

**NATIONAL CANCER INSTITUTE
CLINICAL TRIALS
COOPERATIVE GROUP PROGRAM
GUIDELINES**

**CANCER THERAPY EVALUATION PROGRAM
DIVISION OF CANCER TREATMENT AND DIAGNOSIS
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH**

October 1, 2006

PART 1: Description of the Program and Its Policies..... 10

I. Introduction..... 10
A. General Description of the Program 10
B. Brief History 10
C. Group Membership 11
D. Quality Assurance and Service Centers 11
E. International Groups 12

II. Purpose of the NCI Clinical Trials Cooperative Group Program 12

III. Goals of Group Research..... 13
A. Improve Therapy 13
B. Adjunct Studies 13
C. Cancer Control and Prevention 13
D. Clinical Trials Methodology 13

IV. Overview of Group Research..... 13
A. General Considerations 13
B. Development of Research Plans 14
C. Flexibility 14
D. Collaboration with CTEP Staff and Other NCI Staff 14
E. Group Prioritization of Scientific Research and Efficiency of Study Development 14
F. Conduct of Group Clinical Research 15
G. Cancer Trials Support Unit (CTSU) 15
H. Timely Completion of Studies – Participation in CTSU and Intergroup Studies 16
I. Intergroup Collaborations 16
J. Collaborations with Other NCI-funded Programs and Investigators 17
K. Maximizing Available Financial Resources 17
L. Biological Specimen Banks 17

V. Terms and Conditions of Award..... 19

A. Awardee Rights and Responsibilities 19
1. Operations Center Rights and Responsibilities 21
1.1 Organization Structure, By-laws, and Standard Operating Procedures 21
1.2 Study/Protocol Development 21
1.3 Quality Control of Group Clinical Trials 23
1.4 On-site Auditing 24
1.5 Compliance with Federal Regulations Concerning Clinical Research 25
a) Office for Human Research Protection (OHRP) Assurances 25
b) Institutional Review Board (IRB) review of Group protocols 25
c) Assuring appropriate informed consent: 25
d) IRB review of the Operations Center and the SDMC 25
e) Inclusion of women and minorities in clinical research 25
f) Inclusion of children 26
g) Data and Safety Monitoring Policy and Plans 26
h) Data Sharing Policy 26
i) Education on the Protection of Human Subjects Participants 27
j) Other Federal Regulations 27

1.6	NCI Clinical Trials Policy	27
1.7	Adverse Event Reporting and Patient Safety	27
1.8	Biological Specimen Collection and Banking	27
1.9	Correlative Science and Reference Laboratory Support	27
1.10	Publications	28
1.11	Group Meetings	29
1.12	Group Communications	29
1.13	Cancer Trials Support Unit (CTSU) Interactions	30
1.14	Conflict of Interest	30
2.	Statistics and Data Management Center (SDMC) Rights and Responsibilities	31
2.1	Organization Structure and Facilities	31
2.2	Study/Protocol Development	31
2.3	Data Management Policies and Practices & Submission of Data to CTEP	31
2.4	Study Monitoring	31
2.5	Compliance with Federal Regulations	33
2.6	NCI Clinical Trials Policy	33
2.7	Adverse Event Reporting	33
2.8	Support for On-Site Audit Program	33
2.9	Independent Research	33
2.10	Study Analyses and Publications	33
2.11	Group Meetings – Report of Studies	33
2.12	Support or Group’s Participating Site Performance Monitoring Program	34
2.13	Cancer Trials Support Unit (CTSU) Interactions	34
2.14	Conflict of Interest	34
3.	Investigators and Participating Site Rights and Responsibilities	35
3.1	Participation in Group Activities	35
3.2	Implementing the Core Data Collection Method and Strategy of the Group	35
3.3	Complying with Quality Assurance & Control of Therapeutic/Diagnostic Modalities	35
3.4	Investigational Agent Responsibilities	36
3.5	Human Subjects Protection	36
3.6	Adverse Event Reporting	36
3.7	Submission of Specimens	36
3.8	Cancer Trials Support Unit (CTSU) Interactions	36
3.9	Conflict of Interest	37
4.	Scientific and Administrative Committee Rights and Responsibilities	38
4.1	Organizational Structure	38
4.2	Scientific Committees	38
4.3	Study Monitoring	38
4.4	Correlative Science Studies/Reference Laboratories	38
4.5	Publication	39
4.6	Administrative Committees	39
B.	NCI/CTEP Responsibilities and Associated NCI/CCCT Staff Responsibilities	40
1.	Coordination of National Priorities	40
2.	Scientific Resource and Liaison Activities	40
2.1	Scientific Resource for NCI-Supported Clinical Investigations	40
2.2	Scientific/Administrative Liaison Activities (Project Scientist)	40
2.3	CTEP Attendance at Group Meetings	41
2.4	Facilitate Completion of Important Trials	41
3.	Study/Protocol Development Process and Protocol Review	41
3.1	Study/Protocol Development Process	41
3.2	Letter of Intent, Concept, and Protocol Review	41
3.3	Protocol Amendment Review	44
3.4	Protocol Closure	44
4.	Data and Safety Monitoring Boards	44
5.	Quality Assurance	45
6.	Data Management and Analysis Review	46

7.	Investigational Agent Development and Regulations _____	46
8.	Compliance with Federal Regulatory Requirements Review _____	47
9.	Requesting Changes in Principal Investigator(s) for Any Group Component _____	47
C.	Collaborative Responsibilities (Groups and NCI/CTEP Staff) _____	48
1.	Development of Intergroup Trials and International Trials _____	48
2.	Investigational Drug Development _____	48
3.	Data and Safety Monitoring Boards _____	48
4.	Group Chairs' Meeting _____	48
5.	Group Statisticians' Meetings _____	49
6.	Group Administrators' Meetings _____	49
D.	Arbitration _____	49
VI.	Miscellaneous Administrative Considerations _____	50
A.	CTEP Staff Administration _____	50
B.	CTEP Program Specialist _____	50
C.	Grants Management Administration in NCI Office of Grants Administration (OGA) _____	50
D.	Changes of Awardee Institution _____	50
E.	Transfer of Group Membership for a U10 Participating Site _____	50
F.	Principal Investigator Not Employee of Awardee Organization _____	51
G.	Funding Decisions on Group Components Not Receiving Meritorious Scores at Review _____	51
H.	Miscellaneous Budgetary Considerations _____	52
1.	Carryover Requests _____	52
2.	Reporting Unexpended Balances _____	52
3.	Requests for Non-competing Supplemental Funding _____	52

PART 2: Guidelines Specific for Submission of Competing Applications.....53

I.	Pre-application Consultation/Letter of Intent and Application Submission Instructions _____	53
A.	General Considerations and Receipt Dates _____	53
B.	Letter of Intent/Preliminary Budget Discussions _____	54
C.	Application Submission Procedures _____	55
D.	Appendix Material _____	56
1.	Operations Center and SDMC Applications _____	56
2.	Participating Site U10 & Other U10 Applications _____	57
E.	Notification of International Involvement in Group Trials _____	57
II.	New and Competing Applications Format and Budget Requests _____	58
A.	General Guidelines _____	58
B.	Common Budget Outline _____	59
C.	Operations Center Application _____	60
1.	Detailed Budget for Initial Budget Period _____	60
1.1	General Information _____	60
1.2	Personnel _____	60
1.3	Consultant Costs _____	61
1.4	Equipment _____	61

Table of Contents - Part 2: Guidelines for Submission of Competing Applications
Top of the Page: Part 2.II.C. – New/Competing Application Format – Ops Center Application - Budget

1.5	Supplies	61
1.6	Travel	61
1.7	Patient Care Costs	61
1.8	Alterations and Renovations	62
1.9	Other Expenses	62
1.10	Consortium/Contractual Costs	62
1.11	Mechanisms for Per-Accrual Reimbursement	62
1.12	Consortium Arrangements	62
2.	Research Plan	63
2.1	Table of Contents	63
2.2	Major Research Objectives	63
2.3	Group Organizational Structure	64
2.4	Research Strategies	64
2.5	Group Administrative Functions and Administrative Committees	64
2.6	Scientific Committees	64
2.7	Cancer Control and Prevention Activities	66
2.8	Study Monitoring	66
2.9	Quality Assurance and On-site Auditing	66
2.10	Overall Accrual Information & Accrual Information by Gender and Ethnicity/Race	66
3.	Human Subjects Research (Human Subjects Protection)	67
3.1	Inclusion of Women and Minority	67
3.2	Inclusion of Children	67
3.3	Data and Safety Monitoring Board and Data and Safety Monitoring Plan	67
4.	Appendix Material	67
5.	Just-in-Time Information	67
5.1	Other Support for Key Personnel	67
5.2	Training on Human Subjects Protection for Key Personnel	68
5.3	On-site Auditing Activities	68
5.4	Provision of Funds to Participating Sites for Accrual	68
5.5	Common Budget Outline	69
D.	Statistics and Data Management Center Application	70
1.	Detailed Budget for Initial Budget Period	70
2.	Research Plan	71
3.	Human Subjects Research (Human Subjects Protection)	72
3.1	Inclusion of Women and Minority	72
3.2	Inclusion of Children	72
4.	Appendix Material	72
5.	Just-in-Time Information	72
E.	Participating Site U10 Applications & Other U10 Applications	74
1.	Detailed Budget for the Initial Budget Period	74
2.	Research Plan	77
2.1	Major Research Interests/Capabilities	77
2.2	Accrual	77
2.3	Scientific Leadership	78
2.4	Administrative Leadership	78
2.5	Publications	78
2.6	Data Quality and Timeliness	78
2.7	Additional Contributions	78
2.8	Gender and Ethnic/Racial Composition of Human Subjects	78
3.	Human Subjects Research (Human Subjects Protection)	79
3.1	Inclusion of Women and Minority	79
3.2	Inclusion of Children	79
4.	Appendix Material	79
5.	Just-in-Time Information	79

F. Competing Supplemental Applications (Interim Review)	80
G. Applications for New Groups and New U10 Applications	80
III. Review Criteria for New and Competing Applications	81
A. General Policies and Procedures	81
1. Role of Peer review	81
2. General Review Procedures	81
3. Review Order for Group Applications	82
B. Review Criteria for the Operations Center Application	83
1. Group Structure, By-Laws, Procedures, and Administrative Committees	83
1.1 General Issues	83
1.2 Group Chair	83
1.3 Membership	83
1.4 Key Personnel	83
1.5 Staff	83
1.6 Patient Accrual	83
1.7 Overall Group Priorities	83
1.8 Major Research Objectives/Merit of Specific Research Plans	83
1.9 Group Cohesiveness	84
1.10 Interdisciplinary Coordination	84
1.11 Mentoring Junior Investigators	84
1.12 Oversight Committees (Board of Directors, Executive Committee)	84
1.13 Administrative Committees	84
2. Study/Protocol Development and Study Monitoring	84
2.1 Study/Protocol Development	84
2.2 Research Methodology	84
2.3 Efficiency of Protocol Development and Study Monitoring	84
2.4 Timeliness of Study Completion	84
3. Quality Control of Group Clinical Trials	85
3.1 Participating Site Performance Evaluations	85
3.2 Educational Functions	85
3.3 Central Review of Major Elements of Clinical Trials	85
4. On-Site Auditing Program	85
5. Compliance with Federal Regulations	85
5.1 OHRP and IRB Regulations	85
5.2 Adequacy of Plans to Include Minorities and Both Genders	85
5.3 Data and Safety Monitoring Boards	85
5.4 Data Sharing	85
5.5 NCI Clinical Trials Policy	86
6. Adverse Event Reporting	86
7. Biological Specimen Collection and Banking	86
8. Correlative Science, Reference Laboratory Support, and Adjunct Studies	86
8.1 Correlative Science Studies/Reference Laboratories	86
8.2 Adjunct Studies	86
9. Publications	86
10. Group Meetings and Group Communications	86
11. Cross-Group CTSU Accrual & Collaboration with Other NCI-funded Programs/Inv.	87
12. Conflict of Interest	87

13. Scientific Committees	87
13.1 Organizational Structure	87
13.2 Major Research Objectives	87
13.3 Intergroup Trial Accrual & Collaboration with Other NCI-funded Programs/Inv.	88
13.4 Protocol Development	89
13.5 Study Monitoring and Quality Control	89
13.6 Publications	89
14. Cancer Control and Prevention Committee	89
15. Budget	89
16. Cancer Trials Support Unit (CTSU) Integration	90
16.1 Regulatory Support System	90
16.2 Communication	90
16.3 Data Management and Information Technology Initiatives	90
16.4 Supportive Functions	90
16.5 Promotion, Education, and Training	90
16.6 Auditing	90
C. Review Criteria for the Statistics and Data Management Center (SDMC) Application	91
1. SDMC Organization and Facilities	91
2. Study/Protocol Development	91
2.1 Study Design and Analysis	91
2.2 Collaboration with the Operations Center	91
3. Data Management	91
4. Study Monitoring	91
5. Publications	92
6. Independent Research	92
7. Support for On-Site Auditing Program, Participating Site Evaluation, Data Submission	92
8. Compliance with Federal Regulations	92
9. Adverse Event Reporting	92
10. CTSU Interactions & Collaboration with Other NCI-funded Programs/Investigators	92
11. Group Meetings	92
12. Budget	92
D. Review Criteria for Participating Site U10 Applications and Other U10 Applications	93
1. Participation in Group Activities and Contribution to Group Science	93
2. Patient Accrual and Intergroup Participation	93
3. Data Collection, Data Quality & Timeliness, and Data Management	93
4. Human Subjects Protection	93
5. Budget	93
E. Review Criteria for Quality Assurance and Service Centers	94
1. General Review Criteria for Quality Assurance and Service Centers	94
1.1 Significance	94
1.2 Approach	94
1.3 Innovation	94
1.4 Investigators	94
1.5 Environment	94
1.6 Protection of Human Subjects from Research Risk:	94
2. Specific Objectives for Consideration in Review of the Radiological Physics Center	94
3. Specific Objectives for Consideration in Review of Quality Assurance Research Center	95
4. Review Criteria for Budgets for Quality Assurance and Service Centers	95
F. Review Criteria for International Groups	96
1. General Review Criteria for International Groups	96
2. Review Criteria for Budgets for International Groups	96
G. Review Criteria for Competing Supplemental Applications (Interim Review)	96

PART 3: Guidelines for Submission of Non-Competing Continuation Applications.....97

I. General Policies and Procedures	97
II. Non-Competing Continuation Applications Format and Budget Requests	98
A. Application for all Group Components (Ops Ctr, SDMC, Participating Sites, & Other)	98
1. Research Plan (Annual Progress Report – Type 5 Application)	98
1.1 Accrual Performance & Accrual by Gender and Ethnicity/Race	98
1.2 U10 Participating Site Performance & Accrual by Gender and Ethnicity/Race	103
1.3 Overall Group Performance for Study Conduct	103
1.4 Protocol Development and Submission	103
1.5 Summary of Research Accomplishments	104
1.6 Research Plans	105
1.7 Auditing Activities	105
1.8 Publications	105
1.9 Training on Human Subjects Protection for Key Personnel	105
2. Budget	105
2.1 General Budget Information	105
2.2 Non-Competing Budget Adjustments/Redistributions	105
2.3 Budget Adjustments by CTEP for Groups and their Components	107
B. Notification of International Involvement in Group Trials	107

PART 4: Attachments.....108

Attachment # 1: Protocol and Information Office Schema for CTEP Review by Study Type _____ 109

Attachment # 2: Protocol and Information Office Summary CTEP Review by Study Type _____ 111

Attachment # 3: Suggested Format for Summary of Data Quality and Data Timeliness _____ 113

Attachment # 4: Suggested Format for Summary Accrual Tables _____ 114

Attachment # 5: Suggested Format for Summary of Publications By Committee _____ 118

Attachment # 6: Suggested Format for Summary of Administrative Committee Activities _____ 119

Attachment # 7: NCI/CTEP and Group Policy on Contract Review _____ 120

Attachment # 8: Suggested Format for Summary of U10 Participating Site Activities _____ 121

Attachment # 9: Suggested Format for Reporting On-Site Auditing Activities _____ 124

Attachment # 10: Suggested Outline for “Interim Review” Application (Budget/Research Plan) _____ 125

Attachment #11: Cooperative Group Common Budget Outline _____ 128

Attachment #12: Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies _____ 131

Attachment #13: NCI Clinical Trials: Prioritization/Scientific Quality Initiative _____ 132

Attachment #14: List of Abbreviations _____ 142

Attachment #15: Website References _____ 143

PART 1: Description of the Program and Its Policies

I. Introduction

These guidelines for the National Cancer Institute (NCI) Clinical Trials Cooperative Group Program have been developed by staff of the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), NCI, in consultation with staff of the Office of Grants Administration (OGA) and the Division of Extramural Activities (DEA), 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 the National Institutes of Health (NIH) staff who are involved with this Program. They are intended to encourage a consistently excellent clinical trials methodology, while at the same time, permitting each Cooperative Group to design innovative therapeutic trials.

