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These guidelines explain the policies and procedures of the National Cancer Institute (NCI) with respect to the Clinical Trials Cooperative Group Program of the Division of Cancer Treatment, Diagnosis and Centers (DCTDC). Some of these guidelines reflect Department of Health and Human Service requirements for federally funded clinical research while others are the result of a consensus among NCI staff and qualified extramural clinical investigators.

These guidelines have been updated to reflect current practices. Although further evolution of these guidelines is inevitable, it is hoped that the codification of NCI policies and procedures will continue to be of practical value to participants in, and reviewers of, DCTDC-supported clinical trials research.

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**CLINICAL TRIALS COOPERATIVE GROUP PROGRAM
GUIDELINES**

**Cancer Therapy Evaluation Program
Division of Cancer Treatment, Diagnosis and Centers
National Cancer Institute
National Institutes of Health**

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I. INTRODUCTION

These guidelines for the National Cancer Institute's (NCI) Clinical Trials Cooperative Group Program have been developed by staff of the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment, Diagnosis and Centers (DCTDC), National Cancer Institute (NCI), in consultation with staff of the Grants Administration Branch (GAB) and of the Division of Extramural Activities (DEA) and Division of Cancer Prevention and Control (DCPC), NCI as well as with the advice of qualified members of the extramural scientific community. Their purpose is to describe the NCI's goals and expectations for the various applicants and investigators, peer reviewers and National Institutes of Health (NIH) staff who are involved with this Program. They are intended to encourage a research philosophy and discipline that will produce consistently excellent clinical trials, while at the same time permitting each Group to develop structures and procedures that best meet its needs.

I.1. GENERAL DESCRIPTION OF THE PROGRAM

The NCI's Clinical Trials Cooperative Groups (henceforth termed the Groups) consist of researchers at institutions affiliated with the Groups, who jointly develop and conduct cancer treatment clinical trials in multi-institutional settings. Administered by CTEP staff, they are a major component of the extramural research effort of the DCTDC, NCI. Each Group is supported to continually generate new trials compatible with its particular areas of interest and expertise, as well as with national priorities for cancer treatment research. Unlike most other major NIH cooperative clinical trials efforts, Group structure and funding are not usually linked to any specific clinical trial(s). This mechanism thus has the potential for considerable flexibility in resource allocation, and for the rapid testing of promising new cancer therapies in large patient populations, since the apparatus for conducting such trials is constantly in place. The Groups have been instrumental in the development of new standards of cancer patient management, and in the development of sophisticated clinical investigation techniques.

I.2. BRIEF HISTORY

The Clinical Trials Cooperative Group Program was conceived in 1955 when Dr. Sidney Farber, Mary Lasker, and others approached Congress with a proposal that it increase support for studies of chemotherapy for cancer. Congress responded by appropriating \$5 million to the National Cancer Institute to establish the Chemotherapy National Service Center. By 1958, seventeen Groups were organized which operated under research grants from NCI; their main thrust was the testing of new anticancer agents from the NCI drug development program. Over the intervening years the Program has evolved into one which places major emphasis on definitive studies of combined modality approaches to the treatment of cancer.

In 1980-81, the mechanism of support for the Clinical Trials Cooperative Group Program was converted from the grant to the cooperative agreement. The purpose of this change was to define the involvement of NCI program staff in the coordination of Group activities.

Approximately 20,000 new patients are accrued onto Group treatment studies each year, 12,000 are evaluated annually on ancillary laboratory correlative studies, and many times the combined number are in follow-up. Thousands of individual investigators participate in Cooperative Group protocols.

The Cooperative Groups are heterogeneous in their research objectives and their structures. These Groups presently are four major types: (1) Groups that are specifically disease oriented (e.g., gynecologic oncology); (2) Groups that are designed to deal primarily with high technology, single modality studies (e.g., radiation therapy), (3) Groups in which the investigators have a particular expertise (e.g., pediatricians); and (4) multimodal national Groups. The common thread, however, is the development and conduct of large-scale trials in a multi-institutional setting.

II. PURPOSE OF THE CLINICAL TRIALS COOPERATIVE GROUP PROGRAM

The essential feature of the Clinical Trials Cooperative Group Program is the support of organizations which continually generate and conduct new clinical trials consistent with national priorities for cancer treatment research. Emphasis is placed on definitive, randomized Phase III studies and the developmental efforts preliminary to them. While a wide variety of investigational efforts are therefore appropriate, this Program specifically does not overlap with or replace funding mechanisms for more narrowly focused, Research Project Grant activities (e.g., RO1, PO1 grants and U01, U19 cooperative agreements).

III. GOALS OF COOPERATIVE GROUP RESEARCH

III.1. IMPROVE THERAPY

Therapeutic research aimed at improving the survival and quality of life for persons with cancer is of highest priority to CTEP.

III.2. ADJUNCT STUDIES

The database of patient information accumulated in the course of treatment research, and the possibilities for large-scale collection of biologic samples with subsequent correlation of specific features with patient outcome, provide the Groups with unique opportunities to address scientific questions about molecular genetics, epidemiology, pathology and other cancer-related topics. Such ancillary investigations can add considerable strength to a Group's total scientific program, and are encouraged. While certain studies may be eligible for inclusion in a Group application for financial support, particularly when the laboratory efforts are integral to the clinical trials proposed, a variety of other funding mechanisms - including investigator-initiated grants (R01s, P01s) and cooperative agreements for discrete projects (U01s, U19s) - may also be appropriate.

III.3. CANCER CONTROL

Groups supported by NCI's DCTDC may serve as research bases for treatment and cancer control research performed by Community Clinical Oncology Program (CCOP) cooperative agreement awardees which are supported by the NCI's Division of Cancer Prevention and Control (DCPC). While this activity, when present, should be an integrated component of the Group's total research program, peer-review of the CCOP research program including cancer control research for the purposes of NCI financial support will be advisory to the DCPC, and generally will be conducted separately from peer review advisory to the DCTDC (see Section VIII, Peer Review).

III.4. CLINICAL TRIALS METHODOLOGY

The Groups provide a unique framework for research in clinical trials methodology. While CTEP encourages development of and experimentation with new study designs within the Group framework, purely statistical research is appropriately funded through other mechanisms.

III.5. STUDY POPULATIONS

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that explains why inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations) which had been in effect since 1990. The 1993 policy contains some provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research," which was reprinted in the Federal Register of March 20, 1994 (59 FR 14508-14513) to correct typesetting errors in the earlier publication, and reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from NCI program staff. Program staff may also provide additional relevant information concerning the policy.

IV. STUDY DEVELOPMENT

IV.1. GENERAL CONSIDERATIONS

Under the cooperative agreement mechanism, the Group and the NCI share the responsibility for ensuring that the best and most important clinical research is conducted, within the limits of available research support and finite patient resources. Similarly, both the Groups and the NCI share responsibility for ensuring that the Clinical Trials Cooperative Group Program functions as efficiently as possible.

Definitive clinical trials should usually constitute the major portion of a Group's activities; they should always serve as the ultimate goal of preliminary developmental trials. It is essential that important, original, and feasible treatment questions be posed, that study questions be answerable in a reasonable period of time, and that the methodology of each study be sound. While all treatment modalities and cancer sites are appropriate for Group study, there is no requirement for each Group to be active in every modality and/or disease. Proper integration of diagnostic or other support modalities is essential, with standards of quality control as rigorous as those applied to treatment modalities.

IV.2. SPECIFIC GROUP RESPONSIBILITIES

In most Groups the process of study generation begins at the level of a disease or modality committee, which develops specific experiments ultimately embodied in Group protocols. This proven organizational approach provides a forum for investigators who share a common area of interest, and an arena in which various ideas must compete if they are to gain the status of a Group study.

IV.2.A. Development of Research Plans

The Group and its research committees should develop, articulate, and follow a comprehensive research plan which summarizes the Group's specific objectives and lines of investigation for each disease or modality that it chooses to study. The purpose of this plan is to focus attention on long-term goals, and to aid the Group in prioritization of competing research ideas. The plan will frequently include small developmental/pilot studies, Phase II studies, as well as large-scale Phase III efforts (see section IV.3.A. regarding national priorities), all designed to take advantage of the Group's experience, expertise, resources, and clinical opportunities.

These comprehensive research plans for each disease and/or modality committee will be a major focus of the peer review process when the Group is reviewed.

IV.2.B. Flexibility

While it is important to establish disease and modality plans, and to implement specific studies in these contexts, the Groups must also be flexible enough to permit creative investigation in light of unexpected opportunities. The potential to respond quickly to

promising data and innovative ideas is an important facet of the Clinical Trials Cooperative Group Program, and Groups should modify plans when the data warrant.

IV.2.C. Collaboration with CTEP Staff

CTEP staff assess particular research trials from the perspective of all scientific opportunities competing for support by the Program, and in the context of established national research priorities. Because of the major effort and commitment of resources required to develop and successfully mount definitive Phase III trials, CTEP staff should be involved by the Group in the planning of such trials at the earliest possible stage (see section IV.3.A. and B.). The same applies to the research plans referred to in section IV.2.A., and especially to broad new initiatives undertaken by the Group.

IV.2.D. Prioritization by the Group

In addition to providing an environment for the development and conduct of good clinical trials, the Group executive leadership has the responsibility for managing the research resources of the entire Group. This task is best accomplished by maintaining a clear sense of scientific priorities for the competing ideas of all of the Group's research committees. As each disease and/or modality committee formulates plans and specific protocols, the Group leadership must prioritize the plans and studies in the context of the Group's overall scientific objectives.

IV.2.E. Efficiency of Study Development

The administrative structure of a Group should support rapid development and activation of the most important protocols. In this regard continual assessment of overall priorities is essential.

IV.2.F. Timely Completion of Studies - Participation in Intergroup Studies

It is essential that all Group studies arrive at their conclusions rapidly enough to be meaningful in light of the rate of evolution of new ideas regarding the disease under study. This goal often can be met by a single Group. When it cannot, however, Intergroup collaboration is a more appropriate method of investigation. Intergroup studies as components of a defined research plan are neither more nor less valuable than single-Group studies; they are, however, more appropriate than single-Group trials that cannot satisfy the requirement for timely completion. A Group is entitled to special recognition by peer review when its investigators have played a major role in the development, leadership, or accrual for Intergroup studies.

Intergroup study guidelines, Guidelines for the Conduct of Intergroup Studies, (revised December, 1993 - available from CTEP staff) have been developed by the Groups and endorsed by CTEP with the intent of facilitating this mechanism of trial conduct. In general, Intergroup collaboration is most likely to succeed when all parties have had an

opportunity to participate in the entire process of study development, thereby developing a sense of commitment to the study, and when the mechanics of trial conduct are established from the inception of the study.

IV.2.G. Maximizing Available Financial Resources

Each Group should attempt to accomplish its major goals within the limits of its peer-reviewed and approved scope of work and its allocated budget. This includes reprogramming non-restricted funds when necessary to support initiatives of the highest priority.

The responsibility for overall financial management also includes careful consideration of the financial impact of research plans, not only on patient care costs but also on the short term and long term costs associated with data collection, data analysis, quality assurance and on-site auditing. To the extent consistent with good science, cost containment at all levels of study conduct should be a factor in protocol design.

IV.3. SPECIFIC CTEP RESPONSIBILITIES

IV.3.A. Coordinate National Priorities

For common and/or treatable malignancies CTEP staff will be responsible for maintaining a clear set of national priorities for treatment research, based upon substantial consultation with experts in the field. In selected disease or modality areas, particularly when spontaneous Intergroup planning does not occur, CTEP staff will coordinate the organization of ad hoc strategy committees which will identify in general terms research issues in need of study in major Phase III trials and establish priorities among those competing ideas. These committees will be composed of investigators with established expertise in the particular field, and in most instances will consist primarily of extramural scientists drawn from the Groups. CTEP staff will be responsible for prompt dissemination of the recommendations of these committees, particularly their statements of research priorities. Phase III studies developed by the Groups should be responsive to these priorities, or be equally worthy of NCI support. Under nearly all circumstances, however, studies are written by Group investigators and represent the work of the Groups.

IV.3.B. Participate in Major Study Development

CTEP staff will continue to be active participants in the development of studies that require a major commitment of financial resources and/or patient accrual. CTEP staff will serve as a resource to the Groups for information on national priorities and ongoing efforts within the scientific community. CTEP staff will formally review study concepts for programmatic interest, and for conceptual duplication with ongoing research elsewhere; to the extent possible CTEP staff will also assess feasibility and proposed

methodology (see IV.3.E.). CTEP staff can most effectively facilitate Intergroup collaboration or marshal special resources early in the process of study development.

IV.3.C. Maintain Active Scientific Liaison

Each Group has a staff physician from the Clinical Investigations Branch, CTEP, who acts as liaison for scientific matters. S/he serves as the primary contact for scientific inquiries, information concerning the content of specific protocol or concept reviews, and feedback on general scientific direction of Group committees or on Group plans. The scientific liaison monitors the Group's progress and attends the Group's meetings. S/he is responsible for knowledge of the Group's repertoire of studies, areas of special interest and expertise, and unique resources. S/he is also responsible for providing the NCI Program Director with ongoing assessments of Group activity from an administrative perspective (the scientific liaison has a general knowledge of the Group's budget, but primary responsibility in that area rests with the NCI Program Director, section IX.1, and the Grants Management Specialist, section IX.2).

IV.3.D. Coordinate Investigational Agent Development

The clinical development of new anticancer agents is a highly important utilization of Group resources, when carried out as a component of an overall strategy for study of a given disease. The Groups are a vital component of the research apparatus necessary for the clinical development of the many new investigational agents sponsored by the DCTDC.

The DCTDC responsibilities for this development are shared by all Branches of CTEP. The Investigational Drug Branch is responsible for 1) planning within CTEP and with members of the extramural community overall strategies for new agent studies in specific tumor types; and 2) coordinating and monitoring the trials of new agents developed by the DCTDC. The Pharmaceutical Management Branch provides for the distribution of investigational new agents for which DCTDC is the sponsor. The Regulatory Affairs Branch maintains close contact and ongoing dialogue with the pharmaceutical industry and with the Food and Drug Administration (FDA) in order to ensure that new agent development complies with Federal regulations and proceeds in a coordinated way. The Clinical Investigations Branch is involved in promoting comparative clinical trials evaluating treatment strategies using new agents versus appropriate control therapies. The Biometric Research Branch assesses proposed designs for evaluating the benefits of investigational agents. The Clinical Trials Monitoring Branch verifies adherence by the Groups to the quality assurance procedures of investigational agent trials. CTEP utilizes a system of Letters of Intent (LOIs) as a mechanism for developing rational strategies for drug development studies. The Investigator's Handbook, A Manual for Participants in Clinical Trials Sponsored by the Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, revised 10/93, fully describes the process for the clinical development of investigational agents and summarizes the responsibilities of investigators conducting these trials.

IV.3.E CTEP Protocol Review

All protocols using Group resources must be filed with the CTEP Protocol and Information Office. Cooperative Group protocols in the following categories must be reviewed and approved by CTEP before activation:

All protocols utilizing resources provided to the Group by DCTDC and investigational agents or investigational devices, regardless of IND- or IDE-sponsor

All protocols requiring accrual of 100 or more patients

All Phase III protocols

Protocols requiring fewer than one hundred patients which utilize commercial agents only will receive full review. However, approval will be based only upon consideration of safety and regulatory issues. This includes BMT studies.

Large clinical trials involve years of effort and a substantial expenditure of resources. When planning a Phase III trial, Group Headquarters must submit a concept summary for CTEP review, including an overview of the study objectives, a brief review of the background or justification for the study, a general description of the patient population, a treatment schema and an estimate of the required accrual. In the event of an Intergroup study, the Coordinating Group must submit the concept, also providing a list of the participating Groups and identification of the study chairman, study coordinators from each participating Group, and modality co-chairs. CTEP will then formally review and provide a written Program Concept Review commenting on study design and programmatic interest.

Accordingly, protocol review will be the final step in an interactive process, at least for large Phase III trials. Major conceptual disagreements should not occur at this stage, but rather have been resolved earlier. Protocol review should serve to check the details of a particular clinical trial prior to its activation.

To expedite appropriate review, each protocol should contain all the information necessary for any reviewer to make an informed decision about its merits. A brief statement concerning the place of a specific protocol in the Group's disease strategy is particularly important for pilot and Phase II studies, and should be included with the background and scientific rationale. Additional details on protocol content can be found in the Investigator's Handbook.

