so in humans, but only in patients receiving the agent at therapeutic levels.

There is, however, no clear evidence at this time that chronic exposure to low-level concentrations of antineoplastic agents has been carcinogenic in health-care workers. Nevertheless, it would seem prudent to consider the adoption of certain precautions in the procedures of workers handling these agents. Several professional organizations have reviewed the data on this subject in an attempt to develop guidelines for safe handling. While there are now several published sets of guidelines, they do not differ significantly.

We have reproduced the *Recommendations for Handling Cytotoxic Agents,* by the National Study Commission on Cytotoxic Exposure in Appendix XIII. Please note that these are guidelines and do not have regulatory or legal force. They are included for your consideration and information.
Other pertinent references include:

- Recommendations for the Safe Handling of Parenteral Antineoplastic Agents. NIH Publication #83-2621. Available from Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
- ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Agents. *Am J. Hosp. Pharm.* 1990: 47: 1033-1049.
- AMA Council Report: Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985: 253: 1590-1592.

16. Monitoring and Quality Assurance
16.1 Introduction

Sponsors and research bases must monitor their clinical trials. In assuring the quality of data, monitoring is a key component of any clinical trials program. Quality assurance and monitoring are concerned with the execution of a trial, rather than its conception, and with the quality of the data that support the scientific conclusions.

Many individual activities are part of quality assurance, and investigators have recognized some of them as vital to the integrity of clinical trials for years. In particular, the quality control of pathology and radiotherapy has been part of the Cooperative Group program for a long time. More recently, investigators have increasingly recognized the importance of verifying the accuracy of other classes of data.

We shall now discuss in more detail the items that form the major focus of the DCTD-sponsored quality assurance effort. Note that the first two classes of concern (protocol compliance and data accuracy) are really central problems in clinical trials methodology. The fact that they are assessed intensively by the on-site audit program should in no way divert attention from their essential importance to the *scientific* content of clinical trials.

16.2 Protocol Compliance
16.2.1 Cooperative Groups

The groups have recognized the importance of assessing the extent of protocol compliance for many years. One of the first areas to receive attention was the confirmation of diagnosis. Today, virtually all groups have Pathology Committees or Reference Panels for selected studies; central pathology review reduces one important source of variability in trial results. Furthermore, most Cooperative Groups have quality control in radiotherapy, which consists at least of reviews of port films by group radiotherapists. These reviews are best done prospectively, so that errors can be detected in time to alter subsequent treatment. In the Cooperative Groups, the medical oncology committee or the protocol chair reviews case report forms to establish whether dose adjustments have followed protocol guidelines, and whether appropriate study tests have been obtained.

In most Cooperative Groups, the protocol chair also reviews each case to determine eligibility, evaluability, and validity of response and adverse event assessment. In some cases, the statistical office accomplishes one or more of these tasks. All of these assessments are performed through review of submitted case report forms.

16.2.2 Cancer Centers

The majority of Cancer Centers have organized procedures to assess protocol compliance centrally and systemically (Section 3, Research Bases). The CTEP on-site audit program evaluates protocol compliance as part of its monitoring visits. Indeed, this is a major focus of a monitoring visit to a Cancer Center, along with the administrative review for central data management, protocol development, and data collection.

16.2.3 CTEP Clinical Agent Development Contractors

Protocol compliance is assessed by the Clinical Trials Monitoring Service (CTMS). Phase 1 and Phase 2/3 contractors submit raw data to CTMS, which reviews it carefully for extent of compliance with the protocol. Reports of these evaluations are provided to the investigator and to CTEP.

16.3 Data Accuracy

The importance of verifying the accuracy of the basic data elements used in the analysis of study endpoints is obvious. Data accuracy is assessed during on-site audits by comparison of the research record (e.g., flow sheets) with the primary patient record. Response assessment may be evaluated by examination of radiographs or scintiscans, where relevant.