A variety of other rules and regulations affect the Cooperative Groups (e.g., NIH Grants Policy, policies of the Office of Human Research Protections, etc.). These Guidelines for the NCI Clinical Trials Cooperative Group Program are intended to cover CTEP's special requirements for the Cooperative Groups and to supplement the NCI Clinical Trials Policy as well as NIH and US Department of Health and Human Services (DHHS) policies. These Guidelines, as well as the Cooperative Groups' policies, must adhere to NCI, NIH, and DHHS policies. Cooperative Groups should contact the responsible NCI Program Director and the CTEP Program Specialist if the Cooperative Groups believe these Guidelines conflict with other applicable federal policies in order to resolve any apparent discrepancies in the interpretation of these Guidelines.

This Guidelines document is divided into four parts. The first part describes the NCI Clinical Trials Cooperative Group Program and its policies and procedures, including the Terms and Conditions of Award. The second part describes the application, budgetary issues, and peer review processes for new and competing continuation applications, including competing supplemental applications. The third part describes the application and budgetary issues for non-competing continuation applications. The fourth part contains attachments relevant to the policies and procedures associated with the Program and with the application and review processes.

A. General Description of the Program

The NCI 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, the Groups represent a major component of the extramural research effort of the DCTD, 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 multi-institutional clinical trials efforts, Group structure and funding are not usually linked to any specific clinical trial(s). This mechanism has the potential for considerable flexibility for responding to new discoveries, 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.

B. Brief History

The NCI Clinical Trials Cooperative Group Program ("the 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 awarding \$5 million to the NCI to establish the Chemotherapy National Service Center. By 1958, seventeen Groups were organized and operated under research grants from NCI, with the main purpose of testing new anticancer agents from the NCI investigational agent development program. Over the intervening years, the Program has evolved into one

that also places a major emphasis on definitive studies of combined modality approaches to the treatment of cancer.

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

Between 2000 and 2004, approximately 25,000 to 32,000 new patients were enrolled onto Group treatment studies each year, 12,000 to 14,000 patients were evaluated annually on ancillary laboratory correlative studies, and many times this combined number were in follow-up. Moreover, thousands of individual investigators participate in Group studies.

The Groups are heterogeneous in their research objectives and organizational structure. The Groups are currently comprised of four major types: (1) Groups that are specifically disease-oriented (e.g., gynecologic oncology); (2) Groups that primarily design and develop studies involving high technology, single modality studies (e.g., radiation therapy); (3) Groups in which the investigators have a particular expertise (e.g., pediatricians); and (4) multi-modality Groups that include a mix of different investigator specialties and disease orientations. The common thread throughout all the Groups is the responsibility to develop, conduct, and participate in large-scale, randomized, clinical treatment trials in a multi-institutional setting.

C. Group Membership

The membership models of the Groups vary widely and have evolved over time. Some Groups have membership models based entirely on individual participation within his/her associated institution while other Groups have membership models based entirely on institutional participation. Institutional membership (i.e., Participating Sites) may be further divided into main member and affiliated member institutions. Groups may also serve as research bases for Community Clinical Oncology Programs (CCOPs), and thus have CCOPs as members. The funding for participation by members of a Group may be equally diverse. Member participation may be compensated through capitation payments, Participating Site U10 grants, or the NCI Division of Cancer Prevention (DCP) in the case of the CCOPs. ([See Investigators and Participating Sites Rights and Responsibilities in Part 1.V.A., Section 3 on page 35.](#)) In all cases, members of the Groups (whether the member is defined as an individual or an institution/Participating Site) must abide by the Constitution and By-laws of the particular Group as well as the policies and procedures of DHHS, NIH, NCI, Office of Human Research Protections (OHRP), Food and Drug Administration (FDA), and Office of Research Integrity (ORI).

D. Quality Assurance and Service Centers

In addition to Groups that develop and conduct large-scale randomized clinical treatment trials in a multi-institutional setting, the Program also supports Quality Assurance and Service Centers which provide quality assessment and support services for the Groups conducting treatment trials (e.g., Quality Assurance Review Center and the Radiology Physics Center). The Quality Assurance Review Center (QARC) provides radiotherapy quality assurance, diagnostic imaging data management, and clinical research support for the Groups. The Radiological Physics Center (RPC) assures Groups that institutions participating in Group clinical trials deliver prescribed radiation doses that are clinically comparable and consistent by assessing the institutions' radiotherapy programs and helping the institutions implement remedial actions to correct deficiencies. The RPC also assists Groups in developing protocols that involve radiotherapy as well as in developing quality assurance procedures.

E. International Groups

Cooperation with other clinical Cooperative Groups outside the United States (US) can be an efficient way of achieving research objectives that are important to patients both in the US and world-wide, especially with respect to assessing treatment strategies for rare tumors and/or contributing to trials in common tumors that would benefit from enhanced accrual. To promote this type of cooperation and collaboration, the NCI Clinical Trials Cooperative Group Program provides limited financial support for International Groups located outside the US that conduct large-scale, randomized clinical treatment trials in a multi-institutional setting (e.g., the National Cancer Institute of Canada's Clinical Trials Group and the European Organization of Research Treatment Centers). This support is mainly for statistical and data management services provided by the International Group's Statistical and Data Management Center and/or Operations Center in order to facilitate collection and analysis of clinical data on trials in which both US Group and International Groups participate, and in some instances, to assist the International Group to conduct trials of its own that may benefit US patients. In some situations, support is provided for data management at local sites outside the US that are part of the International Group when the local site is participating in a clinical trial led by a US Group.

II. Purpose of the NCI Clinical Trials Cooperative Group Program

The essential purpose of the NCI Clinical Trials Cooperative Group Program is to support organizations that continually generate and conduct new clinical trials consistent with national priorities for cancer treatment research. Primary emphasis is placed on definitive, randomized phase 3 studies for cancer treatment and the development efforts preliminary to those trials. 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 Grants (e.g., R01 grants, P01 grants, and U01 and U19 Cooperative Agreements).

III. Goals of Group Research

A. Improve Therapy

Therapeutic research aimed at improving the survival for persons with cancer and/or reducing major morbidity associated with treatment interventions for the cancer patient is of highest priority to CTEP. When appropriate and when resources permit, CTEP also sponsors investigations that are associated with therapeutic interventions that focus on questions related to other clinical benefits such as quality of life.

B. 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 (e.g., essential to provide the appropriate diagnosis for a study patient or to provide an appropriate assessment of a study's primary endpoint), a variety of other funding mechanisms – including investigator-initiated grants (R01s, P01s) and Cooperative Agreements for discrete projects (U01s, U19s) may also be appropriate for funding these adjunct studies.

C. Cancer Control and Prevention

Groups supported by NCI's DCTD may apply in response to CCOP Requests for Applications to receive funding from the NCI Division of Cancer Prevention (DCP) as a CCOP Research Base. The proposed research activity should be an integral component of the Group's overall research plan. However, peer review of a CCOP Research Base grant, including its cancer control and prevention research plan, is performed separately from the peer review performed for a Group under the Cooperative Agreement for the NCI Clinical Trials Cooperative Group Program administered by CTEP.

D. 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 unrelated to Group studies is appropriately funded through other mechanisms.

IV. Overview of Group Research

A. General Considerations

Under the Cooperative Agreement mechanism, the Groups 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 NCI Clinical Trials Cooperative Group Program functions as efficiently as possible. Definitive phase 3 clinical trials should usually constitute the major portion of a Group's activities and 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.

B. Development of Research Plans

The Group and its Scientific Committees should develop, articulate, and follow a comprehensive research plan that summarizes the Group's specific objectives and lines of investigation for each disease that it chooses to study. The purpose of this plan is to focus attention on long-term goals and to aid the Group in the prioritization of competing research ideas. The plan will frequently include small developmental/pilot studies, phase 2 studies, as well as large-scale phase 3 efforts, all designed to take advantage of the Group's experience, expertise, resources, and clinical opportunities. The comprehensive research plan developed by each Scientific Committee will be a major focus of the peer review process when the Group is reviewed.

In most Groups, the process of research plan development and study development begins at the level of a Scientific Committee (e.g., disease site committee), which develops both an overall research plan as well as specific Group protocols. For a description of the development process for specific studies/protocols by the Group, [see Study/Protocol Development in Part 1.V.A., Section 1.2 on pages 21-22](#). For a description of CTEP's review process for study proposals submitted by the Groups, including small pilot or developmental studies, phase 1 studies, phase 2 studies, and large-scale phase 3 trials, [see Study/Protocol Development Process and Protocol Review in Part 1.V.B., Section 3 on pages 41-44](#).

C. Flexibility

While it is important for the Groups to establish research plans and to implement specific studies in the context of these plans, 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 Program. Therefore, Groups should modify plans when the data warrant such an adjustment.

D. Collaboration with CTEP Staff and Other NCI Staff

CTEP staff assesses 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 3 trials, the Group should involve CTEP staff and, as appropriate, NCI disease-specific Scientific Steering Committees, staff from the NCI Coordinating Center for Clinical Trials (CCCT), and other NCI Staff, in the planning of such trials at the earliest possible stage. This includes participation by CTEP staff on early planning Group committees (i.e., core committees) and in other similar planning activities. Likewise, CTEP should also be involved in the development of the Group's comprehensive research plans that articulate its specific objectives and lines of investigation for diseases and broad new initiatives being undertaken by the Group. The Groups also collaborate with staff from other branches of the NCI on particular research trials. Information on other NCI divisions with which Groups collaborate can be obtained from the NCI website at [[Website Reference 1](#)].

E. Group Prioritization of Scientific Research and Efficiency of Study Development

In addition to providing a stable 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. As each Scientific Committee formulates plans and specific protocols, the Group leadership must prioritize

these plans and studies in the context of the Group's overall scientific objectives. The administrative structure of a Group should support rapid development and activation of the most important studies.

F. Conduct of Group Clinical Research

Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and human subjects who participate in research studies. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Groups should strive to comply with this standard to the greatest degree possible since it provides public assurance that the rights, safety, and well-being of trial patients are protected, and that the clinical trial data are credible. Information on GCP standards in FDA-regulated Clinical Trials is provided at [[Website Reference 2](#)].

The integrity of clinical data is a function of the entire process of data collection and analysis. Groups need detailed Quality Control and Quality Assurance plans and systems to assure protocol adherence in the administration of protocol-prescribed therapy and in the uniform collection of data. Vigilance to detect honest errors, whether systematic or random, as well as data falsification, is especially important to clinical trials since independent replication of most trials is not feasible.

G. Cancer Trials Support Unit (CTSU)

In response to the Armitage Report, a 1997 report from the NCI's Clinical Trials Program Review Group, the Cancer Trials Support Unit (CTSU) was established in order to: (1) facilitate physician and patient access to NCI-sponsored clinical trials through an efficient enrollment procedure that facilitates cross-Group accrual and permits non-Group members to enroll patients on NCI-sponsored trials; (2) streamline data entry and collection for clinical trials through the use of standard case report forms and reporting; and (3) reduce the regulatory and administrative burdens on clinical trials by unifying and standardizing Group membership rosters and institutional review board (IRB) approvals. **The CTSU includes only Groups that study treatment of adult cancers. The Children's Oncology Group (COG) does not participate in the CTSU or in its Regulatory Support System at the current time.**

All members of a Group are eligible to participate in any Group trial open in the CTSU, thus allowing investigators to enroll patients in studies that they would not have access to through their own Group; however, the Group member must first register with the CTSU at [[Website Reference 3](#)]. Investigators who have registered with the CTSU gain access to all study protocols as well as other materials available on the CTSU menu, including educational materials for the studies. As of May 2002, qualified physicians who are not members of any Group may join the CTSU and enroll patients on all clinical trials on the CTSU menu. These non-Group-affiliated investigators must demonstrate the same general qualifications as do Group members. Although the CTSU is designed for patient enrollment to phase 3 trials, selected phase 2 trials are also opened in the CTSU on a case-by-case basis. The CTSU has a number of mechanisms available for data collection and management, depending on the needs of the specific trial and the priorities of the Program.

In January 2003, the CTSU initiated the Regulatory Support System (RSS). With the institution of RSS, the CTSU became the central repository for all regulatory documents submitted by sites participating in any phase 1, phase 2, or phase 3 adult Group trial, regardless of whether the trial will be open in the CTSU, with the exception of large-scale prevention trials which typically enroll 10,000 patients or more. In addition, all investigators participating in clinical trials through the Group mechanism must also be NCI registered investigators (Form FDA 1572) and this form must be on file at the CTSU.

It is anticipated that additional functions and systems will be developed in the CTSU to further facilitate patient accrual and streamline data collection and the regulatory/administrative processes associated with the conduct of trials in the NCI Clinical Trials Cooperative Group Program. These additional functions may include electronic remote data capture and a centralized registration and randomization hub for adult Group trials.

H. Timely Completion of Studies – Participation in CTSU and 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. It is equally important that physicians have access to a variety of clinical trials in order to enhance their ability to enroll patients in an appropriate study. A single Group often cannot meet these goals, and therefore, Intergroup collaborations are frequently appropriate. Collaboration among Groups in a study allows broad participation by various investigators in both the development and conduct of the study as well as facilitates the timely completion of the study. A study is considered an Intergroup study if it involves at least two Groups (i.e., a Lead Group and one endorsing Group). Large Intergroup phase 3 studies that have broad endorsement across a number of Groups are sometimes given special designation with an Intergroup study number (e.g., INT-0113); however, all Intergroup studies receive the same recognition with respect to scientific review (see explanation in the next paragraph) regardless of study size.