NOTE: Each protocol should address gender and minority inclusion as stated in the NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research and PHS 398, Rev. 5/95; when Phase III clinical trials are proposed, investigators must show whether clinically important gender or race/ethnicity

differences are to be expected, and the trials should be designed to accommodate any differences (PHS 398, Rev. 5/95, pages 17 and 28-3 0.)

The CTEP Protocol Review Committee (PRC) meets weekly; it is chaired by the DCTDC Associate Director responsible for CTEP (AD, CTEP). The membership includes the entire CTEP professional staff and occasional invited consultants. The PRC bases its judgments on several factors, including:

1. The importance and relevance of the issue being investigated;
2. The soundness of the study's scientific rationale;
3. The adequacy of the design to evaluate the specific research question(s);
4. The appropriateness of statistical methodology (early stopping, sequential design, etc);
5. The timeliness with which the trial will be completed;
6. The adequacy of the modality sections (e.g., chemotherapy, surgery, radiation therapy, pathology) in describing the study's operation;
7. Representation as Study Chairs or Co-Chairs of investigators within the disciplines involved in the study (e.g., medical, pediatric, surgical, gynecologic);
8. The Group's prior performance in similar studies;
9. The apparent feasibility of the study;
10. The resources required to mount the trial (dollars, patients, agents, etc.);
11. Regulatory, human subjects protection, and administrative and contractual concerns, (e.g., industry collaboration, NCI technology transfer objectives); and
12. Adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

Protocols are reviewed within four weeks following receipt by CTEP. The results of the review are provided in a "consensus review", which is sent to the Group. The PRC's options include:

1. approval as written;
2. approval with recommendations;
3. request for clarifications;
4. request for revisions; or
5. disapproval.

In general, disapproval implies that a study is seriously flawed in its rationale or design, or seriously in conflict with national priorities and without sufficient redeeming features of its own. NCI-awarded funds may not be used to support protocols disapproved by CTEP. All disagreements with PRC review, including disapproval, may be appealed to CTEP. If an unresolvable disagreement persists, an arbitration procedure may be invoked which is described in the Terms and Conditions of Award of each cooperative agreement.

IV.3.F. CTEP Amendment Review

Any change to the protocol document subsequent to its approval by CTEP must be submitted in writing for review and approval prior to implementation. These procedures are outlined in the Investigator's Handbook.

IV.3.G. Facilitate Completion Of Important Trials

CTEP staff will take an active role in promoting the timely completion of important studies, for example by encouraging and facilitating Intergroup collaboration when appropriate, or by assisting in the mobilization of other available and required resources.

V. QUALITY CONTROL, STUDY MONITORING, INDEPENDENT DATA AND SAFETY MONITORING COMMITTEES AND ON-SITE AUDITS

V.1. BACKGROUND AND DEFINITIONS

The multi-center nature of Group trials presents a variety of challenging methodologic problems regarding assurance of quality and consistency in study conduct. The need for formal mechanisms of medical review and quality control is obvious and Groups have developed a number of approaches to these issues.

In addition there are special problems in assuring the safety of individual patients participating in each study, in maximizing their likelihood of exposure to optimal treatment, and in general, ensuring that the interests of patient participants are not subsidiary to those of the scientific investigation. The continual assessment of the progress of studies necessary to achieve these ends is referred to in this document as study monitoring.

A related need is for verification of the accuracy of data submitted from individual investigators to the Group. This need overlaps considerably with the obligation of the DCTDC as a sponsor of investigational agents to visit each site where investigational agents are studied, for the specific purpose of: 1) auditing medical records, and 2) assuring compliance with regulatory requirements of the FDA, including appropriate storage and handling of investigational agents. Each Group is therefore required to establish a system of periodic on-site audits of each performance site, with CTEP oversight of the audit program. This dual responsibility of the Groups and the DCTDC is referred to as the on-site audit program. (see the NCI-CTMB Guidelines for On-site Monitoring of Clinical Trials for Cooperative Groups and CCOP Research Bases.)

V.2. QUALITY CONTROL

Quality control is a complex topic spanning the entire range of diagnostic and therapeutic modalities employed by each Group. Generalization concerning optimal

quality control is impossible. Cost and benefit are obviously important factors in this assessment. Examples of the kinds of considerations to be applied follow:

1. Radiation therapy quality control may involve either simultaneous (rapid turnaround) or retrospective review of port films and compliance with protocol-specified doses for individual patients. Minimal standards for acceptability of equipment may be required. Each radiation therapy facility that treats patients on Group studies undergoes periodic physics review and equipment calibration by the Radiological Physics Center (RPC). The RPC in Houston, TX also supplies each Group's radiation therapy quality control office with the physics data necessary to conduct its case-level review.
2. Chemotherapy quality control is usually carried out through retrospective review of submitted flow sheets, with determination of protocol compliance in dose administration and dosage modification. The criteria vary considerably from study to study and from Group to Group and depend heavily on the specific research questions addressed.
3. Surgical quality control includes assessment by surgeons of the adequacy of protocol-specified surgical procedures through review of the operative notes, study-specific surgical forms, and pathology reports. Standards of acceptability for specialized surgical equipment, or requirements for participation in workshops may be necessary in some instances. Where appropriate, surgical modality committees may wish to draft handbooks of acceptable guidelines for surgical procedures used in studies.
4. Pathology review is usually retrospective and may be either by a committee within the Group or by an external reference panel. Pathology review is not mandated by CTEP for all cases, but should be required by the Group when known variability in the accuracy of histologic diagnosis is a potentially serious problem or when pathology data may provide important prognostic information.
5. Appropriate quality control for other therapeutic and diagnostic modalities is as essential to good data quality as those described above. Standardization of decentralized laboratory procedures (e.g., hormone receptor determinations) is an important case in point.

V.3. STUDY MONITORING

All clinical treatment research carries with it the obligation to ensure optimal therapy for participating patients, and optimal conduct of the research such that the patients' participation is meaningful. In this context accurate and timely knowledge of the progress of each study is a critical Group responsibility and includes the following:

1. Precise tracking of patient accrual to individual studies and the mechanisms to ensure adherence to defined accrual goals;

2. Ongoing assessment of patient eligibility and evaluability and correction of specific problems in this regard;
3. Adequate measures to ensure timely submission of protocol-required data for individual patients;
4. Adequate measures to ensure timely medical review and assessment of these individual patients' data;
5. Rapid reporting of treatment-related morbidity in individual patients and measures to ensure communication of this information to all parties to whom it is important;
6. Prompt assessment of the significance of such information in the context of the entire study's experience;
7. Interim evaluation and consideration of measures of outcome (although to the extent consistent with patient safety and good clinical trials practice such interim analyses should be minimized in frequency; access by participating investigators to interim outcome data should be limited as much as possible; see V.4., Independent Data Monitoring Committees.)

V.4. DATA AND SAFETY MONITORING COMMITTEES

For Phase III trials, Groups are required to establish data and safety monitoring committees (DSMCs) that are independent of study leadership, are clearly free of conflicts of interest, and have formally documented policies and procedures which are approved by NCI. The main objectives of the DSMC are to:

1. Ensure that patients in the trial are protected and that their interests are not made secondary to the interests of scientific investigations.
2. Ensure that evaluation of interim results and decision making about continuation, modification, termination of accrual and reporting of results are made competently based on thorough evaluation.
3. Ensure that the credibility of trial reports and ethics of trial conduct are above reproach with no possible appearance of professional or financial conflicts of interest.
4. a. Enable physicians entering patients to remain free of knowledge of interim efficacy data. This permits physicians to continue to approach their patients honestly and avoids the need to modify informed consent based on non-statistically-significant interim results.

- b. Enable study leadership to remain free of knowledge of interim efficacy data so that they may deal honestly with their peers in encouraging them to enter patients in the study and so that they do not put themselves, or the study, at risk by indirectly divulging interim results.

V.5 ON-SITE AUDIT PROGRAM

V.5.A. Purposes

As a sponsor for investigational new agents, the DCTDC is required by FDA regulations to maintain an on-site audit program. Through formal agreements with the FDA, the DCTDC has delegated much of this responsibility to the Cooperative Groups, although CTEP oversees the program. The specific purposes of the audit programs are to document the accuracy of data submitted to the Cooperative Group, and to verify investigator compliance with protocol and regulatory requirements for all clinical investigations.

V.5.B. Patient Case Reviews

By comparison of submitted data with information contained in the patient's actual medical records, this component of the on-site audit program seeks to assure accuracy and completeness of Group information integral to the assessment of:

- a. Patient eligibility;
- b. Compliance with protocol-defined therapy;
- c. Tumor response;
- d. Treatment related toxicity;
- e. Protocol-required laboratory and diagnostic evaluations;
- f. Overall quality of record keeping;
- g. Concomitant therapy or other information which might affect study results but is not recorded on submitted study forms.

V.5.C. Regulatory Requirements

This component of the on-site audit program is intended to assess:

- a. Documentation of Institutional Review Board (IRB) approvals, reapprovals, and protocol amendments;
- b. Documentation of an IRB-approved, properly signed and dated informed consent document for each case audited, that includes an adequate description of the rules and benefits as contained in the model informed consent submitted to the NCI;
- c. Security of investigational drug handling;

- d. Adequacy of NCI drug accountability records (DAR).

V.5.D. Procedures

Each Cooperative Group must establish and follow an on-site audit program and audit procedures, in accordance with guidelines provided by and available from the Clinical Trials Monitoring Branch (CTMB), CTEP ("NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups and CCOP Research Bases"). Each institution must be visited at least once every 36 months but remains at yearly risk of an audit. Audits are conducted by Group peers, but a percentage of institutions will be co-site visited by CTEP CTMB staff or their agents. Protocols to be reviewed are selected by the Group's Statistical and or Headquarters office in accordance with the above guidelines. A sample of investigational agent studies is always included when the performance site has accrued patients to such studies, as are intergroup studies. Individual cases are then randomly selected by the Statistical and/or Headquarters office for review.

A preliminary audit report is to be FAXed to CTMB within one working day of the audit. A final report of each audit is sent by the Group to CTMB within ten weeks of the audit. CTMB staff review the audit findings as well as the Group's evaluation and response.

V.5.E. Group Evaluation and Response

The discovery of actual fraud or other serious research misconduct during a Group audit has been rare. On the other hand, problems covering a wide spectrum of severity and type are often found. Most are appropriately dealt with by constructive suggestions and are easily remedied through education of investigators and data managers. NCI follow-up is required in the event of findings suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards, as well as other matters of sufficient seriousness. In such instances, the NCI/CTMB staff should be notified by telephone immediately, since other Federal agencies may require notification. Procedures for immediate suspension of accrual at the performance site may be required.

After reviewing the audit report and the Group's response, the CTMB staff may require further action such as a written corrective plan submitted by the institution or a repeat audit within a shorter interval than 36 months. In cases of suspected fraud or other serious problem of compliance with regulatory requirements, CTEP may request formal investigation by the US Public Health Service, the FDA, and/or the Justice Department.

VI. GENERAL OPERATIONAL CONSIDERATIONS

Each Cooperative Group consists of three major operational components: the headquarters (including the Group Chairperson's office), the central statistical/data management office, and the participating investigators and institutions. Each

component has general responsibilities in meeting the goals and objective outlined in Parts II-V of these Guidelines, or in completing tasks necessary to accomplish those goals. Each Group is governed by a constitution and bylaws, which describes membership criteria, procedures for selecting Group leadership and other details of governance, and is led by a chairperson who is ultimately responsible for the content and conduct of the Group's research program. Beyond this requirement, the structure and management of the individual Group is the responsibility of the Group itself to determine. The following sections describe the responsibilities and functions of each of the three operational components.

VI.1. HEADQUARTERS

The Headquarters is the direct responsibility of the Group Chairperson. It provides executive leadership and day-to-day administrative management of the Group. Through this office the Chairperson implements the Group's scientific and organizational policies. Specific roles and responsibilities include the following:

1. Providing general scientific oversight, assuring development of research plans for each disease and/or modality in the Group's repertoire and the maintenance of a clear sense of the Group's overall research priorities.
2. Developing and providing to the Group membership and to NCI, a Constitution and By-Laws specifying Group structure and management, procedures for the selection of the Group Chair and other leadership, terms of office, criteria for membership, and other details of governance of the Group.
3. Providing, to the membership and the NCI, policies and procedures for the conduct of the Group's activities.
4. Serving as the Group's communication and information dissemination hub for investigators and institutions within the Group and individuals and organizations outside of the Group.
5. Providing overall management of the Group's resources, assuring allocation to high priority projects and to the most productive activities and members.
6. Providing logistical and financial support to the Group's scientific committees, monitoring their productivity, and providing for the election/appointment of their leadership.
7. Providing organizational and logistical support for the Group's meetings.
8. Conducting periodic review of the performance and membership status of each performance site (member, affiliate member, CCOP institution, other) according to criteria established by the Group; this review should examine scientific contributions, patient accrual and follow-up, data accuracy and timeliness,

- protocol compliance, audit results and adherence to regulatory requirements. [See Section V].
9. Establishing a Data and Safety Monitoring Committee for Phase III trials in accordance with NCI Guidelines (see Section V.4) and providing organizational and logistic support.
 10. Providing logistical and clerical support to the process of protocol development; developing and implementing standards for protocol format; assuring the timeliness of protocol development.
 11. Assuring internal Group and CTEP review and approval of protocol concepts, final protocol documents, and study amendments; advising CTEP of changes in protocol status.
 12. Producing and maintaining current and accurate Group records.
 13. Overseeing Group compliance with regulatory requirements concerning the use of investigational agents, the reporting of adverse experiences, and the protection of human research subjects (see also 19. and 20. below).
 14. Providing guidance to the membership regarding clinical trials practices, including ethical issues involved in clinical research and conflict of interest considerations.
 15. Developing procedures for study monitoring to assure compliance with protocol design and protection of patients from research risks.
 16. Encourage and provide financial support for the integration of community participation (patients and patient advocates) in the Group's activities by including them in Group meetings and on appropriate committees.
 17. Foster and monitor the inclusion of women and racial/ethnic minorities in the Group's clinical trials.
 18. Coordinating the Group's on-site audit program. [This function may alternatively be placed under the Group's Statistical Office].
 19. Tracking the progress of the Group's research and assuring that results of Group trials are published in appropriate peer-reviewed literature in a timely manner and in accord with Group publication policies.
 20. Assisting member institutions in the process of preparing competing continuation applications.
 21. Verifying that all member and affiliate institutions have an approved Cooperative Project Assurance (CPA) or Multiple Project Assurance (MPA) as required on

file with the Office for Protection from Research Risks (OPRR), DHHS. Physicians in private practice must have an approved Non-Institutional Investigator Agreement (NIA) on file with the Headquarters/Operations Office.

22. Monitoring and maintaining appropriate records of protocols, assurances and annual certifications of IRB review and approval (HHS Optional Form 310) for all performance sites.
22. Providing third party payments to relevant participating institutions which do not hold cooperative agreements from the NCI.
23. Managing and allocating financial resources from the Developmental Fund. The purpose of the Developmental Fund is to provide the Group leadership with resources to support new initiatives, special high-priority projects, and limited funding for candidate members.

VI. 2. STATISTICAL/DATA MANAGEMENT OFFICE

A Group's statistical and data management staff are integral collaborators in all stages of study development, conduct, analysis and reporting. The general operational responsibilities usually assumed by this component include:

1. Ensuring study feasibility and appropriateness of study design with respect to stated study objectives.
2. Ensuring that there are clear and consistent definitions of study objectives, eligibility criteria, primary analysis endpoints, evaluation criteria (such as toxicity and response definitions) and guidelines for removal of patients from protocol therapy.
3. Developing non-standard designs when necessary to achieve specific study objectives.
4. Implementing plans for interim monitoring of study data, including planned interim analyses of studies and timely reporting to the DSMC of all toxicities. Interim study reports should be prepared according to Group policies in this regard. In general, reports of accrual, eligibility, evaluability, and toxicity should be made for each open study on at least a semi-annual basis..
5. Implementing appropriate registration, randomization procedures and accrual tracking procedures.
6. Designing, developing and implementing forms required to collect Group study data.
7. Providing for all aspects of the collection and management of Group study data.