In many of the early on-site audits performed, CTEP was concerned about the absence of formalized procedures at many centers for assessing these important issues internally. Many institutions lacked central registration mechanisms to enroll patients on trials. Centralized systems of data management were often not available. Some institutions lacked clear procedures for certifying the accuracy of research data. Formal procedures for evaluating the accuracy of response assessment, for example by second-party review, were commonly lacking. As institutions have recognized the importance of these tools for the conduct of clinical trials and have brought them "on-line," the quality of data has improved commensurately.

16.4 Procedural Requirements

As an IND sponsor, the DCTD must verify that its investigators adhere to the various procedural requirements of investigational agent trials. The specific procedural activities checked at the time of the on-site audit are:

- **Informed Consent** - Investigators must be certain that the patient signs the IRB-approved version of the informed consent prior to initiation of protocol-directed therapy. The consent form must be a document specifically written for the protocol, and must address all elements required by Federal regulations.
- **IRB Approval** - Each protocol must have full approval by the IRB named in the assurance for the institution prior to patient entry. There should be written verification of this action and of at least annual review. Substantive protocol amendments must also be approved by the IRB.
- **Agent Accountability** - Each investigator must assure that:
    - All IND agents supplied by DCTD are used only for patients on the specific protocol for which the agents were requested and approved by CTEP
    - Logs are maintained that record the disposition of each unit of agent received from CTEP for the protocol.

On-site auditors will also review the completeness of reporting adverse events and the quality of record keeping with particular reference to the completeness of the source documentation.

Each of these areas is reviewed at the time of on-site audit. In addition, many Cooperative Groups and Cancer Centers maintain internal procedures to assure the quality of data on their trials and assure that regulatory requirements have been met.

16.5 Components of the Quality Assurance Program Implemented by CTEP

16.5.1 Monitoring

Monitoring includes following the overall progress of the study to ensure that projected accrual goals are met in a timely fashion and excessive accrual is avoided; that eligibility and evaluability rates do not fall below acceptable standards; and that risks of the study do not outweigh benefits. Poor performance in any of these areas is cause for concern. Because these activities are performed during study execution, they may lead directly to improved conduct of the trial.
The Cooperative Groups are performing these tasks according to systematic, formalized procedures. For Phase 1 studies, the CTMS performs these duties.

Cancer Center studies are monitored by the CTMS with direct oversight from CTMB.

16.5.2 The On-Site Auditing Program

16.5.2.1 Purpose of Site Visit Audits

- Verification of data accuracy by comparison of the primary medical record with the case report form maintained by the research base for analysis
- Verification of the presence of an IRB-approved consent form signed by the patient prior to the initiation of protocol therapy
- Verification of IRB approval (and at least annual review and reapproval) of each sponsored study
- Verification that procedures for agent accountability meet the requirements of federal regulations and CTEP procedures, including maintenance of NCI Agent Accountability Records.

16.5.2.2 Outline of Audit Procedures

- Trials to be audited are those involving DCTD investigational agents and selected prevention trials
- All audits will be conducted by persons knowledgeable about clinical trials methodology and the Federal regulations and NCI policies pertinent to clinical trials
- Audits will be randomly timed
- Audits will be conducted at an average rate of once every three years (except CTMS monitored Phase 1 trials).

16.5.2.3 Adaptations of Basic Procedures to Specific Needs

These basic procedures have been adapted to the several types of clinical trials organizations supported by NCI in the following way:

- Cooperative Groups - Each Group will perform its own program of on-site audits, to be conducted by its staff and/or members with direct oversight by CTMB. CTEP or CTMS staff will attend a percentage as observers.
- Clinical Agent Development Contractors - On-site audit visits are made to the Phase 1 contractors three times each year and to the Phase 2/3 contractors once annually. All are site visited by the CTMS. Noncontract studies may be assigned to CTMS monitoring at CTEP discretion.
- Others - This category comprises all others performing DCTD IND agent studies, including RO1/PO1 holders (conducting clinical IND agent trials as part of grant-related activity), and new agent studies groups. Audits will be conducted by teams composed of CTMS staff, CTEP staff, and outside physicians, as deemed necessary by CTEP.
- Cancer Centers – Audits will be conducted by teams composed of CTMS staff, CTEP staff and outside physicians. Audits will occur once every three years.