The Cancer Trials Support Unit (CTSU) described in the preceding section (Section G) was established to facilitate physician access to phase 3 treatment trials developed by all Groups, not just the Group to which a physician or institutional member belongs. If physicians do not belong to the Group leading a CTSU trial, they can specify that the accrual “credit” designated for patients they enroll on the trial be allocated to a Group of which they are members. In this way, a Group will receive recognition during peer review by Subcommittee H-Clinical Groups (the chartered peer review subcommittee for the NCI Clinical Trials Cooperative Group Program) for participation of its members in trials, even if the Group does not endorse the trial (i.e., recognition of accrual). A Group can also officially endorse another Group’s trial and thus receive additional recognition during peer review by Subcommittee H-Clinical Groups (i.e., recognition of scientific contribution to the study in addition to recognition of accrual) as well as recognition in the form of a publication credit. **The NCI is specifically directing reviewers on Subcommittee H-Clinical Groups to consider a Group’s endorsement of, and active, meaningful participation in, studies being led by another Group to be equivalent in merit to that given to the lead Group for the study. This policy applies to all Intergroup studies even if the Intergroup study is not available on the CTSU (e.g., phase 2 study).**

I. Intergroup Collaborations

Most Disease Committees within the Groups participate in Intergroup collaborations. These Intergroup collaborations are highly valued by the Groups, NCI/CTEP, and the individual investigators since they allow for cross-Group participation in important trials that require significant patient accrual – beyond the accrual potential of any one Group – to answer the research questions being addressed. This Intergroup collaboration may be particularly important in phase 3 trials for uncommon disease types.

There is wide variation in the organizational structure of the various disease-site-specific Intergroups; however, they all have internal Standard Operating Procedures and policies as well as formal reporting relationships to their respective, sponsoring Groups. 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. CTEP staff members also participate in the Intergroup process to facilitate these important collaborative activities.

Since Intergroup trials require enrollment from multiple Groups and participation from multiple co-Principal Investigators to be successful, the NCI has specifically developed well-defined review criteria for the Groups that emphasize the importance of Intergroup participation. Reviewers are instructed to consider a Group endorsement with active, meaningful participation in an Intergroup study that the Group does not lead to be as important as the scientific contribution the Group provides through development and accrual to its own studies. (See [Scientific Committees - Major Research Objectives in Part 2.III.B, Section 13.2 on pages 85-86.](#))

The CTSU provides physician access to most phase 3 trials; however since phase 1 and phase 2 trials may not be open in the CTSU, another mechanism exists to facilitate collaboration among Groups. This mechanism is described in the Guidelines for the Conduct of Intergroup Studies (revised June 1993 and available from CTEP staff), which were developed by the Groups and approved by CTEP prior to the establishment of the CTSU with the intent of facilitating collaborations in the development and conduct of trials. These 1993 Guidelines still serve to guide the development of Intergroup collaboration on studies that are not open in the CTSU.

The Clinical Trials Working Group (CTWG) initiative, established in January 2004 by the NCI Director, also endorsed the concept of increased collaborative team science and clinical trials cooperation in its summary report to the National Cancer Advisory Board (NCAB) in June 2005. Information on the CTWG and a copy of its report to the NCAB is available at [[Website Reference 39](#)].

J. Collaborations with Other NCI-funded Programs and Investigators

Groups are also encouraged to collaborate with other NCI-funded programs and investigators (e.g., NCI Cancer Centers, Specialized Programs of Research Excellence [SPOREs], early clinical trials networks, other NCI-supported multi-site clinical trials networks, and R01 and P01 investigators). These collaborations may include advancing research ideas from pilot studies to phase 3 trials (with hand-offs between various NCI-funded programs where appropriate), providing correlative science services for large, multi-site studies, and participation in multi-site trials conducted throughout the NCI-supported clinical trials system. These types of collaborations should be considered positively at the time of peer review.

K. 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. Groups are also encouraged to seek non-CTEP sources of funding to accomplish their full research agenda. Indeed, the clinical trials resources of the Groups serve as unique assets in competing for other NIH funding as well as private sources of funding to support specific aspects of a Group's overall research program.

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 it is practical and consistent with good science, cost containment at all levels of study conduct should be a factor in protocol design.

L. Biological Specimen Banks

The advent of powerful molecular technologies and the emergence of targeted therapeutics have opened the door to developing more effective and, in some cases, individualized treatment of patients with cancer. Development of effective therapeutic interventions, based on the comprehensive analysis of critical pathways of cancer initiation and progression, requires access to biological specimens from patients treated in prospective randomized trials. Such high-quality biological specimen banks containing uniformly collected specimens with validated clinical and outcome data are essential for development and delivery of new diagnostic and predictive tools. In particular, Groups conducting phase 3 clinical trials are uniquely positioned to provide high-quality biologic specimens associated with detailed treatment histories, recurrence data, and careful follow-up from patients over long periods of time

The infrastructure needed to ensure the collection and storage of high-quality, well annotated human specimens (as well as the access to these specimens) from patient populations entered into NCI-funded, phase 3 clinical trials is funded and administered by DCTD, jointly by CTEP (through the Group's

Cooperative Agreement award under the NCI Clinical Trials Cooperative Group Program) and by the Cancer Diagnosis Program (through a U24 Cooperative Agreement award mechanism for resource-related research projects). For information on the U24 Cooperative Agreement award mechanism administered by the Cancer Diagnosis Program (CDP), see RFA-CA-05-017 entitled "Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials" at [\[Website Reference 4\]](#). Group biological specimen banks will function under the rules developed for this U24 Cooperative Agreement. Eligible Groups may apply for funding through this U24 Cooperative Agreement award mechanism if they have current NCI funding for conducting phase 3 cancer clinical trials and have one or more operating specimen banks with access to detailed demographic, clinical, treatment, and outcome data for the cases (patients) whose specimens make up the bank.

The funding provided by the U24 Cooperative Agreement award is intended to support the activities necessary to operate a well-developed bank. The range of activities that can be covered includes support and training of staff to collect and ship biological specimens from the collection sites to the central banks, to oversee receipt of specimens, and to process specimens at the central bank, including conducting pathologic review and providing histology services. The funding can also cover costs for equipment and supplies, including shipping materials and shipping costs, storage costs (such as liquid nitrogen for freezers) and costs for informatics to track specimens, as well as miscellaneous costs such as costs for travel to required meetings and maintenance contracts and subcontracts to participating institutions. Additional support can be obtained to cover some of the costs associated with review of requests for specimens and data, and retrieval and shipment of specimens to researchers and/or return of blocks to the collecting institutions for patient care or legal requirements. The costs of organizing or operating data centers beyond those incremental costs directly associated with transmission of data related to operation of the banks are not covered by this funding mechanism. A Group may request funding to cover costs associated with its biological specimen banks that are not covered by the U24 Cooperative Agreement award in its Cooperative Agreement award under the NCI Clinical Trials Cooperative Group Program.

More information on funding of biological specimens collected from NCI-funded phase 3 cancer clinical trials, including the Terms and Conditions of Award for the U24 Cooperative Agreement is provided at [\[Website Reference 4\]](#) and on the CDP website at [\[Website Reference 5\]](#).

V. Terms and Conditions of Award

A. Awardee Rights and Responsibilities

The awardee's programmatic responsibilities for the conduct of the research supported by this U10 Cooperative Agreement are described in this document (NATIONAL CANCER INSTITUTE (NCI) CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES), the NCI CLINICAL TRIALS POLICY, the INVESTIGATOR'S HANDBOOK (A Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis, NCI), and the NCI-CANCER TREATMENT MANAGEMENT BRANCH (CTMB) GUIDELINES FOR ON-SITE MONITORING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS, CCOP RESEARCH BASES, AND THE CANCER TRIALS SUPPORT UNIT (CTSU), and any subsequent modifications of these documents. Specific portions of these documents, as enumerated in the following sections, are incorporated by reference as Terms and Conditions of Award. In particular, the NCI Clinical Trials Policy requires Clinical Terms of Award for clinical studies and trials when they are a component of any proposed research being funded by the NCI. The Policy requires studies to be monitored commensurate with the degree of potential risk to study subjects and the complexity of the study.

The four documents referenced above are available from the Cancer Therapy Evaluation Program (CTEP) upon request. The URLs for each of these documents are also listed below:

NCI CLINICAL TRIALS COOPERATIVE GROUP PROGRAM GUIDELINES [[Website Reference 6](#)]

NCI CLINICAL TRIALS POLICY [[Website Reference 40](#)]

INVESTIGATOR'S HANDBOOK [[Website Reference 7](#)]

NCI-CTMB GUIDELINES FOR ON-SITE MONITORING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS, CCOP RESEARCH BASES, AND THE CANCER TRIALS SUPPORT UNIT (CTSU) [[Website Reference 8](#)]

Cooperative Groups consists of four main components: (1) Operations Center (including Group Chair's office); (2) Statistics and Data Management Center (SDMC); (3) Group committees (Scientific and Administrative Committees); and (4) Member Participating Sites and investigators. Each component has responsibilities for meeting the goals and objectives outlined in these Guidelines. Each Group is governed by a Constitution and By-laws that describes membership criteria, procedures for selecting Group leadership, and other details of governance. Each Group is led by a Chair who is ultimately responsible for content and conduct of the Group's program. Beyond these requirements, the structure and operational management of the Group and its components is the responsibility of the Group itself to determine.

Sections 1 through 4 below describe the rights and responsibilities of each of the four main components with respect to the Terms and Conditions of Award. Also described in this section are the rights and responsibilities of NCI/CTEP staff ([See Part 1.V., Section B on pages 40-47](#)), collaborative responsibilities of the Groups ([See Part 1.V., Section C on pages 48-49](#)) and the arbitration process for resolving disagreements between award recipients and NCI/CTEP ([See Part 1.V., Section D on page 49.](#))

Throughout these Terms and Conditions of Award, “participant” refers to all awardees as well as Participating Sites and/or individual investigators, both funded and unfunded, with whom they are participating or collaborating. Since some Groups define members as individual investigators or groups of investigators and other Groups define members as institutions, throughout these Terms and Conditions of Award, “Participating Site” refers to all members of a Group no matter how the membership is defined within that particular Group.

The specific responsibilities of the four main components of a Group are described in detail on the following pages; however, responsibilities assigned to the Group Operations Center may be delegated by the

Operations Center to the Statistics and Data Management Center or to another Group component, and vice-versa.

For awardees representing Quality Assurance and Service Centers or International Groups, programmatic responsibilities will usually not involve all four main components of a Group as described on the following pages. In most cases, the programmatic responsibilities for these awardees will be limited to those responsibilities described under the rights and responsibilities of the Statistical and Data Management Center since the focus of these entities is mainly on the collection, transfer, and assessment of data collected or therapy delivered on a clinical trial or participation in trials rather than on the development of a specific scientific agenda and series of clinical trials.

1. Operations Center Rights and Responsibilities

The Group's Operations Center is under the leadership of the Group Chair, who coordinates all the scientific and administrative decisions related to Group-funded activities and the Group's Participating Sites with the assistance of the staffs of the Statistics and Data Management Center. The Group Chair or designee is also responsible for communication about these activities with the appropriate CTEP staff.

The Group's Operations Center is responsible for coordinating protocol development, protocol submission, study conduct, performance reporting, quality assurance including quality control and study monitoring, protocol amendments/status changes, adherence to requirements regarding investigational agent management and all federal regulations. In addition, the Operations Center is responsible for the financial management of the Group, including issuing subcontracts or purchased services agreements related to patient case reimbursements as well as overall management of the funds associated with the Cooperative Agreement. Specific responsibilities of the Operations Center include the following:

1.1 Organization Structure, By-laws, and Standard Operating Procedures

The Operations Center is responsible for development and maintenance of an organizational structure for the Group, including a Constitution and By-laws for the Group. The organizational structure should include the Scientific and Administrative Committees that the Group will need to support its research objectives. The Operations Center is also responsible for the preparation and maintenance of Standard Operating Procedures (SOPs) that cover all aspects of Group activities.

1.2 Study/Protocol Development

It is the responsibility of the Group to develop the details of research studies, including definition of objectives and approaches, planning, implementation, and analysis as well as publication of results, interpretations, and conclusions of the studies. The Group shall, with CTEP assistance, develop Group research goals in accordance with national research goals and develop studies for clinical cancer research in accordance with the Group's research interests, abilities and goals. The Group Chair shall designate other Group investigators to serve as Study Chairs for each proposed study/protocol. The Operations Center is responsible, in accordance with the Group's Constitution and By-laws as well as with its Policies and Procedures (as defined in its SOPs), for establishing procedures for development and submission of Group studies/protocols to the CTEP Protocol and Information Office (PIO) in a timely fashion for review and approval by NCI.

Protocols should be developed, submitted, and implemented in accordance with instructions set forth in the DCTD Investigator's Handbook [[Website Reference 7](#)]. Since public funds are used to support Group studies sponsored under this Cooperative Agreement, no Group study using funds supplied under this Cooperative Agreement can be opened without prior approval from the CTEP Protocol Review Committee (PRC) as detailed below. In addition, Group phase 3 studies using funds supplied under this Cooperative Agreement cannot be conducted under a company IND; all phase 3 IND studies supported, in whole or in part, under this Cooperative Agreement must be conducted under a Group IND or a CTEP IND.

- a) Submission of a protocol for a phase 1 or phase 2 study involving a CTEP-sponsored investigational agent (CTEP IND agent) should be preceded by a written Letter of Intent (LOI) from the Group to the CTEP LOI Coordinator declaring interest in conducting a particular study. LOIs should be submitted using the "Letter of Intent Submission Form" template for CTEP review, provided on the CTEP website at [[Website Reference 9](#)]. Protocols for phase 1 and phase 2 studies must be submitted within a specified time period following CTEP approval of the LOI for the study. If the Group is unable to complete the protocol for the study within the specified time period, CTEP can rescind its approval of the LOI for development by that Group.
- b) Submission of a protocol for a phase 3 study should be preceded by a Concept describing the Group's proposed phase 3 evaluation. Concepts should be submitted using the "Phase 3

Concept Submission” template available on the CTEP website at [[Website Reference 10](#)]. A phase 3 protocol may be submitted **only** after official notification of approval from CTEP of the study Concept. The anticipated source of agent supply and distribution for each agent to be employed in a treatment trial must be explicitly stated in the Concept, including requests for CTEP-sponsored IND agents and/or distribution by CTEP’s Pharmaceutical Management Branch of commercial and/or investigational agents. A phase 3 trial’s protocol document must be submitted within a specified time period CTEP approval of the Concept for the study. If the Group is unable to complete the protocol for the study within the specified time period and the Concept is considered high-priority, CTEP may rescind its approval of the Concept for development by the Group and may reassign responsibility for development of the Concept to another Group.