8. Participating in the establishment and conduct of quality control (see V.2) and study monitoring (section V.3) procedures. The Statistical Office may coordinate the Group's on-site monitoring program.
9. Preparing interim study reports according to Group policies in this regard. In general, reports of accrual, eligibility, evaluability, and toxicity should be made for each open study on at least a semi-annual basis.
10. Contributing to all decisions regarding the conduct of Group studies.
11. Performing statistical analyses that use state-of-the art methodology and provide unbiased results.
12. Co-authoring articles and abstracts based on protocol results and other Group data where appropriate; publishing on methodologic issues in cancer clinical trials.

VI.3 PARTICIPATING INVESTIGATORS/MEMBERSHIP CATEGORIES

Investigators participating in Cooperative Group research may come from a wide variety of academic and practice settings. Recognizing current realities of oncologic practice, the NCI provides various mechanisms of financial support for motivated investigators, including the Primary Member cooperative agreement (for members and their affiliates supported directly by NCI's DCTDC), the Community Clinical Oncology Program (CCOP) cooperative agreement (for members supported directly by NCI's DCPC), and third-party payments (subcontracts or purchased service agreements) for member institutions that do not hold cooperative agreement awards, Cooperative Group Outreach Program (CGOP) institutions and/or other performance sites. Individual Cooperative Groups use some or all of these mechanisms. Participating investigators may receive additional headquarters office funds for the conduct of administrative, scientific, laboratory or high priority tasks which are within the workscope of the Group.

The Group shall establish policies and procedures for credentialing participating institutions and conducting periodic review of the performance and membership status of each performance site. This review should examine scientific and administrative contributions, patient accrual, data accuracy and timeliness, protocol compliance, and audit results.

VI.3.A. Primary/Full/Main Members

Primary/Full/Main member institutions are, for the most part, academic centers. In addition to patient accrual, substantial importance is placed on scientific and administrative contributions to the Group. Each Group establishes its own specific criteria for membership and a formal process for application. Institutions are generally initially admitted for membership on a provisional basis. Eligibility for institutional

cooperative agreement awards is limited to institutions which have been granted full membership by the Group, and continued NCI funding is contingent upon maintenance of satisfactory membership status, progress and accrual by the institution and the Group as a whole. Investigators at primary member institutions are expected to:

1. Actively participate in the Group's scientific committees.
2. Serve as Study Chairs responsible for the development and conduct of specific Group studies.
3. Contribute their independent laboratory and clinical research experience to the Group.
4. Actively participate in Group meetings.
5. Accrue patients to Group protocols.
6. Submit timely and accurate patient data to the statistical office.
7. Author manuscripts and abstracts to disseminate the results of Group studies.
8. Participate in the Group's on-site audit program.
9. Serve on Group administrative committees.
10. Periodically serve on NCI site visit teams and peer review committees.
11. Develop community outreach programs that involve patients and patient advocates in the Group's research in a productive and meaningful manner. This effort should be coordinated with the Headquarters/Operations Office.
12. Foster and monitor accrual of women and racial/ethnic minorities to Group trials.
13. Assume responsibility for all Group activities conducted at his/her own institution and at that institution's affiliate/satellite locations. An affiliate or satellite member of a Group is usually a physician or group of physicians which enters patients on the Group's protocols through a member institution. Specific criteria for affiliate membership are the responsibility of the Group, but must be in accordance with NCI policies as specified in the Investigator's Handbook, Section 13. On-site auditing of affiliates must be in accordance with CTMB guidelines. (See Section V.5.D.)

VI.3.B. Affiliate Members

Affiliate Members are proposed by primary member institutions and represent sites of scientific or clinical expertise that are judged by the primary member institution to

contribute significantly to the quality of that institution's programs. Minimum standards for accrual should be established by the Group for affiliate participation. All nominations for affiliate status should be reviewed by the Group Membership Committee and endorsed by the process established by the Group. Affiliates must comply with all OPRR, NCI and Group policies prior to participation.

VI.3.C. Cooperative Group Outreach Program Participants

The Cooperative Group Outreach Program (CGOP) was established in 1977 to involve community physicians, hospitals and their patients in clinical cancer research. The Program supports community investigator networks through funds provided by the Division of Cancer Treatment, Diagnosis and Centers to a Cooperative Group headquarters or statistical center. CGOP investigators affiliate with a funded Cooperative Group, generally through a primary member. They submit data in the same format and according to the same standards as any other member or affiliate investigator. Quality control is assured by the usual Group monitoring and evaluation procedures.

VI.3.D. High Priority Trials Initiative Participants

The High Priority Trials Initiative was implemented by NCI in order to increase accrual to designated studies selected by the Cooperative Group Chairpersons and endorsed by the Board of Scientific Counselors, DCTDC. The Office of Cancer Communications, NCI promotes the designated trials, and clinical trials research in general, through Public Relations activities designed to educate physicians and the public regarding opportunities to participate in clinical trials research. High Priority Trials investigators affiliate with the Cooperative Group through the Operations Office. They submit data in the same format and according to the same standards as any other member or affiliate investigator. Quality control is assured by the usual Group monitoring and evaluation procedures.

VI.3.E. Minority Accrual Initiative Program Participants

The Minority Accrual Initiative was conceived in 1990 in an effort to increase the accrual of racial/ethnic minority patients onto Group clinical trials and to investigate the basis for observed differences in cancer outcome among racial/ethnic groups. Activities supported through this program include reimbursement of performance sites for increases in accrual of minority patients over previously established baselines; translation of patient education materials into languages other than English; training for investigators to enhance skills for recruiting minority patients; and the recruitment of translators and patient advocates to help with accrual and follow-up of minority patients. These efforts are supported by funds provided to the Operations Office; performance sites submit data in the same format and according to the same standards as any other member or affiliate investigator.

VI.3.F. Community Clinical Oncology Program (CCOP) Participants

CCOP participants are funded by the Division of Cancer Prevention and Control (DCPC). They are community-based organizations which participate in Cooperative Group treatment protocols and cancer prevention and control research studies based in Cooperative Groups or in cancer centers. DCPC periodically publishes a Request for Applications (RFA) for CCOP funds in which the application process, eligibility and funding criteria are described. CCOP participants affiliated with a Cooperative Group have access to Group protocols approved by the Group and by NCI for CCOP accrual, and submit data in the same format and according to the same standards as any other member or affiliate investigator. Group operations/statistics offices are funded by DCPC through separate research base awards to support the additional administrative responsibilities for and analysis of the data supplied by CCOP members. Duplicative funds should not be requested in applications to be funded by DCTDC, nor may funds awarded to the Groups be rebudgeted for accruals.

VII. APPLICATION PREPARATION - SPECIAL INSTRUCTIONS**VII. 1. GENERAL INFORMATION**

Financial assistance is provided to the Groups by NCI in order to help cover the costs involved in performing peer-reviewed and approved research-related activities. It is recognized that available funding in recent years has not been adequate to offset research costs completely. For clinical trials research, research costs include:

1. Data Management - the time and effort related to the data management inherent in patient accrual and follow up.
2. Physicians - the time and effort involved in direct interactions with the patient due to the participation of the patient in the research, and the time and effort related to the intellectual activities required for development and implementation of clinical trials.
3. Laboratory investigations - the time and effort related to additional laboratory investigations specific to the research goals of the project, i.e., not associated with conventional patient care.
4. Administrative - the time and effort related to necessary management-related activities, compliance with regulatory activities, quality assurance and study monitoring procedures. If a site serves as a center for satellites, it must have resources to assure proper monitoring of these sites.
5. Supplies, Equipment, and Other - the costs associated with miscellaneous supplies, equipment, and other expenses and costs necessary to conduct the research.

6. Travel - for the purpose of meeting to develop the research agenda, discuss research results and to perform on-site audits of primary patient data.

Applicants are instructed to develop their requested budgets, and the Initial Review Groups (peer reviewers) are instructed to recommend budgets, based on the FTEs required to accomplish the approved activities. The costs requested are inherently related to the implementation and maintenance of basic systems, the numbers of patients accrued, and the complexity of the study data being processed, but must also be related to the accuracy, quality and timeliness of the information collected. All budget requests must be fully justified.

All new, competing continuation and competing supplemental (Types 1, 2 and 3) applications for support through the Clinical Trials Cooperative Group Program are submitted on Form PHS 398 (Rev. 5/95). These forms are available at most institutional offices of sponsored research; from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 6701 Rockledge Drive, Room 3032, MSC 7762, Bethesda, MD 20892-7762, telephone 301/435-0714; and from the Cancer Therapy Evaluation Program. The standard instructions included in the PHS 398 (Rev. 5/95) application kit are designed primarily for individual research projects, and do not address the unique goals and policies of this Program; this section supplements those instructions.

It is strongly recommended that a letter of intent indicating the name of the Principal Investigator, Institution(s), Group and estimated cost be submitted six months in advance of the application submission deadline. A member institution which intends to apply or reapply out of cycle with the parent Group should submit a letter of intent as early as possible prior to the submission of the application. In cases where a new Group submits an application(s) or a member institution application will be in sequence with the competing continuation parent group, only the Group Chairperson need submit a letter of intent. Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NCI staff to estimate the potential review workload and avoid conflict of interest in the review.

The Letter of Intent should be sent to:

Chief, Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment, Diagnosis and Centers
Executive Plaza North,
Room 741
Bethesda, MD 20892-7436
(301) 496-6056

EXPRESS MAIL ADDRESS:
National Cancer Institute

6130 Executive Blvd.
 Room 741
 Rockville, MD 20852

FAX NUMBER: (301) 402-0557

The receipt dates and review schedule are as follows:

<u>Application Due Dates:</u>	Feb 1	Jun 1	Oct 1
<u>Site Visit</u> (if applicable):	Apr/May	Aug/Sep	Dec/Jan
<u>Review Committee Meeting:</u>	Jun/Jul	Oct/Nov	Feb/Mar
<u>NCAB Meetings:</u>	Sep/Oct	Jan/Feb	May
<u>Earliest Possible Funding:</u>	Dec 1	Apr 1	Aug 1

Because of the interrelatedness of various components, all of the individual applications from a particular Cooperative Group should be submitted for review at the same time; similarly, funding recommendations for all of the components are usually of the same duration and time frame. Exceptions include competing supplement applications (see section VII.7), and applications from individual members submitted out-of-sequence with the remainder of the Group (see section VII.8); even in these cases, however, adjustments are made in the award such that funding periods coincide with those of the remainder of the Group.

The guidelines which follow are based upon the operational model of a Cooperative Group described in Part VI, in which there are separate awards for the Headquarters, Statistical/Data Management Office, and individual Primary Group members. This structure is not required. Other models exist and may be more appropriate for some Groups. Nonetheless, this operational model describes the minimum essential elements for a successful Group, and the Group's aggregate application(s) should address these separate considerations regardless of actual Group structure.

All applications, including that of the Headquarters/Operations Office, the Statistical and Data Management Center, and the Primary Members should describe the scientific and administrative experience of key personnel and should include and follow the PHS Form 398 instructions for Biographical Sketches and Other Support information (including support for clinical trials activities.)

On page 2 of the PHS 398 (Rev. 5/95) form, in the section entitled KEY PERSONNEL, it is imperative that all applicants list all individuals and their institutions participating in the scientific execution of the project in the format as specified including those with no requested salary support. All applicants must ensure that the list is complete using as many continuation pages as necessary.

VII.2. HEADQUARTERS (OPERATIONS OFFICE) APPLICATION

The essence of a Group's program of clinical trials should be described in the application for support of its Headquarters. The application should characterize the Group's mission, its plans to accomplish that mission, and present the Group's research accomplishments and its proposals for the upcoming project period. It should outline the Group's strategy for each disease or modality, including rationale and future plans; a clear sense of direction should be evident. The Headquarters application should also contain information describing the Group's organizational structure, and the operating procedures and policies to accomplish major Group objectives and responsibilities.

VII.2.A. Research Plan

The following format is suggested for following items 1-4 of the "Research Plan" section of the standard form 398 instructions.

- a. Major Research Objectives - This section should concisely describe the Group's several major research objectives for the next funding period. This section should include plans for the inclusion of women and minorities as research subjects in Group studies.
- b. Group Organizational Structure - This should include a clear description of the formal organizational structure of the Group, including lines of authority and responsibility, with particular attention to the relationship of the organizational structure to the Group's major objectives. The organizational structure will usually include a number of disease, modality, and administrative committees, in addition to the three major functional components (Headquarters, Statistical/Data Management Office, and Member Institutions). The committees will have various research, quality control, and administrative mandates. Productive interaction of the organizational elements should be described and documented. The current members of the Group's executive committee should be named, along with their subspecialty affiliations. Procedures for the selection of Group leadership should be described. Procedures for credentialing members, for review of their performance, and for ranking member institutions in terms of contributions to the Group, should be described.
- c. Research Strategies - It is essential for the Group and its research committees to develop and articulate comprehensive plans which summarize the Group's specific objectives and lines of investigation for each disease and modality chosen for study (see Section IV.2).

For each DISEASE COMMITTEE, the application should:

- 1) Briefly describe the major scientific accomplishments of the committee during the current project period (interval since last competing application.)

- 2) Identify all protocols (by protocol number) which were active during the current project period, incorporating the information follow. A suggested format is as follows:

	Year 1	Year 2	Year 3Etc.
Initiated	—	—	—
Accruing Patients	—	—	—
Closed to Accrual	—	—	—
Completed Analysis	—	—	—

- 3) Identify and discuss the major current research questions relevant to the purview of the committee.
- 4) Identify and discuss the Group's active and proposed studies in the context of these research questions.
- 5) Identify and describe problems experienced by the committee together with plans designed to address such problems during the next project period.
- 6) List the members of the committee.
- 7) Briefly discuss changes in the committee leadership during the current project period.
- 8) Provide a bibliography (by calendar year for the current project period) for each protocol. Include manuscripts submitted for publication (at the end of each protocol listing).
- 9) Provide a copy of each protocol active at the time of submission of the application.
- 10) Provide a copy of the concept sheets or draft protocols for planned studies (including: statement of study objectives, summary of rationale and pertinent background data, proposed intervention(s) and preliminary statistical considerations).

For each MODALITY COMMITTEE, provide a summary of that committee's scientific and administrative activities using a format such as that suggested in Attachment 1.

- d. Quality Control and On-site Auditing - This section should describe the Group's progress and plans for its programs of quality control (section V.2), and on-site auditing (section V.5).
- e. Group Accrual Statistics - Statistics regarding annual patient accrual, by protocol and institution, for the current project period, will be requested by the review committee prior to the site visit. A patient accession refers to a unique entry on study, not necessarily a patient new to the Group. In the case of entries onto Intergroup studies, the application of the coordinating Group should include data displayed for all participating Groups; applications of participating Groups should indicate their own accrual only. Numbers of patients in active follow-up should be indicated. See Attachment 2 (items 1 and 2) for a suggested format that will aid in the review of your application.
- f. Group Administration - This section should address the major roles and responsibilities of the Group administrative staff described in section VI.1, together with other matters of relevance to the management of the Group. It should document capable, efficient, and responsible management by the Group's leadership, as well as identifying problems and proposed solutions. Applications should clearly document that the proposed Group Chairperson is experienced in dealing with the problems of cooperative clinical cancer research and that s/he has appropriate experience to qualify him/her as the Group's leader.
- g. Accrual of Women and Minorities - Describe the composition of the proposed study population in terms of gender and racial/ethnic group. Include a description of proposed outreach programs for recruiting women and minorities as participants.
- h. Data and Safety Monitoring Committees - the application should describe the Group policies and procedures regarding DSMCs. It should include membership rosters of the committee(s), and procedures for avoiding conflicts of interest, such as financial disclosure procedures.
- i. Group Policies and Procedures - A copy of the Group Constitution and Bylaws, and a current copy of the Group Policies and Procedures, should be provided as an Appendix to the application. The application itself should specifically describe, in addition, Group policies regarding conflict of interest issues, the training of Group investigators, nurses and data managers/clinical research associates regarding ethics in the conduct of clinical research, and procedures in the event of scientific misconduct. The application should document ongoing ethics training of Group participants, collection of conflict of interest statements from relevant members, and other efforts to employ these policies. At the time of the award, the Grants Management Specialist may request an additional copy of the Group's Constitution and Bylaws, and a copy of the Group Policies and Procedures.

- j. Progress Report - A Progress Report is required for competing continuation applications. The progress report may be in the body of the application or submitted as an Appendix to the application. The progress report should include a concise review of the progress of each protocol active during the current project period (accrual, amendments, toxicity, etc.)