Relationship Between the Content of the Site Visit Audits and the Type of Clinical Trials Organization.

Components of the Quality Assurance Program			
	Protocol Compliance	**Data Accuracy**	**Procedures**
Contract & Other Phase 1 Studies	CTMS	CTMS	CTMS
Cancer Centers	CTMS	CTMS	CTMS
Cooperative Groups	Group Note 1	Group Note 2	Group Note 1

CTMS = Clinical Trials Monitoring Service (CTEP monitoring organization, which monitors Phase 1 and some Phase 2 trials, and coordinates On-Site Auditing Program)

Note 1:
Protocol compliance is verified by each Cooperative Group through its quality control program. Much of this is accomplished through a central review of case report forms. However, protocol compliance should also be checked at the time of on-site audits to review patient charts, since information pertinent to the eligibility and evaluability of a patient may be discovered that was not included on the case report form.

Note 2:
Conducted as part of the on-site auditing program of the Cooperative Groups, and co-site visited by NCI.

16.6 Informed Consent and the Monitoring Program

Many have asked about the legality of review of a patient's primary medical record by outside individuals. The answer is straightforward. No Federal law prohibits external review of a patient's medical record. The regulations of informed consent do require, however, that the patient be informed of "the extent to which confidentiality of records will be maintained." This means that there is no rule against chart review by outsiders, but that the patient must be told what will be done. For this reason, CTEP requires that each informed consent document for investigational agent trials it sponsors include a statement with the following language, "A qualified representative of FDA and NCI may review my medical records." CTEP may also suggest that the name of the manufacturer of the agent be included as having access to the records. This access may be necessary for the pharmaceutical company to prepare a New Drug Application (NDA) or Biologic License Application (BLA) for an agent.

Also, please note that medical records are protected from inquiries under the Freedom of Information Act (FOIA). Even if the study is performed under Government sponsorship, any records on the premises of the investigator are not subject to FOIA requests. Furthermore, any patient-related records in Government files are protected from FOIA requests by the Privacy Act. As an additional measure of safeguarding, CTEP removes patient names from any documents in its possession.

16.7 Dealing with Problems Identified During On-Site Audits

CTEP and the Cooperative Groups have a full range of options in dealing with problems identified at the on-site audit. In a great majority of cases, the measures are intended to be constructive, educational, and corrective rather than punitive. The actions that are taken vary with the individual case.

All reports of on-site audits are sent to CTEP electronically. The reports are assessed by CTEP staff on a regular basis. When major problems are identified by a Cooperative Group audit, this information is immediately conveyed to the group chair and CTEP for further action and investigation. After requesting a written clarification, and following review of the case by the Cooperative Group and/or CTEP, appropriate measures will be applied if the original assessment is confirmed. The options for action include:

- Letter of Warning
- Probationary status
- Suspension of patient entry privileges
- Immediate repeat audit
- Removal of access to investigational agents
- Notification of FDA if investigational agents are involved (FDA may conduct its own investigation)
- Notification of the Office of Research Integrity if scientific misconduct is a possibility (ORI may conduct its own inquiry/investigation)
- Notification of the Office of Human Research Protection (OHRP), http://ohrp.osophs.dhhs.gov/index.html, if issues of patient rights, informed consent, or IRB review are involved (OHRP may conduct its own investigation)

The following actions may be taken in instances of suspected data fabrication or falsification or other possible scientific misconduct:

- Replacement of principal investigator
- Termination of grant or contract
- Reanalysis or retraction of published results
- Formal ORI investigation
- Debarment of investigator or other staff from future participation in PHS research.

Nonresearch or Treatment Referral Protocol Use of Investigational Agents

17. Group C
17.1 Definition

Investigational agents that have been given Group C designation by FDA have reproducible efficacy in one or more specific tumor types. Such an agent has altered or is likely to alter the pattern of treatment of the disease and can be safely administered by properly trained physicians without specialized supportive care facilities.