- c) Group phase 2 studies enrolling fewer than 100 patients and not using CTEP-sponsored IND agents (termed “Developmental/Strategy” protocols) must be submitted to CTEP for review by the PRC. The PRC reviewers, however, will focus their comments on the scientific rationale for these studies and the likelihood that the study will lead to a definitive phase 3 trial. If patient safety or regulatory issues are noted by the CTEP review, a response will be required; but the Group assumes full responsibility for the regulatory, patient safety, pharmaceutical, and informed consent review of the study and for ensuring its compliance with all federal and CTEP-specific regulations regarding Group research. CTEP PRC reviewers do not purposefully review or verify these sections of a Developmental Strategy protocol. Groups are also expected to activate Developmental Strategy studies in a timely manner. Although the scope of CTEP review is limited with respect to Developmental Strategy studies, CTEP may require full review of these studies in the event that studies are duplicative and/or programmatic resources to support the clinical trials program are constrained to the extent that prioritization of studies is required with respect to national priorities in cancer treatment/research. [See Study/Protocol Development and Review in Part 1.V.B., Section 3 on pages 41-44](#) for information on Developmental/Strategy reviews as well as other types of CTEP review, including review of protocols for phase 1 studies, phase 2 studies enrolling 100 patients or more, phase 3 studies, and other studies.)
- d) The Operations Center is responsible for communicating the results of the CTEP PRC review to relevant Group committees and Group members.
- e) The Group will not expend any NCI funds to conduct any study disapproved by CTEP unless the arbitration process modifies CTEP’s decision regarding disapproval. ([See Arbitration in Part 1.V., Section D on page 49.](#))
- f) All studies using CTEP-sponsored investigational agents or agents supplied by CTEP under CTEP Collaborative Agreements (such as Cooperative Research and Development Agreements [CRADAs], Clinical Trial Agreements [CTAs], and Clinical Supply Agreements [CSAs]) shall be conducted in accordance with the terms of the NCI/CTEP Intellectual Property Option to Collaborators, found on the CTEP website at [[Website Reference 11](#)], and the NCI Standard Protocol Language for CRADAs and CTAs. When new avenues of cancer therapy involving any investigational agents are pursued, the clinical information obtained in the study should be acceptable to the FDA and other health authorities for inclusion in a possible licensing application.
- g) When NCI/CTEP and the Group contract with the same company (or companies) for support for the same trial (i.e., trials conducted under CTEP Collaborative Agreements), the Group contracts may require CTEP review. ([See Attachment #7 for information on NCI/CTEP and Group policy regarding contract review.](#))
- h) Group SOPs should include time-lines for the development of LOIs, Concepts, and all other studies, from initial submission of the study idea to CTEP through study activation. The SOPs should also include mechanisms for monitoring the performance of the Operations Center and Group committees and investigators in adhering to these time-lines, as well as corrective action plans outlining steps to be taken when these time-lines are not met. Data concerning a Group’s performance in meeting time-lines for study/protocol development should be provided in its Annual Progress Report.

1.3 Quality Control of Group Clinical Trials

The Group is responsible for establishing mechanisms to assure the accuracy and reliability of the Group's clinical trial data. Since quality control and quality assurance are inherently linked, both the Operations Center and the Statistics and Data Management Center are involved in quality control and quality assurance. In addition, the Clinical Trials Monitoring Branch (CTMB) of CTEP provides direct oversight of each Group's monitoring program, which includes on-site auditing as one component. (See [On-site Auditing in Part 1.V.A., Section 1.4 on page 24.](#))

Quality control is a complex undertaking spanning the entire range of diagnostic and therapeutic modalities employed by the Group. Key items that should be addressed in a Group's quality control procedures include the following:

- a) *Participating Site performance evaluations:* Procedures should be in place for placing Participating Sites on probation for inadequate performance and for removing Participating Sites from the Group if performance is not adequate during the probationary period or at any time during which the Participating Site does not meet established Group standards. Performance factors to be considered include the following:
 - i. Accrual of adequate number of eligible patients onto Group trials;
 - ii. Timely and accurate submission of required data;
 - iii. Conscientious observance of protocol requirements;
 - iv. Participation in study development, leadership, and publication; and
 - v. Participation in Group leadership and/or other Group activities.
- b) *Educational functions that address data collection, data management, and overall data quality:* These include, but are not limited to, the following:
 - i. Training of new Clinical Research Associates (CRAs) in the Group's data submission policies and on-going training of all CRAs concerning changes to Group procedures and instructions for data submission in new protocols;
 - ii. Instruction of Study Chairs on their responsibilities for study monitoring;
 - iii. Instruction of Principal Investigators and other investigators at member Participating Sites on their responsibilities for complying with Group SOPs and federal regulations at their institution/site; and
 - iv. Training/guidance provided to all participants on how to comply with NCI/NIH policies and procedures (e.g., policies regarding human subjects protection, ethics, conflict of interest, and procedures such as those regarding use of the CTSU), in addition to the policies and procedures of other governmental agencies (e.g., OHRP, FDA) that are also important to the conduct of clinical trials
- c) *Committees for central review of major elements that affect the outcome of trials, including the following:*
 - i. *Pathology:* Pathology review is usually, but not always, 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 central verification of pathologic diagnosis should be required by the Group in those cases in which known variability in the accuracy of histologic (or other) diagnosis is a potentially serious problem and in which pathology data may provide important prognostic information.
 - ii. *Radiation therapy:* When relevant, central review (either concurrent or retrospective) of treatment-planning studies and compliance with protocol-specified doses for individual patients may be required. Minimal standards for acceptability of equipment may also 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), based in Houston, TX. The RPC can also supply each Group's radiation therapy quality control office with the physics data necessary to conduct its case-level review. The RPC performs dosimetric review of treatment records for several Groups and maintains a database of all radiotherapy facilities involved in clinical trials. More information on the RPC can be obtained at [\[Website Reference 37\]](#). The Quality Assurance Review Center (QARC), a Global Data and Review Center located at the University of Massachusetts Medical School in Worcester, MA, also provides radiotherapy quality assurance and diagnostic

imaging data management programs for Groups. More information on QARC can be obtained at [[Website Reference 38](#)].

- iii. *Chemotherapy*: Central review may be performed of submitted data to determine protocol compliance with dose administration and dosage modification.
- iv. *Surgery*: When relevant, adequacy of protocol-specified surgical procedures may be assessed (e.g., through review of 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. When appropriate, Group surgical committees may wish to draft guidelines for acceptable surgical procedures to be used in specific studies.
- v. *Diagnostic Imaging*: Central review may be conducted of reported responses and to assess adequacy of imaging and staging.

1.4 On-site Auditing

Both the Group's Operations Center and its Statistics and Data Management Center have responsibilities with respect to on-site auditing, and the Group's SOPs should clearly delineate how these responsibilities are apportioned between the two Centers.

As a sponsor for investigational agents and the funding agency for cancer clinical trials, FDA regulations require the DCTD to maintain a monitoring program. The Clinical Trials Monitoring Branch (CTMB) of CTEP provides direct oversight of each Group's monitoring program. All monitoring programs include auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the Groups and to verify investigator compliance with protocol and regulatory requirements. In addition, the monitoring program provides an opportunity for the audit team to share with the staff at the Participating Site information concerning data quality, data management, and other aspects of quality assurance. The main objective of the audit program used by the Groups is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documents.

The NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) require all institutions to be audited at least once every 36 months. In order for the NCI to review the Group's compliance with this requirement, each Group should conduct a comprehensive review of its membership and provide annually an accounting of audit activities for all Participating Sites as described in [On-site Auditing Activities in Part 2.II.C., Section 5.3 on page 68](#). (See the [Suggested Format for Reporting On-Site Auditing Activities in Part 4 – Attachment #9](#).)

The Group's Operations Center is responsible for ensuring that all Group Participating Sites conduct routine audits in accordance with the NCI-CTMB Guidelines for Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) [[Website Reference 8](#)] and that the results of all audits are reported to the NCI in accordance with the Guidelines. The Operations Center is responsible for oversight of all sites enrolling patients on studies based on membership in the Group; this includes ultimate oversight responsibility for affiliated sites of a Participating Site Member. The Operations Center should be aware of all affiliate sites participating in its trials under the aegis of a Member Participating Site. Participating Sites (and affiliates) found not to be in compliance with the NCI Guidelines for On-Site Monitoring by the CTMB may be suspended from participating in Group trials until compliance can be confirmed by CTEP/CTMB.

Additional information on quality assurance required of Groups with respect to trial data (including Operations Center responsibilities) and, in particular, procedures a Group is required to follow in the event any data irregularities are identified through the audit program or other quality control procedures are explained in detail in these Terms and Conditions of Award ([See Quality Assurance in Part 1.V.B., Section 5 on pages 45-46](#)).

1.5 Compliance with Federal Regulations Concerning Clinical Research

The Operations Center is responsible for assuring that the Group is in compliance with all applicable federal regulations concerning the conduct of human subjects research. Policies and guidelines to be addressed include the following:

- a) *Office for Human Research Protection (OHRP) Assurances:* The Operations Center must assure that each Participating Site has a current, approved assurance, a Federalwide Assurance (FWA), on file with OHRP. Information on assurances is available on the OHRP website at [[Website Reference 14\(a\)](#)]. In addition, federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with the reference to risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. Information on this requirement is available on the OHRP website at [[Website Reference 14\(b\)](#)].
- b) *Institutional Review Board (IRB) review of Group protocols:* The Operations Center must assure that each Group protocol is reviewed and approved by each Group Participating Site's IRB prior to patient entry, and assure that each protocol is reviewed annually by the IRB so long as the protocol is active. Each Participating Site is required to forward its regulatory documents to the Regulatory Support System (RSS) of the CTSU. (See [CTSU Interactions in Part 1.V.A., Section 3.8 on page 36.](#)) If the NCI Central Institutional Review Board (CIRB) has reviewed a study protocol, the IRB of the Participating Site may choose to use the facilitated review process available to local IRBs through the CIRB mechanism for that study. Information on the CIRB and the facilitated review process is available on the CIRB website [[Website Reference 13](#)]. The current policies and procedures associated with the CIRB are being developed and may evolve over time. The most recent policy and procedure updates are posted on the CIRB website.
- c) *Assuring appropriate informed consent:* The Operations Center must have procedures in place to ensure that each Participating Site is trained and understands the policies and procedures relevant to ensuring that patients are enrolled on studies with appropriate informed consent per NCI/NIH policy and federal regulations.
- d) *IRB review of the Operations Center and the Statistics and Data Management Center:* An IRB should determine and document that the Operations Center and Statistics and Data Management Center have sufficient mechanisms in place to ensure that (1) data management, data analysis, and Data and Safety Monitoring systems are adequate, given the nature of the research involved; (2) sample protocols and informed consent documents are developed and distributed to each Participating Site; (3) each Participating Site holds an applicable OHRP-approved Assurance (i.e., FWA); (4) each protocol is reviewed and approved by the IRB at the Participating Site prior to the enrollment of subjects; (5) any substantive modification by the Participating Site of sample consent information related to risks or alternative procedures is appropriately justified; and (6) informed consent is obtained from each subject in compliance with DHHS regulations. Information on this requirement for IRB review can be obtained on the OHRP website at [[Website Reference 14\(a\)](#)].
- e) *Inclusion of women and minorities in clinical research:* NIH policy requires that women and members of minority groups and ethnic subgroups be included in all NIH-supported biomedical and behavioral clinical research projects involving human subjects [[Website Reference 15](#)]. Compliance with this policy requires appropriate study designs, targets for total protocol accrual with distribution by ethnic/racial categories and by sex/gender, as well as reporting of accrual by ethnic/racial categories and by sex/gender. Since Groups conduct multiple phase 3 clinical trials, the amended NIH Policy on inclusion of women and minorities in research also applies (see NIH Guide Notice on NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended October 2001 at [[Website Reference 16\(a\)](#)], with a complete copy of the updated Guidelines available at

[[Website Reference 16\(b\)](#)]). A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial groups must be included in clinical trial protocols. Cumulative subject accrual and progress in conducting subset analyses must be reported to NIH in the annual Progress Reports. Final analyses of sex/gender and ethnic/racial differences must be reported in the required Final Progress Report or Competitive Renewal Applications (or Contract Renewals/Extensions) as stated in Section II.B in these amended NIH Guidelines.

- f) *Inclusion of children:* NIH policy requires that children (i.e., individuals under 21 years of age) must be included in all human subjects research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them [[Website Reference 17](#)]. For cancer clinical research, Groups conducting research in adult cancers can provide a rationale for not including children because the majority of children with cancer in the United States are already accessed by a nationwide pediatric disease research network, so that requiring inclusion of children in the proposed adult study would be both difficult and unnecessary (since the research question is already being addressed in children by the pediatric network) as well as potentially counterproductive (since fewer children would be available for the pediatric network study if other studies were required to recruit and include children).
- g) *Data and Safety Monitoring Policy and Plans:* The Group Operations Center must establish a Data and Safety Monitoring Policy for the clinical trials conducted by the Group in compliance with NIH and NCI guidelines for data and safety monitoring for clinical trials. For phase 3 trials, Data and Safety Monitoring Boards (DSMBs) must be established that comply with the “NCI Cooperative Group Data Monitoring Committee Policy” found on the CTEP website at [[Website Reference 18](#)]. Data and Safety Monitoring Plans developed for other Group studies (e.g., phase 1 and phase 2 studies, pilot studies, etc.) must comply with the NIH policy for data and safety monitoring, posted on the NIH website at [[Website Reference 19](#)], with additional description at [[Website Reference 20](#)]. Further information concerning essential elements of Data and Safety Monitoring Plans for clinical trials funded by the NCI is available at [[Website Reference 21](#)]. The Group’s Data and Safety Monitoring Policy must be submitted to and approved by the responsible NCI Program Director.

Group requests for changes in the trial design of open phase 3 trials under DSMB monitoring, including requests for a change in accrual targets, must first be discussed with CTEP before such requests may be submitted to the DSMB for its approval. If CTEP is willing to approve these changes, the Group may then seek DSMB approval before submitting an official amendment to CTEP. The main exception to this policy is when design changes are requested by the DSMB based on safety or outcome data available only to the DSMB.

For information on early study closure of phase 3 studies under DSMB monitoring, see [Study Monitoring in Part 1.V.A., Section 2.4 \(i\)-ii on pages 32-33](#).

- h) *Data Sharing Policy:* The Group is required to have a plan for sharing research data. Information on the NIH policy regarding sharing research data can be found on the NIH website at [[Website Reference 34](#)]. The Group’s policy for data sharing must be submitted to and approved by the responsible NCI Program Director. A template to help Groups develop their own Data Sharing Policies is provided on the CTEP website at [[Website Reference 35](#)]. Per this policy, requests for data will only be considered once the primary study analyses have been published.

Requests for data from clinical trials, conducted under a binding collaborative agreement between NCI CTEP and a pharmaceutical/biotechnology company, that are not under DSMB monitoring but are not yet subject to the Data Sharing Policy (e.g., because the primary study analyses have not yet been published) must be in compliance with the terms of the binding collaborative agreement and must be approved by CTEP (i.e., the NCI Program Director in

conjunction with the CTEP Regulatory Affairs Branch). Release of data may also be subject to the terms of any contracts the Group has with other entities which cover any of the requested data.

- i) *Education on the Protection of Human Subjects Participants:* NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. This policy is available on the NIH website at [[Website Reference 44](#)].
- j) *Other Federal Regulations:* Information on other federal regulations (and their associated citations/URLs) that may be applicable to the Group's research is provided in [Attachment #15](#) under "Other Federal Citations for NIH Grants/Cooperative Agreements Involved in Human Subjects Research."