VII.2.B. Headquarters (Operations Office) Budget

Since the organizational framework of each Group may be different, the headquarters budget should be presented in logical, discrete units, with specific budgets for each unit (e.g., Cooperative Group Outreach Program, Minority Accrual Initiative) as well as the total headquarters request. A specific budget page for the Group's quality control, study monitoring, and on-site audit programs and Independent Data and Safety Monitoring Committees must be included (see Section V).

A separate budget page and item entitled "Developmental Fund" may be included. The purpose is to provide the Group leadership with resources to support new initiatives, special high-priority projects, and limited funding for candidate members. The first year's plans for this Developmental Fund must be carefully justified, and the Group's process for allocating the funds clearly described where relevant. Previous uses of the Fund should also be carefully described; it is a major factor in peer review assessment of subsequent requests.

It is recommended that quality control services, and all research- and reference-laboratories of the Group, be funded via subcontract from, or consortium agreement with, either the headquarters or the statistical and data management office. (The exception to this policy is for quality control facilities providing services to the entire Cooperative Group Program which are funded under individual U10 awards for these purposes - e.g., the Radiological Physics Center). In this way responsibility for resource management rests most clearly and appropriately with the executive leadership of the Group utilizing the quality control services.

The following budget guidelines apply specifically to the headquarters and statistical office budgets; the categories refer to the item entitled "Detailed Budget for Initial Budget Period" on (Form Page 4) of the PHS 398 (Rev. 5/95) grant application kit.

- a. Personnel - Precise justification for the amount of effort requested for each position is essential.
 - 1) Scientific - research costs include the time and effort involved in developing the research agenda and repertoire of protocols for the Group, and analysis and publication of the results of Group research in peer reviewed journals in a timely manner.
 - 2) Data Management - research costs include the time and effort involved in the central collection, computerization and analysis of primary patient

- data; determination of eligibility; registration and randomization; forms development; etc.
- 3) Laboratory investigations - research costs include the time and effort related to additional laboratory investigations specific to the research goals of the project, i.e., not associated with conventional patient care (note: some Cooperative Groups recommend these activities be allocated by NCI directly, through institutional U10 awards),
 - 4) Administrative - research costs include the time and effort involved in the overall management of the Group's resources, compliance with regulatory activities, quality assurance and study monitoring procedures.
- b. Consultant costs - Reasonable consultant costs are allowed, if the consultant is contributing in a substantial way to the conduct or development of Group research. Most of a Group's consultant costs should appear in the Headquarters budget. Clear and quantifiable justification is required. These costs include travel, per diem and consultant fees, if applicable and within institutional policy.
 - c. Equipment - Justification should include percent of time used for Group business as well as necessity for purchase. The amount of funds requested should be based on the percent of usage. Include only those equipment items that are required to conduct Group protocols.
 - d. Supplies - Research costs include those related to communication and information dissemination among Group members. Quantitative justifications based on actual use should be provided.
 - e. Travel - The importance of meetings to the accomplishments of any Group's research objectives is obvious, as is the necessity to maintain careful control of the size of this budget item. The budget for travel must be itemized and justified. It should include: 1) trips by the Group's leadership and investigators on behalf of the Group to the NCI and other national organizations where the results of the Group research must be represented or where Group research strategies are to be discussed; 2) travel for committee members to committee meetings held separately from the semi-annual Group meetings; 3) travel for protocol chairs and others who must perform quality control functions away from their home institution; 4) travel for persons on the Headquarters staff who must attend the Group's semi-annual meetings; 5) travel for the on-site audit program (Section V.4); and 6) a reasonable number of carefully justified trips for provisional or otherwise unfunded Group members to attend the semi-annual meetings in order to encourage participation and assure input from all relevant modalities is also allowable (see above regarding Developmental Fund).
 - f. Patient care costs - See Section VII.4.B.e.

- g. Alterations and renovations - These costs are not allowable in the Cooperative Group Program.
- h. Other expenses - research costs include those related to communication and information dissemination among Group members. Include here costs of equipment rental and maintenance (copiers, telephones, computers), postage, copying and printing, etc., justified quantitatively on the basis of previous experience, where relevant.
- i. Consortium/contractual costs - research costs include support to Group members who are responsible for committees or laboratory investigations, for Group members whose institutions do not receive institutional U10 awards for the research costs related to approved clinical trials activities, or for patient accrual. For example, these allocations may be provided for the Cooperative Group Outreach Program, for the Minority Accrual Initiative Program, for the High Priority Trials Initiative Program and for otherwise unfunded performance sites. These third party costs may be presented as consortium arrangements (for substantive programmatic work), as subcontracts, or as reimbursements based on formulas.

If third party costs are requested for consortium/contractual participants, a separate detailed budget page, with appropriate justification, must be provided for each arrangement. Indirect costs to consortium/contractual participants are included in the direct cost level for the Headquarters. Groups are encouraged to structure their organization in a manner which minimizes the burden of indirect costs on the overall Group budget.

Reimbursement for patient accrual is to be based on formulas that must relate to the institution's membership category, scientific and leadership contributions, and prior performance including accrual and assessment of data accuracy and timeliness. A description of how the formula was determined, including a line item budget breakdown of the research costs, must be included in the application. In addition, the application must include a plan for disbursement of funds that includes consideration of performance and quality factors including eligibility and evaluability rates; data accuracy and completeness; and quality of on-site audits, etc. The funds received by Affiliates for patient accrual should be subject to modification based on results of the Group's performance reviews. These costs should be included in the consortium/contractual costs category of the Headquarter's budget.

Consortium arrangements and all other contractual arrangements, including all mechanisms for reimbursement for patient accrual, must be formalized in writing in accordance with applicable Public Health Service policy requirements (PHS Grants Policy Statement, revised 9/94, page 8-17). A statement that the applicant organization and the collaborating organization have established or are prepared to establish a formalized agreement that will ensure compliance with all pertinent Federal regulations and policies must be included in the

application. Also include all pertinent biographical sketches and a list of all other support for all relevant consortium participants.

VII.2.C. SPECIAL APPLICATION REQUIREMENTS

VII.2.C.1. On-site Auditing Activities

The NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups and CCOP Research Bases require all institutions to be audited at least once every 36 months. In order for NCI staff to review the Group's compliance with this requirement, each Group should conduct a comprehensive review of its current membership and provide in the competing continuation application an accounting in tabular format (see suggested format - Attachment 4) for all institutions to include: (1) date of affiliation with or termination from the Group; (2) accrual for the immediate preceding 36 months broken down by year; (3) the projected accrual for the upcoming year; (4) the date of the institution's last audit; and (5) the date (projected month/year) of the next proposed audit. This table should follow the budget justification section of the application.

In addition, please provide the following information related to the costs of conducting the audits:

- a. For the immediately preceding budget period, the actual total costs (direct and associated indirect) charged to the Headquarters or Statistical Center, as appropriate.
- b. For the current budget period, the estimated total costs (direct and associated indirect) charged to the Headquarters or Statistical Center, as appropriate. If all audits have been completed, please provide the actual total costs charged.
- c. For the upcoming budget period, the estimated total costs (direct and associated indirect) for conducting the planned audits.

Please provide this information in the Budget justification section. The information may be provided in the format of the Group's choosing.

No Group applications will be funded until all of the Group's required audits are conducted and audit reports are received by NCI. New Cooperative Groups should provide a projected accrual, proposed audit dates and estimated audit costs for the upcoming budget period.

V.II.2.C.2. Provision of Funds to Performance Sites for Accruals

If the Headquarters provides funds to performance sites for accruals (including High Priority and Minority Accrual Initiatives) via per-patient reimbursement mechanisms, (e.g., purchased service agreements or subcontracts), the following information must be provided:

- a. For the current budget period, (i) a list of performance sites that received funds to date in that year; and (ii) the total costs provided to each site (direct and indirect) to date in that year; and (iii) the number of patients accrued for each site to date in that year.
- b. For the immediately preceding budget period, (i) a list of performance sites that received funds to date in that year; and (ii) the total costs provided to each site (direct and indirect) to date in that year; and (iii) the total number of patients accrued in that year for each site.
- c. For the upcoming budget period, (i) the estimated number of accruals and (ii) the estimated total costs (direct and indirect) for each performance site.

The above information may be provided in the format of the Group's choosing and should follow the budget justification section of the application.

VII.3. STATISTICAL/DATA MANAGEMENT OFFICE APPLICATION

In most Groups the Statistical and Data Management Office is funded via a separate cooperative agreement. This arrangement is encouraged by NCI. Occasionally, funding of a single Headquarters cooperative agreement includes operations and statistics/data management. In any event, the operational roles and responsibilities discussed in VI.2. should be addressed in a separate application or a separate section of the Headquarters application. It should describe in detail the Group's data management practices and procedures, its quality control and study monitoring methodology, and its analytical techniques and resources.

VII.3.A. Research Plans

The following format is suggested for following items 1-4 of the "Research Plan" section of PHS Form 398 (Rev 5/95) instructions. Wherever appropriate, narrative should supplement (rather than duplicate or replace) standard manuals, which should be supplied.

1. Roles and Responsibilities - list the major objectives of the Group's statistical and central data management staff.

2. Organization and Facilities - describe the organization and facilities to accomplish the complex tasks of central data management, quality control, study monitoring, and data analysis.
3. Data Management Policies and Practices - describe the flow of data following submission from the individual investigator.
4. Quality Control - describe procedures for quality control and accuracy verification.
5. Study Monitoring Procedures - describe the Group's standard methods for ongoing study monitoring, including interactions with study chairs.
6. Study Design and Data Analysis - describe the Group's routine methodologic practices (e.g., methods of sample size calculations, choice of testing and estimation procedures, interim analysis policies, early stopping procedures, etc.) Include plans for the inclusion of women and minorities as research subjects in Group studies (also required in Headquarters application).
7. Partnership in Group Research - describe the role and contributions of the Group's statisticians to Group research. The involvement of statisticians in designing studies should be documented.
8. Independent Research - describe research being conducted by the statistical office of the Cooperative Group using Group resources, including the data base.
9. Past Problems and Plans for the Future - Problems should be frankly described, together with plans designed to address them in the next funding period.

VII.3.B. Statistical Office Budget

Section VII.2.B. also applies to the Statistical/Data Management Office budget requests. Request for computer systems or other major equipment must be very carefully documented with supporting justification and cost analysis.

VII.4. PRIMARY/FULL/MAIN MEMBERS APPLICATIONS

Each primary member application should concentrate on the contributions of the institution to the Group. Specifically, applications should focus on the roles and responsibilities defined in Part VI.3.A. The clinical trials and research strategies of the Cooperative Group are described in the Headquarters application, and should not be repeated in the individual institution applications. Affiliate investigators associated with primary members must satisfy Group criteria for participation, and may request funds from only one source.

Statistics on recent patient accrual, data quality and scientific/administrative leadership will be obtained from the Group Headquarters immediately prior to the peer review site visit, in order to have uniformly collected and reported information from all Group members. For a suggested format see attachment 2, items 1 and 2. Accrual data regarding inclusion of women and minorities as research subjects, however, must also be reported in the institutional application(s). Specific assets of the institution regarding access to particular patient populations or unusual problems related to patient accrual should be included in the application.

VII.4.A. Research Plan

The following format is suggested for following items 1-4 of the "Research Plan" section described in the standard form 398 instructions. Standardized reporting formats and time frames across the Group are strongly advised. Unless otherwise specified, contributions refer to the current project period, or in the case of new applications to the period of time since first affiliation with the Group. Updates will be requested from Group Headquarters immediately prior to the peer review site visit. For a suggested format see attachment 2, items 3-10.

- a. Summarize the institution's cancer research interest and capabilities.
- b. Describe the scientific contributions of the institution's investigators to the Group, focusing on their roles in shaping the Group's research strategies and in scientific committee leadership. Current committee membership should be listed.
- c. Describe the role of the institution's investigators in chairing or otherwise managing protocols currently accruing patients, identifying the investigators involved with the specific protocols.
- d. Describe institutional pilot studies preparatory to Group-wide studies and other clinical research contributions to the Group.
- e. Identify core services provided by the institution, such as laboratory studies or assays for particular protocols, service on site-visit teams or audits, etc.
- f. List all participants from the institution attending Group meetings (including committee and other special meetings) during the current project period.
- g. List authorship by the institution's investigators of Group publications, with separation of articles published, in press, and in preparation.
- h. Describe past and current participation by the institution's investigators in Group administrative committees (e.g., membership, audit, etc.)

- i. Describe institutional procedures for data management and data submission to the Group. Particular attention should be given to management of data from affiliates.
- j. Describe the organization employed for institutional Group participation. Document adequate participation from and interactions among all modalities and disciplines required for conduct of Group studies. Describe the process for determining intra-institutional protocol priorities.
- k. Describe problems with past institutional participation together with concrete plans designed to address such problems during the next project period.
- l. Accrual of Women and Minorities - Describe the composition of the proposed study population in terms of gender and racial/ethnic group. Include a description of proposed outreach programs for recruiting women and minorities as participants.
- m. Describe the existing affiliate network, if any, identifying affiliated performance sites; describe institutional procedures for processing affiliate data and auditing affiliate charts, if relevant; describe communications systems between the institution and its affiliates.

VII.4.B. Budget

Primary members perform two specific activities - they contribute scientific expertise to the Group, and they accrue patients to Group clinical trials. Institutional budgets should request those costs necessary for conduct of Group studies at the institution and for attendance of a reasonable number of investigators at regular Group meetings. The budget of a typical primary member institution is largely devoted to personnel, although variation from this norm is common. Each institution must develop its request based upon its unique requirements. The importance of meticulous justification for all budget items should be apparent. The Group Chairperson should provide each institution with guidance in the preparation of a reasonable request, in the development of a consistent format for budget presentation, and in the use of consistent formulas for institutional travel budgets. As indicated above, s/he will have been provided with guidance on the Group's aggregate budget by CTEP staff. Any specific fiscal or administrative questions should be addressed to the NCI Grants Management Specialist (Section IX.2).

The following budget guidelines apply specifically to primary member institution applications; the categories refer to the items entitled "Detailed Budget for Initial Budget Period" on (Form Page 4) of the PHS 398 (Rev. 5/95) grant application kit.

- a. Personnel- Precise justification for the percent effort requested for each position is essential.

- 1) Data Management - research costs include the time and effort involved in accurate data collection and submission.
 - 2) Other consultant costs (e.g., pathology, radiology).
 - 3) Intellectual - research costs include the time and effort involved in developing the research agenda and repertoire of protocols for the Group, and preparing the results of the Group's research for publication.
 - 4) Laboratory investigations - the time and effort related to additional laboratory investigations specific to the research goals of the project, i.e., not associated with conventional patient care (note: most Cooperative Groups fund these activities in the Group Operations Office cooperative agreements).
 - 5) Administrative - research costs include the time and effort involved in coordinating research activities at the institution, compliance with regulatory activities, quality assurance and study monitoring procedures and participation in the Group on-site audit program.
- b. Consultant Costs- These are not usually appropriate in a primary member institution's budget. Requests should be justified in detail. These costs include travel, per diem and consultant fees, if applicable and within institutional policy.
- c. Supplies/Equipment/Other - Research costs include those associated with communication with the Group office and with affiliate institutions, the costs of compiling and mailing data and the costs of mailing or handling patient-related specimens, forms, and materials (e.g., slides, X-ray films). Significant equipment costs are unusual; all must be carefully justified. The amount of funds requested should be based on the percent of usage.
- d. Travel - Travel for a reasonable number of the institution's participating investigators, data managers and nurses to attend the regular Group meetings should be included in the institutional budgets. Attendance of investigators at meetings on behalf of the Group, or at special (i.e., non-routine) meetings of committees of the Group should generally be funded through the Headquarters or Statistical Office award, rather than the institution award.
- e. Patient Care Costs - Cooperative Group treatment trials always involve treatment which is administered with therapeutic intent to patients who require medical care, and always involves therapy which is either considered standard medical treatment, or can reasonably be expected to be superior to it. Therefore all costs associated with standard treatment are legitimately borne by third party carriers. Only in the most unusual circumstances would a Cooperative Group clinical trial require interventions beyond those considered state-of-the-art care for cancer patients. In those circumstances, a Group may make a case for reimbursement for patient care costs associated with the

research element. The justification should be presented at the level of the Group headquarters application with specific request from each institution based upon likely accrual to the specific protocol. NCI will not support the costs associated with routine medical care.

- f. Consortium/Contractual Costs - Separate budget pages with detailed justification of all requested items should be submitted for each consortium agreement. Include applicable indirect costs.