17.2 Placement of an Agent in Group C

If an agent meets the criteria in the preceding paragraph, CTEP may initiate a formal application to the FDA to authorize Group C distribution for the specific indication. Such authorization is not equivalent to formal FDA approval of effectiveness for this indication.

17.3 Current Group C Agents

A physician should request agents under Group C if he or she wishes to treat a patient with an indication specifically authorized for the requested agents, as listed in Appendix XIV. The list of current agents classified as Group C is subject to change as agents receive FDA approval. The Pharmaceutical Management Branch (PMB) may be contacted for the latest listing or for further information (Appendix IV). All other non-research requests for clinical use are considered a "Special Exception" (see Section 18).

17.4 Use of a Group C Agent

The use of an agent for a Group C-approved indication is fully described in the **GUIDELINE PROTOCOL**. This document is written by CTEP and approved by FDA. It describes the indications, dosage, precautions, warning, and known adverse effects of the agent for the specific indications(s). It also contains a FDA-approved informed consent, which must be used if there has been no local IRB review. Guideline protocols may be obtained by contacting the Pharmaceutical Management Branch (PMB) at the address listed in Appendix IV. Additional information is available by phone at the number listed in Appendix IV.

Please note that:

- Patients treated under Group C guidelines are not part of a clinical trial at the time of the treatment with the Group C agent.
- An agent classified in Group C for a certain indication may still be under active clinical investigation for the same or other indications.
- Group C must not be used to obtain agent to conduct clinical trials.

17.5 Requesting a Group C Agent

- You may request a Group C agent by contacting the Clinical Research Pharmacy Section, PMB, by telephone or in writing. (See Appendix IV for number and address).
- The amount of patient information required varies specifically for each Group C agent. Physicians should contact the PMB for the specific requirements.
- You must have a current FDA Form 1572, Supplemental Investigator Data Form, Financial Disclosure Form, http://ctep.cancer.gov/forms/index.html, and CV on file with CTEP (i.e., signed within the last 12 months).
- If your request is approved you will receive a supply of the investigational agent and an approval letter, a copy of the Guideline Protocol, and procedures for reporting adverse events.
- Reporting requirements for Group C agents vary depending on the investigational agent and are specified in the protocol for the agent.

17.6 Responsibilities When Using Group C Agents

- Agent Accountability: You must record the disposition of investigational agents received on the Agent Accountability Record Form (Section 15 and Appendix XII).
- Adverse Events: Since Group C agents are still investigational agents, physicians using them are obligated to report adverse events to CTEP (Section 11).
- Informed Consent: You must obtain written consent from the patient. The Guideline Protocol contains the required consent form.

- IRB Review: Since administration of an investigational agent under Group C guidelines is not done with a primary research intent, an IRB waiver has been obtained from FDA for most Group C agents. You should, however, check with your IRB to determine whether its local policies require approval.
- In the future, CTEP will consider Group C classification only for those agents whose activity is well enough established that NDA or BLA approval in the relatively near future is considered likely.

18. Special Exceptions

Physicians with patients who are refractory to standard measures, who are not eligible for an ongoing research protocol, and who have a cancer diagnosis for which an investigational agent has demonstrated activity may receive the agent from CTEP as a Special Exception to the policy of administering investigational agents only under a research protocol. If the requested agent is approved for Group C for that indication, it should be requested under the Group C Guidelines (Section 17).

18.1 Definition

The Special Exception mechanism is the functional equivalent of a compassionate IND but differs from it in that the investigator may obtain investigational agents directly from CTEP, instead of having to obtain an IND from FDA. CTEP provides this mechanism as a service to the oncologic community and to cancer patients. Substantial effort on the part of CTEP professional and support staff is committed to maintaining the Special Exception Program.

We expect that patients treated under the Special Exception mechanism are not eligible for established research protocols. Agents available for Special Exception are always in Phase 2 or Phase 3 trials. *Special Exceptions are not granted for Phase 1 agents*.