1.6 NCI Clinical Trials Policy

The NCI Clinical Trials Policy requires Clinical Terms of Award for clinical studies and trials when they are a component of any proposed research being funded by the NCI. The Policy requires studies to be monitored commensurate with the degree of potential risk to study subjects and the complexity of the study [[Website Reference 40](#)].

1.7 Adverse Event Reporting and Patient Safety

The Operations Center must establish a system for assuring timely reporting of all serious and/or unexpected adverse events to ensure potential patient safety issues can be identified and addressed quickly. Adverse events should be reported using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), which is NCI and CTEP's standard language for reporting adverse events in oncology clinical trials [[Website Reference 22](#)]. For agents under CTEP-sponsored INDs, this involves reporting to CTEP via the Adverse Event Expedited Reporting System (AdEERS) according to the CTEP guidelines specified in each protocol. Groups must also use AdEERS for expedited reporting of adverse events for all studies, including studies that do **not** include CTEP-sponsored IND agents since AdEERS provides reporting pathways for studies that do not include CTEP IND agents, as well as pathways for studies that do not include any agents (e.g. surgical only study, radiation only study). Thus, all Group studies funded under this Cooperative Agreement, in whole or in part, must use AdEERS for expedited reporting of adverse events.

In addition, for any study using agents under a CTEP-sponsored IND, any increase in the incidence of expected toxicities and any plans to change a trial design or close a trial early due to toxicity should immediately be discussed with the Investigational Drug Branch at CTEP before any action is taken. For CTEP-sponsored studies that are not being conducted under a CTEP IND, any major patient safety issues (e.g., study closure/suspension for adverse events, inappropriate randomization of patients to treatment arms, etc.) also require immediate notification to the NCI Program Director or his/her designee.

1.8 Biological Specimen Collection and Banking

Collection and banking of tissues and other biological specimens is an increasingly important aspect of Group clinical research. The Operations Center is responsible for coordinating the acquisition and shipping of protocol-specified tumor specimens and biological fluids (with relevant clinical data) to the appropriate laboratories for testing and to a tumor/specimen repository for storage of specimens for future correlative science laboratory studies.

1.9 Correlative Science and Reference Laboratory Support

Correlative studies are increasingly central to the interpretation of clinical trials data, particularly for studies of molecularly targeted agents. While the Disease Committees play a key role in the development and conduct of correlative studies for Group protocols and in the identification of

laboratories to conduct this research, the Operations Center must provide overall coordination and prioritization of the Group's correlative science research agenda. Correlative science research may be conducted and supported either by Reference Laboratories supported by the Group or by laboratories using other sources of funding. Listed below are various resources for correlative science studies:

- a) *Reference Laboratories*: The research performed by these laboratories should be integral to the conduct of a Group's clinical trials (i.e., in the absence of the testing performed by these laboratories, it would not be possible either to conduct the Group's clinical trial or alternatively to interpret results from the clinical trial).
- b) *Alternative sources of support for correlative science research not appropriate for Reference Laboratory support*: The Group is encouraged to establish liaisons with laboratory investigators at or outside of Group member institutions to compete for NIH and other funding sources to support high-quality correlative science projects. Potential collaborators on these funding applications include NCI-funded Specialized Programs of Research Excellence (SPOREs), Cancer Centers, the Early Detection Research Network, R01 holders, and P01 holders. In addition, the Chair's Developmental Fund may be a source of funding for generating preliminary data that will enhance the likelihood of a subsequent successful grant submission.
- c) *Guidelines on the design and development of correlative science studies*: The Diagnostic Evaluation Branch of the Cancer Diagnosis Program (CDP) has provided guidelines for the design and development of correlative science studies. These guidelines are available on the CDP website at [[Website Reference 23](#)].

1.10 Publications

The Operations Center is responsible for timely preparation and submission of all Group publications for peer review. It is anticipated that preliminary results of major phase 3 trials would be presented at a scientific meeting within 6 to 8 months of the study analysis (if not sooner based on the relevance of the results) and a manuscript on the study results would be prepared and submitted for publication within 1 year of the availability of the study results or within 1 year of the presentation of the preliminary results at a scientific meeting.

The definition of publications for this Cooperative Agreement includes Group abstracts, press releases, print-media articles/manuscripts, electronic media articles/presentations, letters, etc., related to findings and results from NCI-sponsored studies.

Groups must adhere strictly to the publication policy described below:

- a) Timely publication of major Group findings is central to the mission of the Group and is a primary means by which the Group's accomplishments can be evaluated. Timely presentation of a study's findings and results is especially important when a DMSB recommends the public release of this information.
- b) The Group should have time-lines for the development of abstracts and manuscripts based on the results from Group clinical trials and should have mechanisms for monitoring the performance of the Operations Center, Statistics and Data Management Center, and Scientific Committees in meeting these time-lines. Corrective action plans should be in place for when these time-lines are not met.
- c) Publication or oral presentation of work done via the Group's Cooperative Agreement requires appropriate acknowledgment of NCI support.
- d) For any study using agent(s) supplied under CTEP Collaborative Agreements (e.g., CRADA, CTA, or CSA), both CTEP and the NCI pharmaceutical/biotechnology collaborator(s) will have a 30-day period in which to review any manuscripts for informational purposes as well as for comment (as per the NCI Standard Protocol Language for CTEP Collaborative Agreements) **prior to submission of the manuscript by the Group for publication**. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to the intellectual property rights of the Collaborator(s), are protected. In addition, the NCI pharmaceutical/biotechnology collaborator(s) will have courtesy review of any abstracts as soon as possible (preferably at least 3 days prior to submission), but in any

case, prior to presentation or publication. **Manuscripts and abstracts should be provided to CTEP for delivery to the NCI pharmaceutical/biotechnology collaborator(s).** Pre-review timing for publications other than abstracts or manuscripts for studies involving agents supplied under CTEP Collaborative Agreements should be discussed with appropriate CTEP staff in the Investigational Drug Branch and the Regulatory Affairs Branch.

- e) For publications associated with NCI-sponsored Group research that do not involve agent(s) supplied under CTEP Collaborative Agreements [except as noted below in section (h)], the responsible NCI Program Director must receive a copy of the manuscript or abstract 30 days **in advance of publication.** Unlike the situation for agent(s) supplied under CTEP Collaborative Agreements, however, no review or comments will be provided by CTEP unless specifically requested by the Group. This is simply a confidential notification. Pre-review timing for publications other than abstracts or manuscripts should be discussed with appropriate CTEP staff.
- f) The NCI will have access to all data generated under this Cooperative Agreement and may periodically review the data. The awardee will retain custody and primary rights to the data consistent with current DHHS, Public Health Service (PHS), and NIH policies. Pharmaceutical/biotechnology companies will have access to all data generated under CTEP Collaborative Agreements; however, the companies may contract directly with the Groups for access to non-Clinical Data Update System (non-CDUS) data and reports.
- g) All Group publications (articles and abstracts) must reference the NCI protocol title in the manuscript or abstract title whenever relevant to the publication.
- h) All press releases issued by the NCI and/or the Group on study findings and results require review by NCI, NIH, and DHHS. Pre-review timing for press releases on study findings and results **must be discussed and approved** with the responsible NCI Program Director.

In addition, NIH-funded investigators are required to submit to the NIH manuscript submission (NIHMS) system [[Website Reference 45](#)] at PubMed Central (PMC) an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. The author's final manuscript is defined as the final version accepted for journal publication and includes all modifications from the publishing peer review process. NIH is requiring that authors submit manuscripts accepted for publication in a journal on or after April 7, 2008. The NIH Public Access Policy applies to all cooperative agreements, contracts, research grant and career development award mechanisms, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The policy applies to peer reviewed, original research publications that have been supported in whole or in part with direct costs from NIH, but does not apply to book-chapters, editorials, reviews, or conference proceedings. More information about this policy or the submission process is available on the NIH Public Access Policy website at [[Website Reference 46](#)]. Other resources including "Frequently Asked Questions" are available on this website at [[Website Reference 47](#)].

1.11 Group Meetings

The Operations Center is responsible for organization of annual or biannual meetings of the Group to review the Group's progress, establish priorities, and plan future activities. Additional meetings among Group members and meetings with NCI staff may be held as needed. Relevant Operations Center responsibilities for meetings include: (a) Arranging for appropriate meeting space and accommodations for attendees; (b) Developing and distributing meeting agendas; and (c) Preparing summaries as appropriate after each meeting for Group members and NCI staff.

1.12 Group Communications

The Operations Center is responsible for establishing routine electronic communication between itself, the Statistics and Data Management Center, and Participating Sites to facilitate protocol development and study monitoring and to facilitate the work of the various Scientific Committees. Relevant communication methods include website postings, e-mail, tele- and video-conferences.

1.13 Cancer Trials Support Unit (CTSU) Interactions

The Operations Center interacts with the CTSU by ensuring that: (1) all approved phase 3 trials and, on occasion, selected phase 2 trials are opened in the CTSU; (2) the design of Case Report Forms in studies are in compliance with the Common Data Element (CDE) system described on the CTEP website at [[Website Reference 24](#)]; and (3) all Participating Sites are instructed to submit their regulatory documents to the Regulatory Support System (RSS) of the CTSU for phase 1, phase 2, and phase 3 trials in adult cancers regardless of whether or not the study will be opened in the CTSU, with the exception of large-scale prevention trials. The Operations Center relies on the RSS to verify that a Participating Site has the regulatory approval to enroll a patient. Additional information on the CTSU and the RSS is available on the CTSU website at [[Website Reference 3](#)]. As stated previously, the CTSU includes only Group trials for adult cancers. The Children's Oncology Group does not participate in the CTSU or its Regulatory Support System at the current time.

1.14 Conflict of Interest

The Operations Center is responsible for establishing a Conflict of Interest Policy for the Group. This policy should ensure that there is no reasonable expectation that the design, conduct, or reporting of research conducted by the Group will be biased by any conflicting financial interest of an investigator. The policy should be in compliance with the general policies of the NCI and the NIH. In particular, the Group's Conflict of Interest Policy should be in compliance with CTEP's Conflict of Interest Policy for Cooperative Group Phase 3 Clinical Trials found on the CTEP website at [[Website Reference 41](#)].

2. Statistics and Data Management Center (SDMC) Rights and Responsibilities

The Statistics and Data Management Center (SDMC) will be responsible for the statistical leadership of the Group research agenda and for all aspects of data management.

2.1 Organization Structure and Facilities

- a) The SDMC must have a defined organizational structure and management plan with clearly defined roles and responsibilities for SDMC staff.
- b) The SDMC must have written Standard Operating Procedures (SOPs) specifying all aspects of data management, study monitoring, and data analysis for Group trials. The SOPs should include plans for training Group investigators and Clinical Research Associates (CRAs) at member Participating Sites and Study Chairs about their responsibilities for data management and study monitoring.
- c) The SDMC must agree to abide by the Constitution and By-laws of the Group.

2.2 Study/Protocol Development

The SDMC is responsible for helping the Group develop the statistical research design and analysis plan for Group studies as well as for providing statistical analysis, interpretations, and conclusions in regard to study data. In addition, the SDMC is responsible for developing the CDE Dictionary, provided at [[Website Reference 24](#)].

2.3 Data Management Policies and Practices & Submission of Data to CTEP

The responsibilities of the SDMC for data management include:

- a) Providing central registration and randomization for all study subjects;
- b) Providing for central storage, security, processing and retrieval of study results:
 - i. The SDMC data management system should incorporate security features consistent with DHHS guidelines.
 - ii. The SDMC should have procedures for backing up the Group's clinical and administrative data, including intermittent duplication of the database with storage at a remote facility.
- c) Protecting patient confidentiality at all steps in the submission and analysis of clinical trials data and ensuring the technical integrity and security of the data management systems.
- d) Providing NCI in a timely manner, upon the request of the Grants Management Officer, 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.
- e) Ensuring that data management operating policies and practices are in compliance with the Group's official policy on sharing research data. ([See Data Sharing Policy in Part 1.V.A., Section 1.5 \(h\) on pages 26-27.](#))

The SDMC is also responsible for timely reporting of data from Group clinical trials to CTEP using the Clinical Data Update System (CDUS). For clinical trials that do not use CTEP IND agents, reporting to CTEP will generally consist of CDUS abbreviated procedures (primarily demographic data). For studies using CTEP IND agents, CDUS complete reporting procedures may be used that capture demographic, adverse event information (by course), and response data. CDUS complete reporting **is required** for phase 1 studies and phase 2 studies using CTEP IND agents, while abbreviated CDUS reporting is usually used for phase 3 studies.

2.4 Study Monitoring

All clinical research carries with it an obligation to ensure optimal therapy for participating patients and optimal conduct of the research such that the patients' participation is meaningful. Accurate and timely knowledge of the progress of each study is a critical Group responsibility that primarily involves the SDMC. General information on study monitoring for Cooperative Group trials is provided on the CTEP website at [[Website Reference 25](#)]. The following elements are considered essential for study monitoring:

- a) Precise tracking of patient accrual (both eligible and ineligible patients) and adherence to protocol-defined accrual goals. In the event that the Group wishes to continue accrual to a study beyond the protocol-specified total accrual goal for eligible and ineligible patients, the Group must seek approval from CTEP prior to continuing patient accrual.
- b) On-going assessment of patient eligibility and evaluability.
- c) On-going assessment of appropriate randomization.
- d) Adequate measures to ensure timely submission of study data. These measures should include procedures for monitoring compliance with Group guidelines for data timeliness on a Participating Site and a study basis, including summary reports to be used for Participating Site Performance Review and for study monitoring (e.g., by the DSMB). These summary reports should also be included in the Group's Annual Progress Report.
- e) Adequate measures to ensure timely medical review and assessment of individual patients' data.
- f) Rapid reporting of treatment-related morbidity information and measures to ensure communication of this information to all appropriate parties.
- g) Interim evaluation of outcome measures and patient safety information.
- h) Study monitoring reports describing patient accrual and demographics, data timeliness, toxicity, and other items as appropriate. Examples of study monitoring reports include reports prepared for Study Chairs, the biannual reports and agendas provided for Group meetings, and reports for Data and Safety Monitoring Committees.
- i) Adequate policies and procedures for early closure of studies. The Group should explicitly describe the policies in place for phase 1 and phase 2 studies as well as those used for phase 3 studies. Statistical guidelines for early closure should be presented as explicitly as possible in the protocol in order to facilitate decisions regarding early closure. NCI/CTEP and the Groups have approved early stopping guidelines for slowly-accruing phase 3 studies ([See Part 4 – Attachment #12](#)). The Group should involve the appropriate CTEP staff in discussions about possible ways to enhance accrual in order to avoid study closure.

Procedures regarding notification of CTEP about early study closure are outlined below and should be incorporated into the Group's closure policy for studies. These procedures also apply to major modifications to study design and to suspension of study accrual and/or treatment (e.g., suspension due to patient safety issues).