Consortium arrangements and all other contractual arrangements, including mechanisms for reimbursement for patient accrual, must be formalized in writing in accordance with applicable Public Health Service policy requirements (PHS Grants Policy Statement, Section 8-17). A statement that the applicant organization and the collaborating organization have established or are prepared to establish a formalized agreement that will ensure compliance with all pertinent Federal regulations and policies must be included in the application. Also include all pertinent biographical sketches and a list of all other support for all relevant consortium participants.

VII.5. Application for New Groups

An organization which chooses to apply to the NCI to establish a new Cooperative Group is strongly advised to consult with CTEP staff at the earliest stage of the planning process. CTEP staff then have maximum opportunity to advise the Group during the preparation of its application(s). While these Guidelines are written specifically for currently funded Cooperative Groups, the principles set forth should be followed in planning a new (first-time) competing application.

VII.6. Competing Continuation Applications

Approximately 4 months in advance of the submission deadline for its competing continuation application(s), the Group Chairperson, Statistician and other executive leadership will be asked to meet with NCI staff to discuss the Group's future directions and plans in detail. While ongoing dialogue is an important feature of the cooperative agreement relationship, this meeting allows both the Group leadership and CTEP staff to focus attention on the application and review process and to discuss a realistic aggregate budget for the Group. Budget information discussed in this regard is, of course, advisory, but will be based on program staff's knowledge of the total clinical trials of the CTEP and the funds likely to be available for competing activities.

The Group executive leadership should work with Group members in the preparation of a standard application format and individual component budgets, developing a total Group application package which, while requesting funds deemed necessary to support the proposed research, is organized and prioritized in accordance with CTEP's budget projections.

VII.7 Competing Supplement Applications

Potential applicants should consult with CTEP staff prior to the submission of a supplemental application. All applications for supplemental support must address a critical need which has developed since review of the basic application. Supplemental applications will not be reviewed if seeking restoration of funds for competing awards made at levels below that recommended by peer review.

VII.8 Applications Out-of-Sequence With the Parent Group's Cycle

These applications are generally from new members of a Group seeking funding for the first time, or are amended applications from previously funded members who received priority scores too low to allow funding at the time of the competing application of the entire Group. Such applications should be submitted in the same format as described in section VII.4., and will undergo peer review using the same criteria as described in section VIII.3.C. Although there is usually no site visit, a supporting evaluation of the institution's performance as a Group member will be obtained from the Group Chairperson by the Scientific Review Administrator of the Clinical Groups Subcommittee. Applications out-of-sequence with the parent Group's review and funding are generally not encouraged. Should an award be made, it will be phased in such that its budget periods and renewal date coincides with those of the Group's. Potential applicants and the Group Chairperson should consult with CTEP staff prior to the submission of such applications.

VIII. PEER REVIEW

Upon receipt, applications will be reviewed for completeness by DRG and for responsiveness by the NCI. Incomplete and non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to these Guidelines will be evaluated for scientific and technical merit by the Clinical Groups Subcommittee (formerly the Cancer Clinical Investigations Review Committee or CCIRC) of the National Cancer Institute in accordance with the review criteria stated below. This chartered peer review subcommittee is multidisciplinary and encompasses all oncologic specialties, cancer control, statistics, and cooperative group administration.

The full subcommittee review is usually preceded by a site visit to the Group's statistical and data management facilities. The site visit team generally consists of subcommittee members plus ad hoc reviewers as indicated by the proposed research plan. The Scientific Review Administrator of the subcommittee is responsible for all aspects of the peer review process, and will negotiate with the Group chairperson the date, duration and content of the site visit. The Scientific Review Administrator will request from Headquarters, for use at the site visit, complete patient accrual records for each institution as well as performance evaluations based on committee membership, data

quality and other Group standards; these may be supplied in the form of tables. The findings of the site visit team are provided to the subcommittee during its consideration of the application at its regular meeting. The initial peer review process provides the NCI with a critical assessment of the Group's research capabilities and plans. It also provides important feedback on the functioning of the cooperative agreement relationship between CTEP and the Group. The major emphasis of the review is on the quality of the future research plans projected for the subsequent period of support requested in the application.

The recommendations and priority score(s) voted by the subcommittee are presented to the National Cancer Advisory Board (NCAB) for second level review and recommendation to the NCI. Final funding decisions are then made by the NCI for those applications recommended for approval by the NCAB.

VIII.1 GENERAL CONSIDERATIONS OF COOPERATIVE GROUP REVIEW

Because of their interrelatedness, all applications from all components of a particular Cooperative Group are reviewed simultaneously (except in the case of member applications submitted out-of sequence with the parent Group, section VII.1.D., or competing supplement applications, section VII.1.C.). Using the operational model of Part VI, the content of the Headquarters application is first evaluated; this review is an integral part of the review of each individual application of the Group, regardless of component. The review group then votes either to (i) recommend the application for scoring or (ii) not recommend it for further consideration. If the application is recommended for scoring, the subcommittee assigns a priority score representing the overall peer review evaluation of the Group and recommends a period of award (generally three to five years). If the Headquarters application is scored, the review group then evaluates the applications of other individual components. The review group also develops budgetary recommendations for each scored application concerning the effort and resources needed to perform the approved research. If the Headquarters application is not recommended for further consideration, the applications of the individual components are not reviewed and the Group's applications cannot be funded.

VIII.1.A Scientific Committee Review

A review of the Group's scientific committees and plans is the first stage of the Group site visit. Its major focus is the research of the Group as reflected in its protocols and working plans. For each area of Group study, all currently active protocols and all correspondence between CTEP and the Group related to each protocol, including the PRC's consensus reviews, are provided to the committee. With this background the team then makes an assessment of the Group's research approach and plans for each area.

VIII.1.B. Group Management, Study Conduct, and Membership

The focus of the site visit then broadens to the whole Group. This includes the Group's science as reflected in its research priorities and clinical trials practices, all aspects of its management and administration (including monitoring of data quality, both centrally and on-site, and adherence to regulatory requirements) as an organizational unit developing and conducting clinical trials, the cohesiveness of its components, and the quality of its primary members. Time is provided for the Group Chairperson to meet with the site visitors in an executive session; some of this time is devoted to a discussion of individual member institution contributions.

VIII.1.C. Parent Committee Reviews

Initial peer review is completed by the Clinical Groups Subcommittee of the National Cancer Institute Initial Review Group. This body reviews the application(s) submitted by the Group as well as the site visit report. The subcommittee brings a broad and consistent perspective to the review of the Clinical Trials Cooperative Group Program; priority scores for each scored application are assigned by the subcommittee.

VIII.2. REVIEW CRITERIA

The review criteria employed by the site visit team and the Clinical Groups Subcommittee for each of the three operational components are summarized in the following three sections.

VIII.2.A. Group Headquarters

1. Merit of Specific Research Plans - How meritorious are the research plans and strategies for each of the major areas of study? Are they appropriate in the context of national priorities? Are guidelines for the inclusion of women and minorities as research subjects being followed?
2. Research Methodology - How well designed are the Group's planned clinical trials? Will their design allow clinically important conclusions to be drawn?
3. Publication Record - Is the Group's research published in a timely manner and in quality peer-reviewed journals?
4. Translational Research - Is there a well defined plan to integrate correlative studies into the overall research effort? While not required, the capacity and expertise within the Group to develop innovative research ideas based on laboratory models and pilot these in limited institution trials with an eye to their potential use as experimental arms in phase III trials is a strength.

5. Key Personnel - Does the research experience and qualifications of the Principal Investigator demonstrate understanding of design, administration, and analysis of multi-institutional clinical trials in cancer treatment and relevant laboratory studies?
6. Patient Accrual - Is the membership of the Group adequate to mount multiple, concurrent, large-scale clinical trials
7. Efficiency of Study Development - Does the process of study development proceed in an efficient and timely manner? Are important studies rapidly developed and implemented?
8. Timeliness of Study Completion - Is the Group able to carry out its planned studies in a reasonable period of time? Is Intergroup collaboration utilized when necessary to satisfy the requirement for timely completion? The Group is entitled to special recognition by peer reviewers when its investigators have played a major role in the development, leadership, or accrual for Intergroup studies.
9. Overall Group Priorities - Are the priorities of the Group appropriate? Are its resources well directed?
10. Developmental Fund Plans - Are the specific plans for the developmental fund appropriate and consistent with the Group's overall goals and priorities? Has the fund been well managed and wisely used in the past?
11. Group Structure and Administration - Is the Group well administered by the Chairperson and the Headquarters staff? Does its organization and infrastructure allow it to meet its major objectives and goals?
12. Group Cohesiveness - Does the Group function as a cohesive research team?
13. Interdisciplinary Coordination - Is there adequate interdisciplinary participation in protocol development and design? Do protocol investigators reflect the modalities utilized?
14. Quality Control - Are the Group's mechanisms of quality control adequate and functioning in a manner which ensures accurate data?
15. Membership - Are the criteria for initial and continuing membership adequate? Do the Group's periodic evaluations of its members result in an optimal membership roster?
16. Companion Research - While not required, Group involvement in epidemiologic, diagnostic, cancer control, quality of life, cost- effectiveness, and prevention research, especially as it relates to or follows logically from the Group's prime therapeutic mission, is a strength.

17. Patient Advocate Participation - Are there defined plans and roles for patient advocates in the Group? Have they been included in the budget to attend Group meetings?
18. Adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.
19. Facilities - Are the offices, computer support systems, and overall parent facility commitment adequate to ensure a smoothly functioning Headquarters/Operations Office? Are there any problems with the structural layout that might serve as an impediment to a focused and well coordinated Operations Office?
20. Staff - Are the roles of the Headquarter's staff adequately defined to accomplish the goals of the Group? Is there an adequately defined staff to cover the multiple tasks which are the responsibility of the Operations Office.
21. Budget - Have costs for travel, office supplies, equipment and data management been adequately justified? Are detailed costs of Affiliate members provided? Are budgetary plans submitted for Group meetings and consultant fees? Have costs for the on-site audit plan been accurately detailed? Is there sufficient funding allotted to carry-out the multiple quality control tasks required?

VIII.2.B. Statistical and Data Management Office

This portion of the evaluation involves two facets: 1) the performance and capabilities of the Statistical and Data Management Office; and 2) the Group's integration of the Statistical and Data Management Offices' roles and responsibilities into the overall research program.

1. Collaboration in Research - Is there adequate statistical and data management collaboration in the development and conduct of the Group's research?
2. Adequacy of Study Design - Are the protocols properly designed statistically? Are the sample sizes adequate to detect realistic and medically important differences? Are the assumptions adequately justified? Is the expected accrual rate carefully estimated? Are the designs used appropriate for the study questions? Are endpoint selections and sequential monitoring plans adequately described and justified?
3. Data Management - Are data management procedures adequate, appropriate, and consistent with accepted standards? Are procedures for the verification of data accuracy adequate? Is there clinical review of study data? Do quality

assurance and quality control programs exist, including on-site audits that assure high-quality research and patient safety?

4. Statistical Analyses - Are analytical techniques, procedures, and policies adequate, appropriate, and consistent with accepted standards? Is there evidence that past publications of the Group Leadership demonstrate thorough and state-of-the-art methodology, awareness of problems of multiple analyses, and sufficient independence and lack of bias of statistical collaborators?
5. Key Personnel - Does the research experience and qualifications of the Principal Investigator demonstrate understanding of design and analysis of multi-institutional clinical trials and relevant laboratory studies? While independent research is not required, involvement in research related to the design, conduct and analysis of cancer clinical trials is a strength.
6. Adequacy of Procedures - Are data management procedures adequate, appropriate, and consistent with accepted standards? Are procedures for the verification of data accuracy in place? Is there clinical review of study data?
7. Adequacy of Staff - Are the statistical and data management staff capable of carrying out their special responsibilities? Are the roles of the staff adequately defined to accomplish the goals and meet the responsibilities? Is there an adequate number of personnel to meet the assigned tasks?
8. Facilities - Are the offices, computer hardware, and overall parent facility commitment adequate to assure smooth and efficient function? Are there deficiencies in the structural layout which might serve as an impediment to coordination of Group research efforts? Are computing resources adequate and appropriate to support Group activities as needed?
9. Budget - Have costs for the on-site audit plan (if relevant) been accurately detailed? Is there sufficient funding allotted to carry-out the multiple quality control tasks required?

VIII.2.C Primary Members

Both scientific and administrative contributions to the Group, and patient accrual and data quality enter into this evaluation.

1. Contributions to Group Science - What are the contributions of the institution's investigators to the Group's research strategies and plans? Do the investigators chair research committees and studies? Although translational research is not required, the ability to conduct pilot trials which can then serve to foster the Group's research goals is a strength.

2. Patient Accrual - Is the record of patient accrual appropriate in the context of Group standards? Are projections for the future reasonable and adequate? Are women and minorities appropriately included as research subjects on Group trials?
3. Key Personnel - Does the research experience and qualifications of the Principal Investigator demonstrate understanding of the conduct of multi-institutional clinical trials in cancer treatment and relevant laboratory studies?
4. Participation in Group Activities and Administration - Do the institution's investigators participate in Group activities and meetings?
5. Interdisciplinary Coordination - To the extent required by the Group's research, is there adequate interdisciplinary cooperation and coordination?
6. Data Quality - Are the recent data complete, accurate, and submitted in a timely fashion?
7. Protocol Compliance - What is the recent record of the quality of protocol participation?
8. Data Management - Are the institution's data management practices and procedures adequate and appropriate?
9. Publication - Do the institution's investigators contribute to publication of Group studies?
11. Adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.
12. Facilities - Are the treatment facilities adequate to carry out clinical research? Does each Affiliate have a well organized central site which will coordinate the activities of its members?
13. Is there adequate data management and high quality nursing support to meet the patient care and data submission needs of clinical trials? Is the relationship between Affiliate and their Main Members carefully explained, including the responsibilities of the P.I. at each institution?
14. Budget - Have costs for on-site auditing of Affiliates been included (if this is the mechanism chosen by the Group for auditing of Affiliates)? Are travel and equipment costs adequately detailed? Is there adequate justification of personnel costs?

IX. MISCELLANEOUS ADMINISTRATIVE CONSIDERATIONS**IX.1. CTEP STAFF ADMINISTRATION**

Within CTEP, major scientific policy and programmatic decisions concerning the Clinical Trials Cooperative Group Program are made on a corporate basis, with involvement by the Program Director, the Branch Chiefs and Section Heads, the CTEP scientific liaison to the Group, and the Associate Director, as necessary and appropriate. Actual programmatic administration is the responsibility of the Program Director, who assures uniformity of implementation across the various Groups.

IX.2. GRANTS MANAGEMENT STAFF ADMINISTRATION

A Grants Management Specialist of the Grant Administration Branch, NCI, is responsible for the fiscal and administrative aspects of each application and award. The specialist works closely with the CTEP Program Director to assure that appropriate science is funded in accordance with applicable laws, regulations, policies and peer review recommendations and to the extent that the budget allows and NCI priorities dictate.

IX.3. NON-COMPETING CONTINUATION APPLICATIONS

Approximately 4 months prior to the award's anniversary date, each cooperative agreement awardee receives a face page for form PHS 2590 (Rev. 5/95) from NIH. CTEP staff will supply a suggested format (Attachment 3) to be followed for the Progress Report Summary section of the application ("Format for Non-Competing Continuation Applications for NCI Clinical Trials Cooperative Group Program Cooperative Agreements"). The intent is to focus the awardee's reporting on the specific information needed for an adequate evaluation of progress. The format will vary depending on the operational component (Headquarters, Statistical/Data Management, or Primary Member), but will be similar to that described above for the competing application.

IX.4. NON-COMPETING CONTINUATION BUDGET ADJUSTMENTS

Adjustments in the relative funding of the various components of a Cooperative Group at the time of non-competing continuation award represent one method of providing the Group leadership with flexibility in allocating the total resources supporting the Group. Such adjustments have the potential to provide the Group and the NCI with a program that ensures that those funds are put to their best use. Requests for the adjustments are initiated by the leadership of the Cooperative Group. They involve negotiation of awards by the NCI to reflect the increased or decreased level of activity at an institution. The effect of any such adjustments may be reflected in the adjustments to the previously committed level of future years' awards. Authority to effect an adjustment rests with NCI Grants Management staff, who act in conjunction with the Program Director.

Initial budget recommendations for subsequent years are based upon the funding level for the competing year. Increases or decreases in cooperative agreement funding may be made on the basis of changes in performance relative to that approved in the last competing application or in the current year. Funds may be awarded upon demonstration of satisfactory progress as detailed in each non-competing continuing application. They are always, of course, subject to the availability of funds. Thus, funding levels can be increased or reduced because of increments or decrements in performance on the part of the cooperative agreement awardee, or the Group as a whole, or a change in the funds available to the government for distribution.