The purpose of the Special Exception mechanism is to make unapproved investigational agents that have a significant activity against specific malignancies available to cancer patients and investigators who otherwise can not participate in a clinical trial.

18.2 Criteria for Approval of a Special Exception Request

Pharmacists of the Pharmaceutical Management Branch and physician staff members of the Investigational Drug Branch review each Special Exception request and make the decision on a patient-by-patient basis, based on the following considerations:

- Is there a research protocol for which the patient is eligible?
- Have standard therapies been exhausted?
- Is there objective evidence that the investigational agent is active in the disease for which the request is being made?

A review of the experience with Special Exception protocols in the past indicated that patients experienced considerable adverse events with little significant benefit. As a result, CTEP has attempted to improve the selection criteria for patients treated under Special Exception. Considerable evidence must attest to the activity of the agent for the requested indication. There should be sufficient data available to provide a reasonable expectation that the agent will prolong survival or improve the quality of life in a cohort of similar patients so treated. Reports of low response rates, or responses of brief duration, or anecdotal reports of an occasional response are not sufficient to justify approval.

- Is the agent likely to benefit this patient?
- Even if the agent has been reported to be active in the disease, the specific circumstances of the patient must be weighed by both his or her physicians and CTEP physicians.

- Please note that the Special Exception service *may not be used as a means to obtain agents to treat a series of patients on protocol, or to do pilot work for an intended study*. CTEP tracks these requests and will take whatever measures are necessary to discontinue such practices by an investigator. (Similar considerations apply to Group C). Agents distributed under Special Exception Service are investigational and are subject to FDA regulation and CTEP policy.

18.3 Requesting a Special Exception Agent

Requests for Special Exceptions may be made in writing or by telephone to the Pharmaceutical Management Branch. You should indicate the patient's diagnosis, previous cancer therapy, current clinical status, intended dose and schedule of the requested agent, any proposed concomitant cancer agents or other therapies, and pertinent laboratory data.

You should explain why the proposed use of the investigational agent is a better selection than a commercially available agent. In addition, the age, sex, and date of diagnosis should be included.

18.4 Responsibilities of Physicians Administering Special Exception Agents

See Appendix XV.

19. Treatment Referral Center (TRC)

19.1 Purpose

The Treatment Referral Center (TRC) is a means for NCI to provide information to community oncologists about therapeutic options for cancer patients with emphasis on referral to Cooperative Group studies or Cancer Centers. The TRC uses the PDQ, http://www.cancer.gov/search/clinical_trials/, and CTEP information systems databases, data supplied by the NCI-designated Comprehensive or Clinical Cancer Centers, and consultations with CTEP physicians to maintain a referral list of the most current active research protocols. For certain high-priority diseases, NCI identifies those stages and amount of prior therapy situations for which it is felt investigational treatments should be available. For each of these patient populations, the TRC will provide a Treatment Referral Center Protocol to the Cancer Centers. If any one of the Cancer Centers feels there are no commercially available treatment options or there is no active clinical trial available for such patient populations, the Cancer Center may choose to use the Treatment Referral Center Protocol as a treatment option.

19.2 Method

Information will generally be provided about treatment options using the following algorithm:

- First priority will be given to suggesting the patient be referred to a major Phase 2 or 3 trial (usually Cooperative Group studies).
- If the patient is ineligible for or unable or unwilling to enter a Phase 2 or 3 trial, then the physician would be offered the following alternatives:
    - Referral to a participating Cancer Center for evaluation for an investigational protocol. These protocols would offer therapies with potential activity in a specific disease
    - Standard treatment options; e.g., commercially available agents
    - Group C or Special Exception agents, if available
    - Referral to the PDQ database for alternative treatment options, including Phase 1 agents.

19.3 Access to the TRC

Physicians at participating Cancer Centers will contact the Pharmaceutical Management Branch to register patients on TRC protocols. Registration procedures and eligibility criteria are provided in the approved TRC protocol.