- i. For any Group phase 1 or phase 2 trial for which CTEP is the IND sponsor of one or more study agents, the Group **must notify and receive approval from the appropriate CTEP staff (i.e., Investigational Drug Branch staff) before initiating study closure**. In the rare case that CTEP is supplying/distributing a non-CTEP IND/commercial agent for a phase 1 or phase 2 study, the Group **must** inform the appropriate CTEP staff (i.e., Clinical Investigation Branch staff member responsible for the disease portfolio) of study closure prior to public notice. For all other phase 1 or phase 2 studies, the Group **must** notify the appropriate CTEP staff prior to submission of the study closure notice to CTEP's Protocol and Information Office in cases where closure (or study modification or suspension) is due to adverse events or other patient safety issues since this information may affect safety in other CTEP-sponsored trials as well as in the CTEP-sponsored study which is being closed.
- ii. For Group phase 3 studies, the Group's DSMB should have reviewed the study and recommended (or at least approved) study closure and the Group Chair should have concurred with this decision, with the exception of phase 3 studies being closed per the early stopping guidelines for slowly-accruing phase 3 studies. **Although CTEP approval of early closure of a phase 3 study is not required when closure is recommended and approved by both the DSMB and Group Chair, the Group must inform and discuss closure of the study with the responsible NCI Program Director or his/her designee before disclosure to Group members, the investigators, the company sponsor (if applicable), the study patients, and the public so that both NCI/CTEP and the Group will be prepared to address public inquiries and other potential issues.** For phase 3 studies conducted under a CTEP IND or for which CTEP supplies/distributes one or more of the study agents, it is also important for CTEP to begin to address issues related to the supply/distribution of the agent, the company sponsor, and regulatory issues, in addition to being able to

address public inquiries about the trial. If the sole reason for closure of a phase 3 study is poor accrual, and the study is not under a CTEP IND or other binding collaborative arrangement and CTEP is not supplying or distributing any of the study agents, the Group does not need to inform and discuss study closure with the responsible NCI Program Director prior to public notification as long as the CTEP members of the Group's DSMB have been previously informed of this possibility and are aware of the DMC recommendation for closure. For additional information related to Group DSMBs, [see Data and Safety Monitoring Policy and Plans in Part 1.V.A., Section 1.5 \(g\) on page 26.](#)

2.5 Compliance with Federal Regulations

The SDMC is responsible for assuring that the Group is in compliance with all applicable federal regulations concerning the confidentiality of patient data (e.g., the Health Insurance Portability and Accountability Act - HIPAA) and ensuring the technical integrity and security of the Group's data management systems. The SDMC is also responsible for complying with all federal regulations related to human subjects protection, including providing educational training on the protection of human subjects to SDMC staff in compliance with NCI/NIH policy.

2.6 NCI Clinical Trials Policy

The NCI Clinical Trials Policy requires Clinical Terms of Award for clinical studies and trials when they are a component of any proposed research being funded by the NCI. The Policy requires studies to be monitored commensurate with the degree of potential risk to study subjects and the complexity of the study [[Website Reference 40](#)].

2.7 Adverse Event Reporting

The Group is responsible for ensuring that all serious and/or unexpected adverse events are reported in a timely manner. The SDMC should assist the Group in meeting this responsibility. Adverse events should be reported using the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v3.0), which is the NCI's standard language for reporting adverse events in clinical trials, and is provided on the CTEP website at [[Website Reference 26](#)]. Expedited reporting of adverse events should be performed via CTEP's AdEERS system according to the guidelines specified in each protocol [[Website Reference 22](#)].

2.8 Support for On-Site Audit Program

The SDMC will provide the support necessary for the Group's on-site audit program to maintain compliance with NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) [[Website Reference 8](#)].

2.9 Independent Research

Independent research by the SDMC should be focused on developing innovative clinical trial designs and analysis methodologies consistent with the Group research agenda and appropriate for planned studies. While CTEP encourages development of and experimentation with new study designs within the Group framework, purely statistical research unrelated to Group studies is appropriately funded through other mechanisms.

2.10 Study Analyses and Publications

The SDMC conducts final study analyses at the protocol-prescribed time and participates on publication writing teams. Cross-protocol analyses may be performed by the SDMC, as necessary, to support the research agenda of the Group.

2.11 Group Meetings – Report of Studies

The SDMC is responsible for providing the Report of Studies at the biannual meetings of the Group. The Report of Studies should include information detailing patient accrual and demographics, data timeliness, toxicity experienced by study participants, and other items as

appropriate, including outcome data as appropriate. The SDMC is responsible, with the Operations Center, for ensuring that copies of the Report are distributed to Group members and to the NCI program staff. If a Group determines that a Report of Studies is not needed biannually, the Group must seek approval from the responsible NCI Program Director, providing the rationale for this request in writing.

2.12 Support or Group's Participating Site Performance Monitoring Program

The SDMC will provide data on a regular basis to the Group committee responsible for credentialing Participating Sites and conducting periodic review of the performance and membership status of each member. Data provided by the SDMC should allow assessment of accrual, data accuracy and timeliness, protocol compliance, and long-term patient follow-up.

2.13 Cancer Trials Support Unit (CTSU) Interactions

The SDMC interacts with the CTSU by ensuring the appropriate transmission of all data collected by Participating Sites in Group-led studies to the SDMC. In some cases, Participating Sites that are members of the Group leading the CTSU study will transmit their data directly to the Group and not through the CTSU.

2.14 Conflict of Interest

The SDMC is responsible for ensuring that it is in compliance with the Conflict of Interest Policy for the Group. This policy should ensure that there is no reasonable expectation that the design, conduct, or reporting of research conducted by the Group will be biased by any conflicting financial interest of an investigator. The policy should be in compliance with the general policies of the NCI and the NIH. In particular, the Group's Conflict of Interest Policy should be in compliance with CTEP's Conflict of Interest Policy for Cooperative Group Phase 3 Clinical Trials found on the CTEP website at [[Website Reference 41](#)].

3. Investigators and Participating Site Rights and Responsibilities

Investigators participating in 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 U10 Cooperative Agreement (for members and their affiliates supported directly by NCI's DCTD), the Community Clinical Oncology Program (CCOP) Cooperative Agreement (for members supported directly by NCI's DCP), and third-party capitation payments (via subcontracts or purchased service agreements) for Participating Sites that do not hold U10 Cooperative Agreement awards. Groups use some or all of these mechanisms. Participating investigators may receive additional Operation Center funds for the conduct of administrative, scientific, laboratory or other high-priority tasks that fall within the work scope of the Group under this Cooperative Agreement.

Investigators at Participating Sites form the cornerstone of the Group's research program, and must perform at a high level through submission of accurate and timely clinical data as well as submission of ancillary materials necessary to support the Group's research agenda (e.g., tumor specimens, imaging studies, pathology slides). The Principal Investigator at each member Participating Site is responsible for the performance of that site as well as any affiliated Participating Sites, and for assuring adherence to Group, NCI, OHRP, and FDA policies and procedures. Investigator and Participating Site responsibilities include the following:

3.1 Participation in Group Activities

Investigators at Participating Sites can participate in Group activities in a variety of ways, including the following:

- a) Offering eligible patients participation in Group studies and entering sufficient patients to meet accrual targets;
- b) Participating in research design and protocol development;
- c) Participating in the Scientific and Administrative Committees of the Group;
- d) Following the Group's Standard Operating Procedures (SOPs) for the conduct of clinical research and complying with the Group's Constitution and By-laws and with federal regulations concerning research. (See [Compliance with Federal Regulations in Part 1.V.A., Section 1.5 on pages 25-27.](#))
- e) Following the CTSU's SOPs for the conduct of trials opened through the CTSU and for the submission of regulatory documents for all trials in adult cancers to the RSS; and
- f) Participating in the biannual meetings of the Group and in other meetings deemed necessary for performance of Group activities.

3.2 Implementing the Core Data Collection Method and Strategy of the Group

It is the responsibility of each Principal Investigator at each member Participating Site to ensure that the procedures for data submission for each Group protocol are understood by all investigators at that site as well as at any affiliated Participating Sites, and that protocol-specified data are submitted accurately and in a timely manner to the Statistics and Data Management Center.

3.3 Complying with Quality Assurance & Control of Therapeutic/Diagnostic Modalities

Investigator and Participating Site responsibilities for quality control include, but are not limited to, the following:

- a) *Pathology*: Submission of appropriate materials to allow verification of pathologic diagnosis, when relevant.
- b) *Radiation therapy*: Submission of appropriate materials to allow review (either concurrent or retrospective) of port films and compliance with protocol-specified radiation doses for individual patients, when relevant.
- c) *Chemotherapy*: Submission of appropriate data to allow determination of protocol compliance with chemotherapy dose administration and dosage modification.

- d) *Surgery*: Submission of appropriate information to allow review of protocol-specified surgical procedures.
- e) *Diagnostic Imaging*: Submission of appropriate imaging studies to allow central review of staging, reported responses, and adequacy of imaging when required by a particular protocol or for an audit.
- f) *On-site Auditing*: Participation in the Group's on-site monitoring program. [See Quality Assurance in Part 1.V.B., Section 5 on pages 45-46](#) for information on the procedures that should be followed in the event that any data irregularities are identified through the audit program or other quality control procedures.

3.4 Investigational Agent Responsibilities

Investigators and Participating Sites should implement the procedures established by the CTSU for assuring that member investigators enrolling patients on Group trials involving CTEP IND agents are NCI registered investigators (i.e., have Form FDA 1572 on file with the NCI). Member Participating Sites must ensure that they, as well as any affiliated Participating Sites, are in compliance with CTEP requirements described in the DCTD Investigators' Handbook for storage and accounting for investigational agents, including complying with NCI/DHHS Drug Accountability Records (DAR) procedures, and are in compliance with FDA requirements for investigational agents [[Website Reference 7](#)].

3.5 Human Subjects Protection

Investigators and Participating Sites should implement the procedures established by the Group for meeting federal regulations for the protection of human subjects. These include the following:

- a) Assuring that the institution has a current, approved Assurance on file with OHRP;
- b) Assuring that each protocol is reviewed by the Participating Site's IRB prior to patient entry;
- c) Assuring that each protocol is reviewed annually by the IRB so long as the protocol is active;
- d) Assuring that each patient (or legal representative) gives written informed consent prior to entry on study;
- e) Assuring that all regulatory documents verifying OHRP assurance and initial and annual IRB approval of protocols as well as IRB approval of required amendments are submitted to the Regulatory Support System (RSS) of the CTSU for all adult cancer trials, excluding large-scale prevention trials.
- f) Assuring that all investigators and staff have undergone educational training on human subjects protection in compliance with NIH/NCI policy as described at [[Website Reference 44](#)].

3.6 Adverse Event Reporting

Investigators and Participating Sites should implement the procedures established by the Group for assuring timely reporting of all serious and/or unexpected adverse events.

3.7 Submission of Specimens

Investigators and Participating Sites should be involved in the acquisition of protocol-specified tumor specimens, biological fluids, and relevant clinical data. Investigators and Participating Sites should ensure that these specimens are submitted with the relevant clinical data to the appropriate laboratories where these specimens will be tested or stored for future studies per protocol guidelines.

3.8 Cancer Trials Support Unit (CTSUS) Interactions

Investigators and Participating Sites interact with the CTSU in adult cancer clinical trials through the following: (1) registration of all investigators participating in clinical trials (investigators must also update their FDA 1572 Forms annually); (2) submission of regulatory documents to RSS for all adult cancer trials, excluding large-scale prevention trials; and (3) submission of data associated with trials open in the CTSU when their Group is not leading the trial or when submission of data to the CTSU is required for all Groups, including the lead Group.

3.9 Conflict of Interest

Investigators and Participating Sites must comply with the Conflict of Interest Policy of the Group to ensure that there is no reasonable expectation that the design, conduct, or reporting of research conducted by the Group will be biased by any conflicting financial interest of an investigator. In particular, the Group's Conflict of Interest Policy should be in compliance with CTEP's Conflict of Interest Policy for Cooperative Group Phase 3 Clinical Trials found on the CTEP website at [[Website Reference 41](#)] which addresses conflicts of interests of investigators involved in development and analysis of CTEP-sponsored clinical trials.

4. Scientific and Administrative Committee Rights and Responsibilities

The Group's Scientific and Administrative Committees are key to the success of the Group and are responsible for the specific research studies/trials conducted by the Group and for setting research agendas for the specific types of cancer that the Group studies.

Scientific Committees are defined as committees that function primarily to develop and conduct clinical trials and studies and have a defined research agenda (e.g., Disease Committee such as a Breast Committee that conducts trials in breast cancer, Radiation Oncology Committee that conducts radiation-therapy trials in selected disease types, other Scientific Committee such as an Experimental Therapeutics Committee or a Correlative Science Committee). Administrative Committees are defined as committees that function primarily by providing essential core service functions to other aspects of the Group's research program (e.g., Patient Advocacy, Clinical Research Associates, Auditing, Pathology, Surgery).

Some committees may function as Scientific Committees in one Group and as Administrative Committees in another Group. For example, a Radiation Oncology Committee would be considered a Scientific Committee if it develops and conducts its own clinical trials; it would be considered an Administrative Committee if it functions primarily by providing support services to Disease Committees that are developing and conducting clinical trials that include radiation therapy as part of the study treatment. Scientific Committees are reviewed independently and Subcommittee H-Clinical Groups reviewers assign individual merit scores to each Scientific Committee. Administrative Committees are considered an integral part of the Operations Center and thus are not assigned individual merit scores. The reviewers' assessment of the Group's Administrative Committees is considered in the priority score each reviewer assigns to the Operations Center application as a whole. (See [Research Plan in Part 2.II.C. - Section 2 on page 63.](#))

4.1 Organizational Structure

The Group's Constitution and By-laws defines the organizational structure, composition, and specific responsibilities of each Group committee.

4.2 Scientific Committees

The primary responsibility of the Scientific Committees is to develop research protocols for the disease types for which the Committees are responsible (study/protocol development). Disease Committees (e.g., Breast, Gastrointestinal, Lung) are responsible for adhering to Group procedures for study/protocol development, including adhering to time-lines for Concept and LOI development and subsequent protocol development for approved Concepts and LOIs. Other Scientific Committees (e.g. Correlative Science, Experimental Therapeutics) are responsible for developing trials and/or adjunct studies for Disease Committee trials that complete the Group's research agenda. Scientific Committees are responsible for adhering to Group procedures for study/protocol development, including adhering to appropriate time-lines for study development.

4.3 Study Monitoring

The primary responsibility for study monitoring resides with the Study Chair, Study Statistician and other members of the Study Committee (i.e., the Study Committee helps develop and oversees conduct of a specific study). The Scientific Committee (e.g., Disease Committee) is responsible for assuring that the Study Committee is satisfactorily meeting its responsibilities for study monitoring. (See [Study Monitoring in Part 1.V.A., Section 2.4 on pages 31-33.](#))

4.4 Correlative Science Studies/Reference Laboratories

Correlative science studies are increasingly central to the interpretation of clinical trials data, particularly for studies of molecularly targeted agents. Scientific Committees play a key role in the development and conduct of correlative science studies associated with Group protocols.

Scientific Committee responsibilities related to correlative science studies and Reference Laboratories include:

- a) *Identification of Reference Laboratories to support a Scientific Committee's correlative science investigations:* The research performed by Reference Laboratories should be integral to the conduct of clinical trials of a Scientific Committee (i.e., in the absence of the testing performed by these laboratories, it would not be possible either to conduct the Committee's clinical trials, or alternatively, to interpret results from these trials).
- b) *Identification of alternative sources of support for correlative science research not appropriate for Reference Laboratory support:* Scientific Committees are encouraged to establish liaisons with laboratory investigators within or outside the Group to compete for NIH and other funding sources for the support high-quality correlative science projects. The Group Chair's Developmental Fund may be a source of funding for generating preliminary data that will enhance the likelihood of a subsequent successful grant submission.