IX.5. CHANGES OF AWARDEE INSTITUTION

Only under exceptional circumstances will NCI permit transfer of a primary membership cooperative agreement from one institution to another, as such a transfer would be without the benefit of peer review of the recipient institution. The Program Director and the Grants Management Specialist should be consulted for further advice if such a request is contemplated by the Group.

IX.6 TRANSFER OF GROUP MEMBERSHIP

Only under exceptional circumstances will NCI permit the transfer of institutional membership from one Cooperative Group to another, as the institutional awardee has undergone peer review only in the context of participation within the original Group. In all cases the transfer must be mutually acceptable to both involved Groups and to the NCI. Data submission to the original Group remains the responsibility of the institution.

IX.7. MULTIPLE GROUP MEMBERSHIPS

Membership of a single institution in two or more Cooperative Groups having largely overlapping research interests and objectives is inappropriate and will be permitted by NCI only on an exception basis. This policy is not intended to prohibit or discourage participation of members of an adult mult-disease, multi-modality group in one or more subspecialty Groups. In such cases, however, particular attention must be given to lines of patient referral and the avoidance of any possibility of selection bias or dual protocol availability for a single patient population at the institution.

IX.8. PIs NOT EMPLOYEES OF AWARDEE ORGANIZATION

If the P.I is not an employee of the awardee organization there must be a formalized agreement in writing delineating the PI's responsibilities. The PI must have a formal appointment with the applicant organization, which is characterized by an official relationship between the organization and the individual. Such a relationship does not necessarily involve a salary or other form of remuneration. In all cases, however, the individual's official organizational relationship must entail sufficient opportunity and

physical resources for the PI to carry out his/her responsibilities for the overall scientific and technical direction of the project and for the organization to provide administrative and financial oversight of the project. Each competing application must include an explanation of the arrangement in sufficient detail to permit evaluation prior to award.

IX.9. INDUSTRY/GROUP/NCI INTERACTIONS

It is appropriate for the Cooperative Group to conduct clinical trials of interest to, and partially supported by, a pharmaceutical firm, provided that the trials have scientific merit in the context of the national research priorities, and are consistent with the overall goals of the Group. A formal policy statement in this regard has been developed by the CTEP, the Cooperative Groups, and representatives of the pharmaceutical industry. It addresses such issues as trial planning, protocol review, resources provided by the private sector for trial conduct, and data rights, confidentiality, and publications. For further information, refer to Appendix 1, "Relationships Between Pharmaceutical Industry and Therapeutic Trials in the Clinical Cooperative Groups Supported by the National Cancer Institute", contained in the Investigator's Handbook, published by NCI, October 1993. In addition, CTEP will provide a suggested protocol section to address intellectual property rights and proprietary data issues.

Information on pharmaceutical industry support for NCI supported studies must be included on the "Other Support" page of the application. If program income is earned it must subsequently be reported and accounted for in accordance with the instructions on the annual financial status report (PHS Form 269).

X. TERMS AND CONDITIONS OF AWARD**A. AWARDEE RIGHTS AND RESPONSIBILITIES**

The awardee's programmatic responsibilities for the conduct of the research supported by this cooperative agreement are described in the CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES (Sections I-IX); the INVESTIGATOR'S HANDBOOK, (a Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute); and the NCI-CTMB GUIDELINES FOR ON-SITE MONITORING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS AND CCOP RESEARCH BASES, and any subsequent modifications of these documents. Specific portions of these documents, as enumerated in the following sections, are incorporated by reference as terms of award. These documents are available from the Cancer Therapy Evaluation Program (CTEP) upon request.

Throughout these Terms and Conditions of Award "Participant" refers to all awardees as well as all institutions and/or individual investigators, both funded and unfunded, with whom they are participating or collaborating.

1. Development of Cooperative Group Research Agenda and Protocols

It is the responsibility of the Cooperative Group (henceforth termed the Group) in accordance with its constitution, bylaws, policies and procedures to develop the details of the research design, including definition of objectives and approaches, planning, implementation, analysis, and publication of results, interpretations and conclusions of studies. The Group shall, with CTEP assistance, develop Group research goals in accord with national research goals and develop protocols for clinical cancer research in accord with the Group's research interests, abilities and goals. The Group Chairperson shall designate other Group investigators to serve as Protocol Chairpersons for each proposed study. Protocols will be developed in accordance with the instructions in the CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES, and the INVESTIGATOR'S HANDBOOK. The INVESTIGATOR'S HANDBOOK is reference handbook for all investigators who use DCTDC-sponsored investigational agents in their clinical trials, irrespective of funding mechanism. The INVESTIGATOR'S HANDBOOK describes, in accordance with NCI-FDA agreements::

- o Requirements for Protocol Development and Submission
- o Ordering Investigational Drugs from NCI
- o Responsibility for Reporting of Results to CTEP
- o Adverse Event Procedures
- o Accountability and Storage of Investigational Drugs
- o Monitoring and Quality Assurance

2. Coordination of Group Activities

In accordance with the Group constitution, bylaws, policies and procedures, the Group Headquarters (or Statistical/Data Management Office as appropriate), under the leadership of the Group Chairperson and with CTEP assistance, is responsible for coordinating protocol development, protocol submission, study conduct, quality control and study monitoring, drug ordering, data management, statistical analysis, protocol amendments/status changes, adherence to requirements regarding investigational drug management and Federally mandated regulations, and protocol and performance reporting. All the scientific and administrative decisions related to the Group funded activities and made by the participating institutions will be coordinated by the Group Chairperson with the assistance of the staffs of the Headquarters, Statistical Office, and/or Data Management Office. The Group Chairperson or designee will be responsible for communication with the appropriate CTEP staff.

3. Protocol Submission

Prior to protocol implementation, the Group Headquarters, under the leadership of the Group Chairperson, will submit the protocols for review to CTEP, or its designated Contractor, in accordance with the instructions in the NCI's INVESTIGATOR'S HANDBOOK and the CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES. It is required that all Phase III protocols be preceded by Concept Review letter describing the hypothesis to be investigated, the general design of the contemplated trial plus relevant information on accrual capabilities to document feasibility. A Letter of Intent (LOI) must be submitted for all Phase II trials that include a DCTDC investigational agent. These two mechanisms for preliminary review are required to expedite protocol development and implementation and to facilitate agreement on study priority and design (see the INVESTIGATOR'S HANDBOOK, pp32-35, for further discussion of these mechanisms).

The Group Chairperson, with the assistance of the Group Headquarter's staff, will communicate the results of the NCI review of protocols to the participating institutions.

4. Group Compliance with Federally Mandated Regulatory Requirements

The Group must be in compliance with all Food and Drug Administration (FDA) regulatory requirements for studies involving investigational agents and NIH policies applying to the conduct of research involving human subjects. These regulations include but are not limited to Title 21 CFR 50,56 and 312 and Title 45 CFR 46. Participants are required to follow established Group procedures for complying with the Federally mandated regulations.

- a. The Group must be able to demonstrate that each participant has a current approved assurance number on file with the NIH Office for Protection from Research Risks (OPRR).
- b. The Group must be able to demonstrate that each protocol and informed consent is approved by the responsible Institutional Review Board (IRB) prior to

patient entry, and that each investigator has a current FDA Form 1572 and curriculum vitae on file with the Pharmaceutical Management Branch, (PMB), CTEP.

- c. The Group must be able to demonstrate that each patient (or legal representative) gives written informed consent prior to entry on study.
- d. The Group must assure timely reporting of all serious and unexpected toxicities to CTEP.
- e. The Group must establish and maintain an on-site audit program in compliance with the NCI-CTMB GUIDELINES FOR ON-SITE MONITORING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS AND CCOP RESEARCH BASES.
- f. The Group must have a method of providing, upon CTEP request, summary efficacy and toxicity data to be included in DCTDC's annual report to the FDA for each investigational agent.
- g. The Group must implement the CTEP requirements for storage and accounting for investigational agents provided under DCTDC sponsorship.

5. Investigational Drug Management

Investigators performing Group trials are expected, in cooperation with the NCI, to comply with all FDA monitoring and reporting requirements for investigational agents. When new avenues of cancer therapy involving investigational drugs are pursued, the clinical information should be acceptable to the FDA for inclusion in a new drug application (NDA).

6. Quality Control and Study Monitoring

- a. The Group shall establish and implement mechanisms for quality control of therapeutic and diagnostic modalities employed in its trials. Participants are required to follow Group procedures for quality control. Quality control at a minimum should consist of:
 - 1) Pathology: Verification of pathologic diagnosis in cases where known variability in the accuracy of histologic diagnosis is a potentially serious problem and where pathology data may provide important prognostic information.
 - 2) Radiation Therapy: Review (either concurrent or retrospective) of port films and compliance with protocol-specified doses for individual patients. Determination of adequacy of radiation delivery with assistance of the Radiological Physics Center (RPC), whose functions usually include equipment dosimetry, periodic institutional visits and other aspects of physics review.

- 3) Chemotherapy: Review of flow sheets with determination of protocol compliance in dose administration and dosage modification.
 - 4) Surgery: Assessment of adequacy of protocol-specified surgical procedures through review of operative notes and study-specific surgical forms.
- b. The Group shall establish and implement mechanisms for study monitoring and quality assurance. Participants are required to follow Group procedures for study monitoring. The Group is responsible for assuring accurate and timely knowledge of the progress of each study through:
- 1) tracking and reporting of patient accrual and adherence to defined accrual goals;
 - 2) ongoing assessment of case eligibility and evaluability;
 - 3) timely medical review and assessment of patient data;
 - 4) rapid reporting of treatment-related morbidity and measures to ensure communication of this information to all parties;
 - 5) interim evaluation and consideration of measures of outcome as consistent with patient safety and good clinical trials practice;
 - 6) timely communication of results of studies; and
 - 7) an on-site monitoring program.

The awardee is responsible for ensuring that all Main Members and Affiliates have routine audits in accordance with the NCI-CTMB GUIDELINES FOR ON-SITE MONITORING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS AND CCOP RESEARCH BASES and that the results of audits are reported to the NCI in accordance with the guidelines. In the event that the NCI determines that the awardee failed to comply with these guidelines, the accrual of new patients to the Group's protocols at the affected Main Member/Affiliate shall be suspended immediately upon notice of the NCI determination. The suspension will remain in effect until the awardee conducts the required audit and the audit report or remedial action is accepted by the NCI.

The awardee will be responsible for notifying any affected Main Member/Affiliate of the suspension. During the suspension period, no funds from this award may be provided to the Main Member/Affiliate for new accruals, and no charges to the award for new accruals will be permitted. The NCI will also notify an institution that is the direct recipient of a cooperative agreement from the NCI if it is necessary to

suspend accrual at that institution or at a third party institution supported under that institution's cooperative agreement.

c. Quality Assurance and Quality Control of Data

The awardee must follow NCI-approved procedures developed by the Group for the prevention and/or identification of false or otherwise unreliable data and for quality assurance of data collected by the Group. The awardee must follow Group procedures for the assurance of data quality and quality control in accordance with Group guidelines and NCI policies.

In the event that there is a finding through the quality assurance and/or quality control programs of any indication of a pattern of non-compliance with protocol or regulatory requirements or a finding of possible alteration of data, these findings must be reported in accordance with the NCI-CTMB GUIDELINES FOR ON-SITE MONITORING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS AND CCOP RESEARCH BASES.

The awardee must follow policies developed by the Group and approved by the NCI for auditing the accuracy of scientific data submitted by Group participants.

7. Data Management and Analysis

The Group shall establish and implement mechanisms for data management and analysis that ensure that data collection and management procedures are: (a) adequate for quality control and analysis; (b) as simple as appropriate in order to encourage maximum participation of physicians entering patients and to avoid unnecessary expense; and (c) sufficiently uniform across Groups. Participants are required to follow Group procedures for data management and analysis.

8. Data and Safety Monitoring Committees

The Group must establish and maintain a Data and Safety Monitoring Committee (DSMC) for Phase III clinical trials. The policies and procedures of the DSMC must be approved by the NCI. The Group must comply with the approved policies and procedures of the DSMC.

9. Protocol Closure

The Group shall establish and implement mechanisms for interim monitoring of results and monitoring protocol progress. If the Group wishes to close accrual to a study prior to meeting the initially established accrual goal, the interim results and other documentation should be made available to NCI staff for review and concurrence prior to implementation of the decision by the Group. It is recommended that statistical

guidelines for early closure be presented as explicitly as possible in the protocol in order to facilitate these decisions. In the event that the DSMC has recommended early closure, DSMC procedures regarding notification of CTEP must be followed.

10. Protocol Reporting Requirements

Reporting requirements will be in agreement with FDA regulations and NCI procedures. Interim reports of each activated and ongoing study shall appear in the minutes of each Group meeting and shall include specific data on patient accrual as well as, when appropriate, detailed reports of treatment-associated morbidity. Quarterly accrual information must be provided by the Headquarters or Statistical Office as appropriate to NCI for all active studies. A system for providing such information in a timely manner should be in place. Participants must provide accrual data to the Group in accordance with Group procedures.

11. Adverse Event Procedures

In order to be in compliance with FDA regulations, all recipients of NCI support for clinical trials, including Groups responsible for coordinating and monitoring such trials, must promptly notify the NCI and any other sponsors of the trial of adverse events (i.e., adverse drug reactions) according to directions provided in the adverse event reporting section of the protocol.

The awardee will notify all institutions/investigators participating in this project, funded or unfunded, about the above requirement and about the institutions'/ investigators' responsibility to report adverse events as specified in the protocol.

The awardee will promptly notify the Investigational Drug Branch (IDB) Drug Monitor for DCTDC-sponsored investigational agents and the NCI Program Director for other agents, of serious or life-threatening events, as instructed in the protocol.

12. Performance Review

The Group shall establish and follow policies and procedures for credentialing participating institutions and conducting periodic review of the performance and membership status of each Main Member/Affiliate. This review should examine scientific contributions, patient accrual, data accuracy and timeliness, protocol compliance, long-term patient follow-up and audit results. This mechanism will include a procedure for the Group Chair to recommend an adjustment of funds within the Group as appropriate for the level of participation in Group activities, including (but not limited to) accrual. This procedure can be either prospective (i.e., reimbursement by the case) or retrospective (financial adjustment at the time a non-competing continuation [Type 5] award is made).

13. Procedures in the Event of Scientific Misconduct

If a duly authorized governmental or institutional body issues a final determination that scientific misconduct has occurred or if the awardee determines that other events have occurred which have significantly affected the quality or integrity of the Group data or patient safety, the awardee is responsible for notifying the Group Data and Safety Monitoring Committee (DSMC), the CTMB, the collaborating investigators, the appropriate Institutional Review Boards (IRBs), and other sponsors of the affected work.

The awardee is also responsible, if the events described above have occurred, for ensuring that submitted but unpublished abstracts and manuscripts are corrected, if possible. If publication deadlines have passed or if abstracts and/or manuscripts containing the affected data have already been published, the awardee is responsible, within 90 days after learning of the event(s) significantly affecting the quality of the Group data or patient safety, for submitting to NCI a re-analysis of the results deleting the false or otherwise unreliable data, and disclosing within the text the reason(s) for the reanalysis. The awardee must submit the reanalysis for publication. The NCI may disseminate information about the reanalysis as broadly as it deems necessary.

The awardee must use its best efforts to notify all scientists, research laboratories, and other organizations to which the awardee has sent research materials affected by false or otherwise unreliable data.

True copies of data files and other supporting documentation from studies affected by scientific misconduct or other findings affecting the quality or integrity of data or patient safety shall be made available to the NCI in a timely manner upon the request of the Grants Management Officer, NCI. The NCI reserves the right to reanalyze, to publish, or to distribute its analyses of these data when it is in the interest of public health. Prior to release, publication or distribution of such analyses, the NCI will provide such analyses to the awardee.

14. Data Files Available to NCI Upon Request

Upon the request of the Grants Management Officer, NCI, true copies of data files and supporting documentation for all NCI-supported protocols that have a major impact on patterns of care, as determined by the NCI, shall be made available to the NCI in a timely manner.