4.5 Publication

Timely publication of the findings of Scientific Committees is important not only in informing the scientific community of these discoveries, but also in providing a quantitative measure of the Scientific Committees' accomplishments. Scientific Committees should comply with the Group's policies and procedures for publication, especially time-lines for submission of manuscripts following the final planned analysis of clinical trials data. It is expected that the Group's policy on publications will ensure, in particular, that the results of large phase 3 studies are submitted for publication in a timely regardless of whether or not the results would change the standard of care.

4.6 Administrative Committees

Some Group Administrative Committees (e.g., Patient Advocacy, Clinical Research Associates, Auditing, Pathology, Surgery) are considered to be Administrative Committees since they function primarily by providing essential core service functions to other aspects of the Group's research program. For example, a Patient Advocacy Committee may provide guidance to a Scientific Disease Committee (e.g., Disease Committees) by obtaining appropriate review and input from patient advocates with respect to clinical trials supported by the Disease Committee. Administrative Committees should have clearly described responsibilities and mechanisms for measuring the performance of the Committees in meeting those responsibilities. Administrative Committees need not have explicit scientific research agendas, although the activities of these Committees should be important or even essential to accomplishing the Group's research agenda (e.g., Audit Committee).

B. NCI/CTEP Responsibilities and Associated NCI/CCCT Staff Responsibilities

The role of the Cancer Therapy Evaluation Program (CTEP) staff, as described throughout these Terms and Conditions of Award, is to assist, facilitate, and assure optimal coordination of Group activities. This Cooperative Agreement is part of a larger NCI-sponsored clinical trials program that also includes investigational agent development. CTEP staff has very specific and well-defined responsibilities for the oversight and review of Group clinical trials and for investigational agent development that meets DCTD/CTEP responsibilities as sponsor of Investigational New Drug Applications (INDs) as defined in the Code of Federal Regulations (CFR) 21 Part 312. The responsibilities of CTEP staff are described below. In addition, CTEP staff work with the staff of the NCI Coordinating Center for Clinical Trials (CCCT) regarding adherence to the requirements of the NCI Clinical Trials Policy when appropriate.

1. Coordination of National Priorities

CTEP staff is responsible for maintaining a clear set of national priorities for treatment research, based upon substantial consultation with experts in the field. In selected disease areas, particularly when spontaneous Intergroup planning does not occur, CTEP staff with support from the CCCT will coordinate the organization of disease-specific Scientific Steering Committees as well as ad hoc strategy meetings that will identify, in general terms, research issues in need of study in major phase 3 trials and establish priorities among competing ideas. These Scientific Steering Committees and ad hoc meetings will be composed of investigators with established expertise in the particular field of interest and will consist primarily of extramural scientists. CTEP staff will be responsible for prompt dissemination of the recommendations from these Committees and meetings, particularly their statements of research priorities, and the Groups will be encouraged to address these priorities. Furthermore, though the protocol review process, CTEP staff help to ensure that national priorities are being met and that wasteful duplication of effort is avoided. For specific information on the disease-specific Scientific Steering Committees, [see Attachment #13: NCI Clinical Trials: Prioritization/Scientific Quality Initiative](#). The CCCT also provides coordination across all NCI-funded programs involved in clinical studies/trials to maximize the efficiency of the NCI clinical trials system, avoid duplication of efforts related to clinical trials, and identify opportunities for collaboration.

2. Scientific Resource and Liaison Activities

CTEP staff serves as both a resource and liaison for Groups and their members.

2.1 Scientific Resource for NCI-Supported Clinical Investigations

The responsible NCI Program Director, the Associate Director (AD), CTEP, DCTD and staff of the various CTEP branches, including the Clinical Investigations Branch (CIB), the Investigational Drug Branch (IDB), the Regulatory Affairs Branch (RAB), the Pharmaceutical Management Branch (PMB), and the Clinical Trials Monitoring Branch (CTMB), as well as staff from other DCTD programs, including the Biometric Research Branch (BRB), the Cancer Imaging Program (CIP), Radiation Research Program (RRP), and the Cancer Diagnosis Program (DCP), all serve as resources available to Groups for specific scientific information with respect to treatment regimen, clinical trial design, investigational agent management and regulatory issues.

The DCTD staff listed above will assist the Groups, as appropriate, in developing information concerning the scientific basis for specific trials and also will be responsible for advising the Groups of the nature and results of relevant trials being carried out nationally or internationally. CIB and IDB staff will also provide updated information to the Groups on the efficacy and adverse events associated with new investigational agents supplied to Group members under a CTEP-sponsored IND. In addition, CIB staff advises the Groups of potential agents/interventions that will be relevant to new avenues of cancer therapy.

2.2 Scientific/Administrative Liaison Activities (Project Scientist)

The responsible NCI Program Director is the NIH/NCI Program Official responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice.

Each Group also has assigned to it a staff physician from CIB who acts as liaison for scientific and administrative matters. The CIB liaison or Project Scientist 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. On occasion, the responsible NCI Program Director may also serve as a Project Scientist. The CIB liaison or Project Scientist monitors the Group's progress, attends the Group's meetings, and is responsible for knowledge of the Group's repertoire of studies, areas of special interest and expertise, and unique resources. The CIB liaison is also responsible for providing the responsible NCI Program Director with on-going assessments of Group activity from an administrative perspective and should have general knowledge of the Group's budget. Primary responsibility for a Group's budget, however, resides with the responsible NCI Program Director and the CTEP Program Specialist. (See Parts 2 and 3 of these Guidelines for information on budgetary issues for the Groups related to new and competing applications as well as non-competing continuing applications.) The CTEP Program Specialist may be delegated by the responsible NCI Program Director to request and receive budgetary and administrative materials from the Groups on either an ad hoc or routine basis. The CTEP Program Specialist will frequently perform liaison activities concerning budgetary and administrative matters on behalf of the responsible NCI Program Director, interfacing primarily with the Group Administrators.

2.3 CTEP Attendance at Group Meetings

CTEP staff and other NCI staff, as designated by the responsible NCI Program Director, will attend the semi-annual Group meetings and core scientific Group meetings, as appropriate. As part of their liaison responsibilities, CTEP staff, when available, will attend other Group scientific meetings and may also attend Group Executive Committee meetings.

2.4 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.

3. Study/Protocol Development Process and Protocol Review

The CTEP study/protocol development and review processes are described in detail below.

3.1 Study/Protocol Development Process

CTEP staff will be active participants in development of Group studies that require a major commitment of financial resources and/or patient accrual. CTEP staff will serve as a resource to the Groups during the protocol development process for information on national priorities and on-going efforts within the scientific community. CTEP staff can most effectively facilitate Intergroup collaborations and/or marshal special resources by early involvement in study development.

3.2 Letter of Intent, Concept, and Protocol Review

CTEP is responsible for reviewing Group protocols, which must be mutually acceptable to both the Group and to the CTEP Protocol Review Committee (PRC). Protocols for phase 3 trials should be preceded by Concepts and protocols for phase 1 or phase 2 studies of CTEP-sponsored IND agents should be preceded by Letters of Intent (LOI). These two mechanisms for preliminary review expedite protocol development and implementation and facilitate agreement on study priority and design. (See the Investigator's Handbook on the CTEP website at [\[Website Reference 7\]](#) for further discussion of these procedures as well as for templates for Concepts and LOIs.) All communication concerning concepts, LOIs, and protocols are handled through the CTEP Protocol and Information Office (PIO). Protocol review is the final step in an interactive process, particularly for large phase 3 trials, and major conceptual disagreements should not occur at this stage, but rather should have been resolved at earlier stages of review. The principles for CTEP review of Concepts, LOIs, and protocols are similar.

The CTEP Protocol Review Committee (PRC) meets weekly. PRC is chaired by the Associate Director (AD), CTEP, DCTD. The PRC membership includes:

- CTEP professional staff (including CIB, IDB, RAB, PMB, and CTMB);
- Professional staff of other DCTD programs (including BRB, CIP, RRP, and CDP);
- Representatives from other NCI divisions and federal agencies; and
- Invited consultants or expert external reviewers, including patient advocacy representatives, under appropriate confidentiality and conflict of interest agreements.

The PRC bases its judgments on several factors, including:

- a) Strength of the scientific rationale supporting the study;
- b) Medical importance of the question being posed;
- c) Avoidance of undesirable duplication with other on-going studies;
- d) Appropriateness of study design including interim monitoring plans;
- e) Satisfactory projected accrual rate & follow-up period for timely completion of the study;
- f) Appropriateness of patient selection, patient evaluation, assessment of toxicity/adverse events and response to therapy, and follow-up;
- g) Apparent feasibility of the study, including data documenting the tolerability and safety of the proposed treatments
- h) Adequacy of the modality sections in the protocol (e.g., chemotherapy, surgery, radiation therapy, pathology) in describing the study's operation;
- i) Adequacy of the protocol pharmaceutical section and instructions for drug administration;
- j) Adequacy of regulatory issues (e.g., guidelines for reporting adverse events);
- k) Adequacy of human subjects protection (e.g., adequacy of model informed consent);
- l) Administrative and contractual concerns (e.g., industry collaboration, NCI technology transfer aims);
- m) Adequacy of plans to include and minorities and their subgroups and both genders, as appropriate, for scientific research goals (plans for recruitment/retention of patients); and
- n) Adequacy of associated/embedded quality of life studies, correlative science studies, imaging studies, etc.

In general, Concepts, LOIs, and protocols are reviewed by CTEP with responses back to the Group within 4 to 6 weeks following receipt by CTEP, unless the review of the protocol is postponed for a short period due to availability of reviewers, particularly when reviewers with a specific, special expertise are required. In the case of reviews that require combined review with another agency (e.g., FDA), the time period for response may also be longer as a combined CTEP/Agency response is formulated; however, in those cases, the Group will be made aware of the progress of the approval process for the Concept or protocol. The results of the review are provided in a "consensus review" which is sent to the Group along with the appropriate time-line for responses/revisions and completion of protocol documents. The PRC discusses the Concept/LOI/protocol after hearing the review of each assigned reviewer and makes a decision that the science and safety of the study are one of the following:

- *Approved as written or with recommendations* – The investigators are requested to give serious consideration to any recommendation included in the consensus review but they are not obligated to amend the study. If changes are made prior to activation of the study, the investigators must send CTEP a revision for review that details any changes in the previous CTEP-approved document.
- *Pending* – The PRC has significant questions about the proposed study. The proposed study can be approved if the investigators satisfactorily address the concerns included in the written consensus review (i.e., comments requiring a response). The investigators should submit a revised document within 30 days of receipt of the consensus review.
- *Disapproved* – In the judgment of the PRC, the study cannot be approved. The PRC disapproves relatively few submitted studies and only does so when it feels that a proposal is unnecessarily duplicative, is irretrievably flawed in concept, design, safety, or feasibility;

or is not a high priority with respect to national priorities in cancer treatment/research. In some cases, PRC will recommend changes in the study that, if adopted, may allow a revised study to be approved.

All phase 3 studies also require approval by the NCI Central Institutional Review Board (IRB) prior to activation.

Studies that require fewer than 100 patients (including both eligible and ineligible patients), that are not developed/submitted by Cancer Center CCOP Research Bases, and that do not use CTEP-sponsored IND agents, are termed “Developmental Strategy” protocols. The PRC reviewers focus their comments on the scientific rationale for these studies and the likelihood that they will lead to a definitive phase 3 trial. If patient safety or regulatory issues are noted, a response will be required but the Group assumes full responsibility for the regulatory, patient safety, pharmaceutical, and informed consent review of such studies and for ensuring compliance with all federal and CTEP-specific regulations regarding Group research. CTEP reviewers do not purposefully review or verify these sections of the protocol. Although the scope of the CTEP review is limited with respect to Developmental Strategy studies, CTEP may require full review of these studies in the event that 1) the studies are duplicative and/or 2) programmatic resources to support the clinical trials program are constrained to the extent that prioritization of studies is required with respect to national priorities in cancer treatment/research. All treatment studies that are submitted by Cancer Center CCOP Research Bases, however, require full CTEP review, even if fewer than 100 patients are required.

Any separate, correlative science study that uses ≥ 100 biologic specimens from Group trials (or ≥ 100 patients for a separate, non-treatment adjunct study) must undergo CTEP PRC review. Any separate, correlative science study that uses < 100 biologic specimens from Group trials (or < 100 patients for a separate adjunct study) must be submitted to CTEP for tracking purposes (“File Only”), but does not undergo PRC review. These requirements apply even if the study is not associated with a formal protocol document (i.e., the research plan must still be approved by CTEP or filed depending on the number of patients and/or specimens involved). For correlative science proposals seeking to use specimens from Intergroup trials in which patient specimens have been banked, PRC review can be substituted by review by an Intergroup Correlative Sciences Committee consisting of Group representatives and CTEP representatives according to an agreement between the particular Intergroup and CTEP.

For a complete summary of the different types of protocol review, including review of protocols for phase 1 studies, phase 2 studies enrolling 100 patients or more, and other studies, [see Part 4 – Attachment #1: Protocol and Information Office Schema for CTEP Review by Study Type](#) and [Attachment #2: Protocol and Information Office Summary of CTEP Review by Study Type](#).

If a proposed Concept/LOI/protocol is disapproved, the specific reasons for the disapproval will be communicated to the Group in the consensus review. A study may be disapproved for a variety of reasons including: (1) it may be seriously flawed in its rationale or design; (2) it may be in conflict with national priorities; (3) it may be duplicative of an existing CTEP-sponsored study; and (4) it may be infeasible due to unavailability of a study agent. NCI will not provide investigational agents for a protocol that has not been approved. NCI-awarded funds may not be used to support protocols disapproved by CTEP. CIB staff 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. All disagreements with PRC review, including disapproval, may be appealed to CTEP. If an irresolvable disagreement persists, an arbitration procedure, which is described in the Terms and Conditions of Award of each Cooperative Agreement, may be invoked. (See [Arbitration in Part 1.V., Section D on page 49.](#))

Review of the approval process for Concepts, LOIs, and protocols was evaluated by the Clinical Trials Working Group (CTWG) of the National Cancer Advisory Board (NCAB). A report of the CTWG entitled “Restructuring the National Cancer Clinical Trials Enterprise” was accepted by the NCAB in June 2005. The protocol review process described above may undergo change in the

future with respect to evaluation of Concepts based on the implementation of the report's recommendations. (See [Attachment #13: NCI Clinical Trials: Prioritization/Scientific Quality Initiative](#)). Cooperative Groups will be expected to comply with new requirements for Concept evaluation as they evolve in this new process. These changes will be detailed in the NCI Policy on Clinical Trials as they are developed.