15. Notification of Patients by the Awardee During Patient's Lifetime

In order for there to be an appropriate response in the event the NCI determines, either while a protocol is active or (if relevant) during the lifetime of the subjects following protocol closure, that a medically important toxicity or side effect is associated with protocol-directed treatment or that the medical care of one or more subjects may have been compromised by scientific misconduct or other finding affecting the integrity of the data or patient safety at the awardee institution or at a third-party institution, funded or

unfunded, the awardee shall assure that the institution(s) responsible for these subject(s) accrual, whether funded or unfunded, will have procedures in place to: (i) contact each subject individually at his or her last known address on file with the institution and which give each subject contacted appropriate information and the right to communicate with an appropriate institutional representative and, in the event of misconduct, to meet with a physician not connected with the clinical trial or study in which the subject has participated; and (ii) encourage subjects to notify the institution of any changes of address. The procedure must provide for informing the subjects fully of: the consequences of the toxicity or misconduct for their care and well-being, if any, and the availability of follow-up; and their opportunity to examine any portion of their medical records relevant to the potential effect of the toxicity or side effect upon them or that may be affected by scientific misconduct or other findings affecting the quality or integrity of the data or patient safety.

It is understood that under regulations at 45 CFR Section 74.53, NCI has a right of access to research records pertinent to the NCI funding. In exceptional circumstances, such as a public health emergency, the institutions will be required to provide subject names and treatments to the NCI in a format which allows direct notification of the patient by the NCI.

16. Progress Reporting

Annual progress reports will be submitted to the NCI in accordance with the instructions in the CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES.

B. NCI STAFF RESPONSIBILITIES

The role of the Cancer Therapy Evaluation Program (CTEP) staff as described throughout these terms and conditions of award is to assist and facilitate but not to direct research activities. This cooperative agreement is part of a larger program of investigational agent development in the NCI. Each of the CTEP staff listed below has very specific and well defined responsibilities in terms of investigational agent development and the role of DCTDC as a drug sponsor as defined in CFR 21 Part 312.

1. Scientific Resource for NCI-Supported Clinical Investigations

The NCI Program Director, the Associate Director, CTEP (AD, CTEP), and staff of the Clinical Investigations Branch (CIB), the Investigational Drug Branch (IDB), the Biometric Research Branch (BRB), the Regulatory Affairs Branch (RAB), the Pharmaceutical Management Branch (PMB) and the Clinical Trials Monitoring Branch (CTMB) will serve as resources available to Cooperative Groups for specific scientific information with respect to treatment regimen, clinical trial design, investigational agent management and regulatory issues. The CIB Senior Investigator(s) designated by the NCI Program Director will assist the Group as appropriate in developing information concerning the scientific basis for specific trials and also will be responsible for advising

the Group of the nature and results of relevant trials being carried out nationally or internationally. The CIB Senior Investigators and IDB Drug Monitors will also provide updated information on the efficacy and toxicity of investigational new agents supplied to Group members under an Investigational New Drug (IND) Application sponsored by the Division of Cancer Treatment, Diagnosis and Centers (DCTDC). The CIB Senior Investigator will advise the Cooperative Groups of potential studies which will be relevant to new avenues of cancer therapy.

2. Protocol Development

A protocol is the detailed written plan of a clinical experiment. The protocol must be mutually acceptable to the Group and to the CTEP Protocol Review Committee (PRC). Communication with CTEP staff at the various stages of protocol development is encouraged. The CIB Senior Investigator will assist the Group in protocol design as may be appropriate by providing information regarding: (a) the existence and nature of concurrent clinical trials in the area of research, pointing out possible duplication of effort, (b) information including relevant pharmacokinetic and pharmacodynamic data concerning investigational agents, and (c) availability of investigational agents, including biologic response modifiers. The CIB Senior Investigator will also comment on the scientific rationale and value of the proposed study, the design, the statistical requirements, and the implementation of the study, if indicated.

CTEP staff will review and provide a Program response through the AD, CTEP, to Concepts for Phase III protocols and Letters of Intent for Phase II protocols, commenting on study originality and programmatic interest. These two mechanisms for preliminary review are required to expedite protocol development and implementation and to facilitate agreement on study priority and design (see the "INVESTIGATOR'S HANDBOOK," pp32-35, for further discussion of these mechanisms).

3. Review of Proposed Protocols

Group protocols will be reviewed by the CTEP Protocol Review Committee (PRC) which will meet weekly. It will be chaired by the AD, CTEP or his/her designee. Ad hoc reviewers, external to NCI, will be utilized when deemed appropriate by the committee chairperson. Formal protocol review and CTEP approval prior to activation are required for the following types of studies: (a) all protocols utilizing DCTDC resources and investigational agents regardless of IND-sponsor; (b) all protocols that permit entry of one hundred or more patients; and (c) all phase III protocols. In addition, protocols requiring fewer than one hundred patients which utilize commercial agents only will receive full review. This includes BMT studies. However, approval will be based only upon consideration of safety and regulatory issues. Other protocols will be filed with CTEP for information purposes but will not require CTEP approval. Advisory reviews of such protocols may be provided to the Group at CTEP's discretion. For all protocols that require review, the AD, CTEP will provide the Group with a consensus review that describes recommended modifications and other suggestions, as appropriate (see the

Investigator's Handbook," pp 43-47, for further information regarding protocol review at CTEP).

The major considerations relevant to Protocol Review by CTEP include: (a) the strength of the scientific rationale supporting the study, (b) the medical importance of the question being posed, (c) the avoidance of undesirable duplication with other ongoing studies, (d) the appropriateness of study design including interim monitoring plans, (e) a satisfactory projected accrual rate and follow-up period, (f) patient safety, (g) compliance with Federal regulatory requirements, (h) adequacy of data management, (i) appropriateness of patient selection, evaluation, assessment of toxicity, response to therapy and follow-up.

If a proposed protocol is disapproved, the specific reasons will be communicated to the Group chairperson as a consensus review within 30 days of protocol receipt by the NCI. NCI will not provide investigational drugs or permit expenditure of NCI funds for a protocol that it has not approved. The CIB Senior Investigator will be available to assist the Group in developing a mutually acceptable protocol, consistent with the research interests, abilities and strategic plans of the Group and of the NCI.

4. Review of Quality Control and Study Monitoring

The CTMB staff, will review and provide advice regarding mechanisms established by the Group for quality control of therapeutic and diagnostic modalities employed in its trials. The CTMB staff will review and approve the mechanisms established by the Group for study monitoring including the Group's on-site auditing program.

CTEP and/or its contractor staff may attend, as observers, the on-site audits conducted by the Group. The frequency of participation by an NCI representative as observer will be determined by the NCI.

5. Review of Data Management and Analysis

The BRB staff will review mechanisms established by the Group for data management and analysis. When deemed appropriate staff will make recommendations to ensure that data collection and management procedures are: (a) adequate for quality control and analysis; (b) as simple as appropriate in order to encourage maximum participation of physicians entering patients and to avoid unnecessary expense; and (c) sufficiently uniform across Groups. The NCI will have access to all data although they remain the property of the awardee institution. Data must also be available for external monitoring as required by NCI's agreement with the FDA relative to the NCI's responsibility as drug sponsor.

6. Data and Safety Monitoring Committees

The NCI Program Director, assisted by the BRB staff will assess Group compliance with NCI established policies on Data and Safety Monitoring Committees (DSMCs) for

Cooperative Group Phase III trials. One or more CTEP staff will serve as non-voting members on the DSMC.

7. Protocol Closure

The AD, CTEP, may request that a Phase I or Phase II protocol study be closed to accrual for reasons including: (a) insufficient accrual rate; (b) poor protocol performance; (c) patient safety; (d) study results are already conclusive; and (e) emergence of new information which diminishes the scientific importance of the study question.

NCI will not provide investigational agents or permit expenditures of NCI funds for a Phase I or Phase II study after requesting closure (except for patients on treatment and follow-up).

The AD, CTEP, may request that the Group DSMC consider closing a Phase III protocol to accrual for reasons including: (a) insufficient accrual rate; (b) poor protocol performance; (c) patient safety; (d) study results are already conclusive; and (e) emergence of new information which diminishes the scientific importance of the study question.

NCI will not provide investigational agents or permit expenditures of NCI funds for a Phase III protocol that has been closed (except for patients on treatment and follow-up).

8. Involvement in Investigational Drug Management

The NCI will have the option to cross file or independently file an IND on investigational agents evaluated in trials supported under cooperative agreements. This would apply to drugs not developed in the NCI drug development program.

The NCI Program Director, assisted by the RAB staff and the PMB staff will advise investigators of specific requirements and changes in requirements concerning investigational drug management that the Food and Drug Administration (FDA) may mandate.

9. Review of Compliance with Federally Mandated Regulatory Requirements

The CTMB staff and the RAB staff will review and provide advice regarding mechanisms established by the Group to meet Food and Drug Administration (FDA) regulatory requirements for studies involving DCTDC-sponsored investigational agents and Office for Protection from Research Risks (OPRR) requirements for the protection of human subjects.

10. CTEP attendance at Cooperative Group Meetings

CTEP staff, as designated by the NCI Program Director, will attend the semi-annual Group meetings and will be invited as a non-voting observer to Group Executive Committee Meetings.

11. Facilitate Completion Of Important Trials

CTEP staff will take an active role in promoting the timely completion of important studies, for example by encouraging and facilitating Intergroup collaboration when appropriate, or by assisting in the mobilization of other available and required resources.

C. COLLABORATIVE RESPONSIBILITIES

1. Development of Intergroup Trials

The CIB Senior Investigators will conduct disease or modality oriented strategy meetings for the purpose of jointly developing the DCTDC Clinical Trials Cooperative Group Program priorities for future protocol development. Group investigators, NCI staff and other extramural investigators will attend these meetings. The Groups and CTEP staff will work together to facilitate the timely development of protocols resulting from the consensus developed at such strategy meetings.

2. Investigational Drug Development

When new avenues of cancer therapy involving investigational drugs are pursued, the clinical information should be acceptable to the FDA for inclusion in a New Drug Application (NDA). In collaboration with NCI staff, the Group will develop protocols to obtain such information as needed.

3. Data Safety and Monitoring Committees

The appropriate conduct of the Group DSMC procedures are a collaborative responsibility of the Group and CTEP members.

4. Cooperative Group Chairpersons' Semi-Annual Meetings

The Chairperson of each Cooperative Group, the NCI Program Director, the CIB Senior Staff, and other NCI personnel as indicated will meet semi-annually to discuss issues of relevance to the Clinical Trials Cooperative Group Program.

5. Cooperative Group Statisticians' Meeting

Each Group's Chief Statistician, the NCI Program Director, the BRB staff, and other NCI personnel as indicated will meet together annually to discuss issues of relevance to the Clinical Trials Cooperative Group Program.

D. ARBITRATION

Any disagreement that may arise on scientific/programmatic matters (within the scope of the award), between award recipients and the NCI may be brought to arbitration. An arbitration panel composed of one Group nominee, one NCI nominee, and a third member with clinical trials expertise chosen by the other two will be formed to review the CTEP decision and recommend an appropriate course of action to the Director, DCTDC. The arbitration procedures in no way affect the awardee's right to appeal an adverse determination under the terms of 42 CFR Part 50, Subpart D, and 45 CFR Part 16. The Group will not expend NCI funds to conduct any study disapproved by CTEP unless CTEP's disapproval has been modified by the arbitration process outlined above.

ATTACHMENT 1 - Sample Format**Clinical Trials Cooperative Group Guidelines****MODALITY COMMITTEE SUMMARY OF ACTIVITIES**

A modality committee is herein defined as a medically specialized committee which is not disease-specific. Examples include committees for pathology, radiation oncology, surgery, transplant, immunology, etc.

For each MODALITY COMMITTEE prepare a separate summary of the activities of that committee, utilizing the following format:

I. ADMINISTRATIVE ASPECTS

- A. Define the functions of the committee, describing the scope of its responsibilities, the frequencies of its meetings, and membership requirements.
- B. Describe the role of each of the modality committees in the various activities of the Group, including items such as service by members on executive and administrative committees, participation in Group meetings, and specialized review for various disease areas.

II. SCIENTIFIC CONTRIBUTIONS

- A. Briefly describe the process by which the modality discipline contributes to protocol initiation, design and monitoring.
- B. Describe the major scientific accomplishments of the modality committee during the current award period.
- C. Briefly describe the most important scientific plans and goals of the committee for the upcoming award period.

III. QUALITY CONTROL PROGRAMS**A. PATHOLOGY**

- 1. Describe the process employed by the Group for pathology review.
- 2. Describe the process involved in deciding whether to conduct pathology review in a protocol under development. Does the Group have its own data from previous studies on which to base a decision not to perform pathology review?

ATTACHMENT 1: Modality Committee Summary of Activities page 2

3. Describe the mechanism by which the Group ensures prompt submission of pathology review materials from member institutions and how pathology review impacts upon therapy.
4. How many Phase III studies were active at the time of submission of the competing application? What percentage of these studies require pathology review?
5. What is the annual number of patient accessions in each of the past 3 years into protocols for which pathology review is being conducted? For each year, provide the percentage of reviews which have been completed.
6. Does the Group audit a percentage of cases with pathology review in protocols which do not have standard pathology review?
7. Are pathologists involved in protocol design and development?
8. What percentage of trials with pathology requirements included pathologists among the principal investigators/study chairs?

B. RADIATION THERAPY

1. Discuss the radiation review process for the Group, including such issues as:
 - a. the decision during protocol development to include radiotherapy review
 - b. what is evaluated during the review
 - c. who conducts the review
 - d. who receives the results of the review
 - e. how port film and physics reviews are performed and integrated
 - f. the requirement for simulators for each participating institution
 - g. how radiation therapy review is incorporated into institutional performance assessment
2. For those protocols which involve radiation therapy:
 - a. what percentage of the Group's active phase III protocols involve radiation therapy?
 - b. what percentage has a radiotherapy co-chairman?
 - c. which protocols require radiotherapy quality control review?
 - d. which protocols require rapid turnaround review?

ATTACHMENT 1: Modality Committee Summary of Activities page 3

3. Describe Group interactions with the Radiologic Physics Center
4. Discuss the mechanism employed by the Group to ensure prompt submission of radiotherapy materials by member and affiliate institutions.

C. SURGERY

1. Describe the process by which surgical quality control review is conducted by the Group. Is the review conducted by surgeons? Does it include review of operative data, protocol-specific surgical data forms, and pathology reports?
2. What proportion of the active Phase III protocols with a surgical component presently require surgical quality control review? What were the annual patient accessions for the past three years into protocols requiring surgical quality control? For what percentage of these has quality control been completed?
3. Briefly describe the mechanism by which the Group ensures prompt submission of surgical quality control review materials from member institutions.
4. Are surgeons involved in protocol design and development?
5. What percentage of trials included surgeons among the principal investigators/study chairs?
6. Does the Group have a surgical handbook of standards for acceptable surgical procedures to aid with protocol development?

D. OTHER MODALITY COMMITTEES (e.g., Chemotherapy): Please follow the above general format in submitting summary information.

ATTACHMENT 2 - Sample Format

Clinical Trials Cooperative Group Guidelines

MEMBER INSTITUTION SUMMARY OF ACTIVITIES
 (see text, sections VII.2.A.e. and VII.4.A.)

INSTITUTION _____ PRINCIPAL INVESTIGATOR

COOPERATIVE AGREEMENT # _____ DATE

1. Case accession by calendar year of the current project period (please prepare separate tables for therapeutic and non-therapeutic studies)

<u>From the Member Institution</u>	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Etc.</u>
Phase II	_____	_____	_____	
Phase III	_____	_____	_____	
Pilot	_____	_____	_____	
Subtotal	_____	_____	_____	
%Eligible	_____%	_____%	_____%	_____%
%Evaluable	_____%	_____%	_____%	_____%

From Affiliated Institutions (funded and Unfunded)

Phase II	_____	_____	_____	
Phase III	_____	_____	_____	
Pilot	_____	_____	_____	
Subtotal	_____	_____	_____	
% Eligible	_____%	_____%	_____%	_____%
%Evaluable	_____%	_____%	_____%	_____%
<u>Total</u>	_____	_____	_____	

ATTACHMENT 2: Member Institution Summary of Activities page 2

2. Number of follow-up cases at end of calendar year:

	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Etc.</u>
From primary and affiliated institutions	—	—	—	

3. Group administrative and scientific participation during the current project period.

<u>Investigator Name</u>	<u>Committee</u>	<u>Activity</u>
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4. Protocol Chairmanships

<u>Open protocol and #</u>	<u>Investigator name</u>
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<u>Protocols in follow-up and #</u>	<u>Investigator name</u>
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5. Institutional pilot studies and other research contributions to the Group.

6. Services to the Group (core lab, site visit, etc) during the current project period.

7. Number of quality assurance audits of the institution during the current project period, and problems identified, if any.

8. Disciplinary actions imposed by the Group during the current project period.

9. Group-related publications (annual bibliography limited to the current project period) authored by institutional investigator(s).

10. Ranking of institution's performance overall by Group leadership (by quartile; see VII 2 A.b.)

ATTACHMENT 3

(Revised 8/96)

**SUGGESTED FORMAT FOR NON-COMPETING CONTINUATION APPLICATIONS FOR
NCI CLINICAL TRIALS COOPERATIVE GROUP
PROGRAM COOPERATIVE AGREEMENTS**

The annual non-competing continuation (Type-5) cooperative agreement application serves as a report to the funding agency on the achievements of the awardee in the previous funding period and presents the plan of activity for the upcoming funding period along with the associated cost projections. The application is due two months prior to the anniversary date of the Group award.

Separate applications are required for each cooperative agreement supported by NCI, and thus are usually submitted from the headquarters office, the statistical/data management office and from those funded member institutions with individual cooperative agreements. For Cooperative Groups which have merged functions in one way or another into fewer cooperative agreements, each activity should be separately reported in the relevant application along with its associated budget. Each application begins with the face page and the detailed budget pages as described in the Instructions for the PHS 2590 (Rev. 5/95), Application for Continuation of a PUBLIC HEALTH SERVICE GRANT. The budget presentations for the separate components should be in accord with the support recommended on the NIH Notice of Grant Award for the continuation period and in sufficient detail to assure that NCI staff (CTEP and GAB) are advised of proposed budget commitments. For allowable expenditures see Clinical Trials Cooperative Group Program Guidelines.

A. GROUP HEADQUARTERS/STATISTICAL OFFICE APPLICATION(S)

Please prepare the Group Headquarters/Statistical Office cooperative agreement application(s) according to Instructions for the PHS 2590 (Rev. 5/95) except as noted below:

1. BUDGETS AND BUDGET JUSTIFICATIONS (Form Page 2 and Form Page 3)

The budget section should begin with summary budget pages, followed by separate detailed budgets and justifications for each component or activity including separate budgets/tables for individual consortia. (See Section II VII.2.B. Headquarters (Operations Office) Budget).

2. IMMEDIATELY FOLLOWING FORM PAGE 3, THE FOLLOWING IS REQUIRED:**a. On-site Auditing Activities**

The NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups and CCOP Research Bases require all institutions to be audited at least once every 36 months. In order for NCI staff to review each the Group's compliance with this

requirement, each Group should conduct a comprehensive review of its current membership and provide in the non-competing continuation application an accounting in tabular format (see suggested format - Attachment 4) for all institutions to include: (1) date of affiliation with or termination from the Group; (2) accrual for the immediate preceding 36 months broken down by year; (3) the projected accrual for the upcoming year; (4) the date of the institution's last audit; and (5) the date (projected month/year) of the next proposed audit.

In addition, please provide the following information related to the costs of conducting the audits:

- 1) For the immediately preceding budget period, the actual total costs (direct and associated indirect) charged to the Headquarters or Statistical Center, as appropriate.
- 2) For the current budget period, the estimated total costs (direct and associated indirect) charged to the Headquarters or Statistical Center, as appropriate. If all audits have been completed, please provide the actual total costs charged.
- 3) For the upcoming budget period, the estimated total costs (direct and associated indirect) for conducting the planned audits.

Please provide this information in the Budget justification section. The information may be provided in the format of the Group's choosing.

- b. If the Headquarters provides funds to performance sites for accruals (including High Priority and Minority Accrual Initiatives) via per patient reimbursement mechanisms, (e.g., purchased service agreements or subcontracts), the following information must be provided:
 - 1) For the current budget period, (i) a list of performance sites that received funds to date in that year; and (ii) the total costs provided to each site (direct and indirect) to date in that year; and (iii) the number of patients accrued for each site to date in that year.
 - 2) For the immediately preceding budget period, (i) a list of performance sites that received funds to date in that year; and (ii) the total costs provided to each site (direct and indirect) to date in that year; and (iii) the total number of patients accrued in that year for each site.
 - 3) For the upcoming budget period, (i) the estimated number of accruals and (ii) the estimated total costs (direct and indirect) for each performance site.

The above information may be provided in the format of the Group's choosing and should follow the budget justification section of the application.

3. BIOGRAPHICAL SKETCH (Form Page 4)

Include biographical sketches for new participants in administrative and scientific leadership roles only. Limit to two pages each.

4. OTHER SOURCES OF SUPPORT FOR THE GROUP;

- a. Include in the listing all sources of support (both NCI and non-NCI) for the Group's headquarters and/or statistical office for all research activities. For that support which is linked to specific studies, indicate which studies receive this support, the associated dollar amounts and the nature of any costs not normally supported by NCI.
- b. Unmet funding needs: Outline in detail funding needs beyond those which can be met by the Group's committed budget for the upcoming year and which the Group feels are required for its continued function; describe the justification precisely. Requests for additional funds must be for efforts within the Group's approved workscope. How would additional funding affect the quality of research currently in progress? What new initiatives would be possible? Would this represent a one-time request or a continuing obligation?

5. PROGRESS REPORT SUMMARY (Form Page 5) - ORGANIZATION OF THE APPLICATION ACCORDING TO THE FOLLOWING FORMAT IS SUGGESTED.**a. ADMINISTRATIVE****1) Achievements:**

Briefly describe the Group's significant achievements in the past year in its administrative activities. These might include: organizational or structural aspects, data management practices and procedures, statistical approaches, compliance with regulatory requirements, quality assurance practices, efficiencies in protocol development, growth in membership, educational activities, etc., including changes in primary personnel, their roles and responsibilities.

2) Proposed Activities:

Outline planned new initiatives in terms of organizational and administrative activities for the upcoming year for the Group as a whole.

3) Special Emphasis Issues:

a) Scientific prioritization - Describe the process used by the Group for setting priorities regarding the use of (limited) Group resources to accomplish its approved workscope.

b) Ethics and integrity in the conduct of clinical research -

- i) ethics training - Describe current Group procedures for education of Group members regarding the ethical requirements of clinical trials research, including the mechanism (such as the Affirmation of Integrity statement) by which the Group assures that all its members who handle clinical trials data know the Group policy towards scientific misconduct.
 - ii) conflict of interest policy - Briefly describe Group policies and procedures regarding the evaluation of potential conflicts of interest. Include a table listing Group members to whom the conflict of interest policies are applicable, stating their position in the Group.
 - iii) procedures in the event of scientific misconduct - Describe Group procedures in the event of detection of scientific misconduct. Describe the instructions given Group members regarding reporting concerns about possible scientific misconduct.
- c) Quality of Group data - Describe mechanisms in place which provide quality control of the data set used for Group analyses.
- d) Data and Safety Monitoring Committees - Briefly describe how decisions made by the Group Phase III Data and Safety Monitoring Committee(s) are made independently from study coordinators and involved investigators. Describe the composition of the DSMC.
- e) Group membership and accrual - Describe the following:
- i) Group membership categories, including a complete list, by membership categories, of all performance sites.
 - ii) Overall accrual to Group studies, separated into therapeutic and non-therapeutic study categories.
 - iii) Inclusion of women and minorities in clinical trials research. Total Group patient accrual by study shall be reported in the parent Cooperative Group application in accordance with the guidelines for the PHS 2590 (Rev 5/95), pages 8-9, using the table on Form Page 5. Describe, where relevant, initiatives to improve access by underserved populations to clinical trials participation.
 - iv) Accrual to NCI-designated High Priority Trials, if relevant.
 - v) Outreach efforts, including accrual through the Group's utilization of the Cooperative Group Outreach Program (CGOP) and Community Clinical Oncology Program (CCOP) mechanisms, if relevant.

- 4) Outline the Group's most important problems and proposed solutions.
- b. COOPERATIVE GROUP COMMITTEES AND LABORATORIES -
PROGRESS REPORT (organized by Committee: include all committee and laboratory progress reports in the Headquarters application)
- 1) Achievements - Summarize the most significant achievements in the past year for each committee or laboratory (limit to one page per committee)
 - 2) Review of studies - Briefly describe new findings and changes in the status of committee studies.
 - 3) Membership - Briefly describe changes in the membership of each committee focusing particularly on changes in leadership responsibilities.
 - 4) Plans - Briefly discuss changes in the research focus of each committee including projected new initiatives, future directions, and priorities.
 - 5) To aid in the review of your application information for each committee or laboratory should be arranged in a tabular format as shown in sample tables 1 - 3.
- c. BIBLIOGRAPHY
- 1) Arrange in tabular form such as shown in sample table 4, the Group Bibliography, beginning with the most recent publications, abstracts and presentations. Attach any additional pages required to complete the bibliography. Do not include publications which had complete citations in a previous application.
 - 2) Arrange in tabular form such as shown in sample table 5, a complete listing of manuscripts and abstracts which have been submitted but not yet published.
- d. PERFORMANCE REVIEW
- 1) Describe the process by which the performance of each participating institution (members, affiliates, CCOPs, CGOPs, etc.,) is assessed. Include the current ranking of participants by these criteria. How has the evaluation impacted on the funding of the participants?
 - 2) List all institutions against which disciplinary action (probation, suspension of registration, etc.,) was taken on the basis of a site visit, performance review, etc. Describe circumstances leading to the action and the nature of the action taken.
- e. ACCRUAL TABLES

The Headquarters application should provide two types of accrual tables summarizing Group activities (see suggested formats, attached). The first should provide total Group accrual displayed by protocol [sample tables 1 (therapeutic) and 2 (non-therapeutic)]; the second should provide total Group accrual displayed by performance site [sample tables 6 (therapeutic) and 7 (non-therapeutic)].

For sample table 1, Intergroup studies should be separated into two categories: a) those studies for which the Group serves as the coordinating center, and b) the additional studies to which the Group contributes patients. The Intergroup coordinating center is asked to provide in its application complete accrual information for the study with a breakdown by the contributing Groups. A participating Group other than the coordinating center is asked to provide in its application information limited to that Group's activities.

Sample tables 6 and 7 should contain accrual data for the entire Group, in tabular form such that the accrual for each member and its affiliated performance sites are displayed without duplication. Data for performance sites affiliated directly with the Group Headquarters should be displayed with the notation "Headquarters" where the member's name would otherwise be displayed.

Please note that applications from individual Group institutions holding cooperative agreements are to include sample tables 6 and 7 specific for that institution and its affiliates. The Group statistical center should provide the information to the member institution for inclusion in its application.

6. GENDER AND MINORITY INCLUSION (Form Page 5)

The Table on Form Page 5 must be filled out in accordance with the instruction in Section A. 5. a. 3) e) iii) above.

B. GROUP MEMBER INSTITUTION APPLICATIONS

In some Groups, member institutions receive cooperative agreements directly from NCI, thus requiring separate grant applications to be submitted by the member institution with the guidance of the Group leadership. Please prepare the member institution applications according to the Instructions for the PHS 2590 Rev (5/95), Application for Continuation of a PUBLIC HEALTH SERVICE GRANT, except as noted below:

1. Briefly describe any changes in institutional profile, personnel, or affiliations relevant to the accrual of patients onto Group studies.
2. Discuss the scientific contribution of the member institution in terms of specific study leadership, pilot study contribution, authorship, Group meeting participation, etc.
3. Briefly describe the participation of personnel in administrative activities of the Group.

4. The member institution application should include tables displaying institutional/affiliate accrual to therapeutic (Table 6) and non-therapeutic (Table 7) Group protocols by Phase; these should be prepared by the Group statistical office and supplied to the member institution for inclusion in the application.
5. Gender and Minority Inclusion: Patient contribution by study will be reported in the parent Cooperative Group application in accordance with the instructions in the PHS 2590, Rev 5/95, therefore, institutional applicants are not required to report the study population by protocol. However, the table at the bottom of Form Page 5 of the PHS 2590 should be filled in, providing a summary of institutional accrual to Group studies for the following time period: either a) the twelve month period ending one month before the receipt date of this application, or b) the most recent calendar year. Institutional applications should discuss special resources which it provides to the Group in terms of special patient populations and affiliations. Include minority and medically under-served populations, as appropriate. Please provide written explanations of local demographics or other obstacles which may influence the ability of your institution to recruit women and minority patients in representative proportions, and efforts to overcome such obstacles.
6. Budget and Budget Justification.

Complete in accord with the instruction sheet for PHS 2590 (Rev. 5/95). Applicants requesting awards which are larger than the committed level should provide detailed justification for any increases and should enclose a supporting letter from the Group Chairperson.

* Arrange the protocols by disease committee and then by protocol number.

** For the 12 month period ending one month before the application deadline.

SAMPLE TABLE 2

ACCRUAL SUMMARY FOR COMPANION (i.e., NON-THERAPEUTIC) STUDIES *

COMMITTEE(where applicable)

CATEGORY	NUMBER OF PATIENTS * (12 MONTH TOTAL)
LABORATORY/CORRELATIVE	
SUPPORTIVE CARE	
QUALITY OF LIFE	
EPIDEMIOLOGY	
NURSING	
OTHER (SPECIFY)	

* For the twelve month period ending one month before application deadline

SAMPLE TABLE 3
PATIENTS BEING FOLLOWED AS OF ONE MONTH PRIOR TO APPLICATION DEADLINE
COMMITTEE

CATEGORY	NUMBER OF PATIENTS					
	PILOT STUDIES	PHASE I STUDIES	PHASE II STUDIES	PHASE III STUDIES	OTHER STUDIES	TOTAL
Patients in Follow-up on Currently Active Studies						
Patients in Follow-up on Studies Closed to Accrual						

**SAMPLE TABLE 4
GROUP BIBLIOGRAPHY
COMMITTEE**

NCI PROTOCOL NUMBER	PUBLICATION (TITLE & CITATION)	DATE PROTOCOL OPENED	DATE CLOSED TO ACCRUAL

* Please sort the citations by Committee and within that sort by NCI protocol number. Include a set of reprints as an appedix.

SAMPLE TABLE 5

SUBMITTED MANUSCRIPTS AND ABSTRACTS NOT YET PUBLISHED*

COMMITTEE

NCI PROTOCOL NUMBER	PUBLICATION (TITLE & CITATION)	DATE PROTOCOL OPENED	DATE CLOSED TO ACCRUAL	DATE SUBMITTED

* Please sort the citations by Committee and within that sort by NCI protocol number. Include a set of reprints as an appendix.

SAMPLE TABLE 6

PATIENT ACCRUAL BY INSTITUTION FOR EACH THERAPEUTIC PROTOCOL
 (REPORTING PERIOD* ____ TO ____)

(PLEASE PROVIDE THIS TABLE AS AN ASCII FILE ON DISK)

MEMBER INSTITUTION	C O D E	INSTITUTION** CITY & STATE	PROTOCOL NUMBER	PHASE	NUMBER OF PATIENTS ENTERED
<u>EXAMPLE:</u>					
U. Oregon	M	U. Oregon	7903	2	3
U. Oregon	C	Bay Region Hosp. Coos Bay, Oregon	7827	3	3

* Separate 12 month accrual data into two tables. The first ending December 31 and the second beginning January 1, and ending one month prior to the application deadline.

** Identify affiliated institutions through which patients were accrued. Precede the name of the institution by "M" for MEMBERS, "C" for CCOPS, "G" for CGOPs, or "O" for other institutions.

SAMPLE TABLE 7

PATIENT ACCRUAL BY INSTITUTION FOR EACH NON-THERAPEUTIC PROTOCOL
 (REPORTING PERIOD* ____ TO ____)

(PLEASE PROVIDE THIS TABLE AS AN ASCII FILE ON DISK)

MEMBER INSTITUTION	C O D E	INSTITUTION** CITY & STATE	PROTOCOL NUMBER	PHASE	NUMBER OF PATIENTS ENTERED
<u>EXAMPLE:</u>					
U. Oregon	M	U. Oregon	7903	2	3
U. Oregon	C	Bay Region Hosp. Coos Bay, Oregon	7827	3	3

* Separate 12 month accrual data into two tables. The first ending December 31 and the second beginning January 1, and ending one month prior to the application deadline.

** Identify affiliated institutions through which patients were accrued. Precede the name of the institution by "M" for MEMBERS, "C" for CCOPS, "G" for CGOPs, or "O" for other institutions.