Phase 3 Concepts for the first disease sites selected to be part of the NCI Clinical Trials System Prioritization/Scientific Quality Initiative (i.e., Gastrointestinal Cancer and Gynecologic Cancer) will be evaluated and approved by Scientific Steering Committees for these disease sites. These Committees will include representatives from the Cooperative Groups, Cancer Centers/SPORES, CCOPs, Patient Advocacy Community, and other selected individuals/groups, as appropriate, in addition to representatives from CTEP and other branches/divisions of the NCI as outlined in the implementation plan in [Attachment #13](#). Through this process, individual Groups will be encouraged to collaborate and coordinate their efforts with Cancer Centers and SPORES. By involving all stake-holders, including the NCI/CTEP, in the development and evaluation of Concepts at an early stage, it is expected that the final review and approval of these concepts by CTEP can be accomplished in an expedited manner in most cases.

3.3 Protocol Amendment Review

Any change to the protocol document subsequent to its approval by CTEP must be submitted to CTEP's Protocol and Information Office (PIO) in writing for review and approval by CTEP prior to implementation of the change, with the exception of administrative updates. All amendments to phase 3 studies currently also require approval by the NCI's Central IRB, with the exception of administrative updates. Additional information on the procedures for protocol amendment can be found in the Investigator's Handbook, available on the CTEP website at [\[Website Reference 7\]](#).

3.4 Protocol Closure

CTEP may request that a phase 1 or phase 2 study be closed to accrual for reasons including the following: (1) insufficient accrual rate; (2) poor protocol performance; (3) protection of patient safety; (4) study results are already conclusive; (5) emergence of new information that diminishes the scientific importance of the study question; and (6) unavailability of study agent. NCI will not provide investigational agents or permit expenditures of NCI funds for a phase 1 or phase 2 study after requesting closure (except for patients on treatment and follow-up). The responsible NCI Program Director may request that a Group's DSMB consider closing a phase 3 protocol to accrual for the same reasons as those listed above for phase 1 and phase 2 studies. NCI will also not provide investigational agents or permit expenditures of NCI funds for a phase 3 trials that has been closed (except for patients on treatment and follow-up).

4. **Data and Safety Monitoring Boards**

The responsible NCI Program Director, assisted by the Biometric Research Branch (BRB) staff, will assess Group compliance with NCI established policies on Data and Safety Monitoring Boards (DSMBs) for Group phase 3 trials. These policies must address both the membership of the DSMB and its operational policies. One or more CTEP staff and BRB staff serve as non-voting members on the Group's DSMB. The membership of the Group's DSMB and its policy must be approved by the responsible NCI Program Director. In addition, the responsible NCI Program Director is also required to review and approve the Group's policy regarding its data and safety monitoring plans for phase 1 and phase 2 trials as well as pilot studies and feasibility studies. Information on NIH DSMB policies is provided at [\[Website Reference 19\]](#). Information on CTEP's policy on monitoring of phase 3 trials by Group DSMBs is provided on the CTEP website at [\[Website Reference 18\]](#).

Although CTEP and BRB staff serve as non-voting members on Group DSMBs, CTEP staff members recuse themselves from review of substantive protocol amendments (e.g., amendments for increases in sample size or significant changes in trial design) for any study that is also under review by a DSMB of which they are members, if confidential outcome data on that study have been previously presented

to the DSMB. When this situation arises, the amendment is reviewed by CTEP and BRB staff members who are not members of that DSMB.

For additional information on DSMBs, [see Data and Safety Monitoring Policy and Plans in Part 1.V.A., Section 1.5 \(g\) on page 26.](#)

5. Quality Assurance

The Clinical Trials Monitoring Branch (CTMB) is responsible for establishing guidance for the conduct of quality assurance audits. CTMB provides oversight and monitors compliance of the Groups, CCOP Research Bases, and CTSU with the NCI's monitoring guidelines. Compliance with applicable federal regulations is also monitored by CTMB.

In addition, CTMB staff serves as an educational resource to the cancer research community on issues related to monitoring and regulatory requirements for the conduct of clinical trials. CTMB staff review audit reports and findings and assess the adequacy and acceptability of any corrective actions. To assure consistency in the conduct of on-site audits, CTMB staff or its designee(s) may attend certain on-site audits.

The CTMB has designed the CTMB Audit Information System, an information system that permits the on-line submission by the Groups of all data related to quality assurance on-site monitoring [[Website Reference 12](#)]. This includes the submission of audit schedules, acknowledgment of receipt of preliminary reports, transmission of final audit reports, and tracking of follow-up responses to audit findings. The system allows restricted access to the stored data and keeps a record of any data changes. The CTMB Audit Information System can be accessed only after providing a username and password. A major component of the CTMB Audit Information System is a module that maintains a roster of Participating Sites in each Group. This roster information is used for determining Group compliance with monitoring requirements.

The Operations Center is responsible for ensuring that all Group Participating Sites have routine audits in accordance with the NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) [[Website Reference 8](#)] and that the results of audits are reported to the NCI in accordance with the guidelines. In the event that the NCI/CTMB determines that a Group Participating Site fails to comply with these guidelines, the CTMB may, in consultation with the Group, suspend the Participating Site immediately from participating in Group studies. The suspension will remain in effect until the Group conducts the required audit and the audit report or remedial action is accepted by the NCI. The Operations Center will be responsible for notifying any affected Participating Site of the suspension. During the suspension period, no funds from this award may be provided to the Participating Site for new accruals, and no charges to the award for new accruals will be permitted. The NCI will also notify a Participating Site that is the direct recipient of a Cooperative Agreement from the NCI if it is necessary to suspend accrual at that Participating Site or at a third party institution/site supported under that Participating Site's Cooperative Agreement.

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 reviews and approves 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. Participating Sites found not to be in compliance with the NCI guidelines for On-Site Monitoring by the CTMB may be suspended from participating in Group trials until compliance can be confirmed by CTEP/CTMB.

Any data irregularities identified through quality control procedures or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB, CTEP, NCI. The CTMB must be notified **immediately by telephone** [301-496-0510] of any findings suspicious and/or suggestive of intentional misrepresentation of data and or disregard for regulatory

safeguards for **any of the three** (regulatory, pharmacy, and patient care) **components of an audit**. Similarly, any data irregularities identified through other quality control procedures suspicious and/or suggestive of intentional misrepresentation of data must be **immediately** reported to CTMB. It is the responsibility of the Cooperative Group, CCOP Research Base, or CTSU to **immediately** notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized that the irregularity/misrepresentation does not need to be proven, a reasonable level of suspicion suffices for CTEP notification. It is also essential that involved individual(s) and/or institutions follow their own institutional misconduct procedures in these matters.

6. Data Management and Analysis Review

At the request of CTEP, the Biometric Research Branch (BRB) staff will review mechanisms established by the Group for data management and analysis. When deemed appropriate, BRB staff will make recommendations to ensure that data collection and management procedures are adequate for quality control and analysis, yet sufficiently simple to encourage maximum participation of physicians entering patients onto studies and to avoid unnecessary expense. In addition, the NCI will have access to all Group data although the data remain the property of the awardee institution for the Cooperative Agreement. Data must also be available for external monitoring as required by NCI's agreement with the FDA relative to the NCI's responsibility as agent sponsor.

7. Investigational Agent Development and Regulations

The clinical development of new anticancer agents is a highly important use of Group resources. The Groups are a vital component of the research apparatus necessary for the clinical development of the many new investigational agents sponsored by CTEP/DCTD.

Various branches within DCTD share the responsibilities for investigational agent development, as described below.

- The Investigational Drug Branch (IDB) is responsible for: (1) planning, within CTEP as well as with members of the extramural community, overall strategies for studies of new agents in specific tumor types and (2) coordinating and monitoring trials of new agents developed by the DCTD.
- The Pharmaceutical Management Branch (PMB) provides for the distribution of investigational new agents for which DCTD is the sponsor.
- The Regulatory Affairs Branch (RAB) maintains close contact and on-going dialogue with the pharmaceutical collaborator and with the FDA to ensure that new agent development complies with federal regulations and proceeds in a coordinated way.
- The Clinical Investigations Branch (CIB) is involved in promoting comparative Group clinical trials evaluating treatment strategies using new agents versus appropriate control therapies.
- The Biometric Research Branch (BRB) assesses proposed designs for evaluating the benefits of investigational agents.
- The Clinical Trials Monitoring Branch (CTMB) verifies adherence by the Groups to the quality assurance procedures of investigational agent trials.

As previously stated, CTEP uses a system of Letters of Intent (LOIs) as a mechanism for developing rational strategies for investigational drug development studies. See the Investigator's Handbook, provided on the CTEP website at [[Website Reference 7](#)], for a full description of the process for the clinical development of investigational agents and summary of the responsibilities of investigators conducting these trials.

8. Compliance with Federal Regulatory Requirements Review

CTMB and RAB staff will review general policies and procedures periodically, as needed, and provide advice regarding mechanisms established by the Group to meet FDA regulatory requirements for studies involving DCTD/CTEP-sponsored investigational agents and OHRP requirements for the protection of human subjects.

9. Requesting Changes in Principal Investigator(s) for Any Group Component

The responsible NCI Program Director must approve any proposed changes in the Principal Investigator (PI) for any Group U10 Cooperative Agreement. The institution's business office should forward the name of the proposed Principal Investigator in a memorandum to the responsible NCI Program Director requesting approval, with a copy to the CTEP Program Specialist. The curriculum vitae (CV) of the proposed Principal Investigator should be included as an attachment. The memorandum should be countersigned by the current Principal Investigator (if available), the business official who has responsibility to sign for the grant, and the proposed Principal Investigator. Group leadership should also indicate its approval of this change to CTEP through a memorandum or email from the Group Chair to the responsible NCI Program Director and the CTEP Program Specialist.

C. Collaborative Responsibilities (Groups and NCI/CTEP Staff)

Because of the significant resource, regulatory, and general administrative issues involved in Group activities, the Groups should collaborate closely with CTEP staff; this includes early on in the development of phase 3 trials (whether single Group, Intergroup, or international trials) as well as in the development of general research strategies and new initiatives.

1. Development of Intergroup Trials and International Trials

CIB staff will conduct scientific-oriented strategy meetings, attended by Group investigators, other extramural investigators, and NCI staff, for the purpose of jointly developing the NCI Clinical Trials Cooperative Group Program priorities for future study development. The Groups and CTEP staff will work together to facilitate the timely development of Intergroup trials resulting from the consensus developed at such strategy meetings.

CIB and other CTEP staff will also work with the Groups to facilitate international participation in trials, as appropriate. When investigators outside the US are members of a US Group and wish to participate in a US Group Trial, they must meet the same Group membership requirements as US members, including being audited by the Group per CTMB guidelines for international Participating Sites, filing FDA 1572 Forms, etc. However, when trials call for collaboration with a separate international organization for its participation in a US Group trial, there are varying degrees of logistical and regulatory complexity involved, depending on a number of factors. In these cases, it is critical that proposals for large-scale international trials be discussed with CTEP staff in advance for general advice and guidance regarding whether the advantages of international collaboration will outweigh the expected resource costs.

With respect to participation of US Groups in trials led by a non-US organization, there are also numerous logistical, regulatory, and company-sponsor issues that must be addressed in addition to approval of the non-US trial by CTEP. Again, it is critical for any proposal for participation of a US Group in a non-US trial be discussed in advance with CTEP staff to determine whether participation in such a study is feasible.

A guidance document from CTEP entitled, ***Cooperative Group Guidelines for the Development, Conduct and Analysis of Clinical Trials with International Collaborating Institutions***, is available on the CTEP website at [[Website Reference 36](#)]. This document addresses the various regulatory issues involved in the conduct of international trials that involve participation/leadership of US Groups.

2. Investigational Drug Development

When new avenues of cancer therapy involving investigational drugs are pursued, the clinical information from the trial should be acceptable to the FDA for inclusion in a potential licensing application. Therefore, in collaboration with NCI staff, the Group will develop protocols to obtain such information, as needed.

3. Data and Safety Monitoring Boards

The appropriate conduct of Group DSMB procedures is a collaborative responsibility of the Group and CTEP members. Information on the CTEP policy for DSMBs is available on the CTEP website at [[Website Reference 18](#)]. The Group's Data and Safety Monitoring Policy must be submitted to and approved by the responsible NCI Program Director.

4. Group Chairs' Meeting

The Chair of each Group, the responsible NCI Program Director, the CIB scientific/administrative liaisons, and other Group and NCI personnel, as appropriate, will meet whenever necessary to discuss issues of relevance to the NCI Clinical Trials Cooperative Group Program. These meetings are scheduled when CTEP and/or the Group Chairs identify significant issues that require discussion.

5. Group Statisticians' Meetings

Each Group's Chief Statistician ("Group Statistician"), the responsible NCI Program Director, the BRB staff, and other Group and NCI personnel, as appropriate, will meet whenever necessary to discuss issues of relevance to the NCI Clinical Trials Cooperative Group Program. These meetings are scheduled when CTEP and/or the Group Statisticians identify significant issues that require discussion.

6. Group Administrators' Meetings

Group Administrators, CTEP staff, and other Group and NCI personnel, as appropriate, will meet whenever necessary to discuss issues of relevance to the NCI Clinical Trials Cooperative Group Program. These meetings are scheduled when CTEP and the Group Administrators, in conjunction with the Group Chairs and/or Group Statisticians, identify significant issues that require discussion.

D. Arbitration

If a proposed study is not approved by CTEP, it may be revised (taking into consideration comments and recommendations made in the consensus review) and resubmitted by the Group. If the CTEP Protocol Review Committee disapproves the study a second time, the Group can request arbitration pertaining to the scientific merits of the study. 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, DCTD.

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.

VI. Miscellaneous Administrative Considerations

A. CTEP Staff Administration

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

The responsible NCI Program Director for the NCI Clinical Trials Cooperative Group Program or his/her designee has responsibility for addressing and approving non-competitive award (Type 5) budget requests, any supplemental budget requests, and competitive award (Type 2) renewal budgets. The responsible NCI Program Director will administer these tasks in conjunction with the Grants Management Specialist in the Office of Grants Administration (OGA) and will be assisted by the CIB scientific/administrative liaisons for the Groups as well as the CTEP Program Specialist for the Groups.

B. CTEP Program Specialist

The CTEP Program Specialist for the Groups works closely with the responsible NCI Program Director in reviewing administrative materials supporting Group requests, performing budget analyses, and facilitating the completion of action items involving coordination between CTEP, the NCI Office of Grants Administration (OGA), and the Groups. The CTEP Program Specialist exchanges information with the Group Administrators and OGA staff on administrative changes and priorities.

C. Grants Management Administration in NCI Office of Grants Administration (OGA)

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

D. Changes of Awardee Institution

Only under exceptional circumstances will NCI permit transfer of a Cooperative Agreement from one institution to another, since such a transfer would be without benefit of peer review of the recipient institution. Any such request should be approved in accordance with the Group's Constitution and By-laws (e.g., approval required by the Group's oversight committee such as its Board of Governors or Executive Committee). The responsible NCI Program Director and the CTEP Program Specialist should be consulted for further advice if the Group contemplates such a transfer request. Any such request, if accepted, will require a full PHS 398 application or electronic SF424 Research & Related (R&R) application, a detailed plan regarding policies and procedures related to personnel issues, Group resources, etc., and approval and oversight by the responsible NCI Program Director.

E. Transfer of Group Membership for a U10 Participating Site

Only under exceptional circumstances will NCI permit transfer of a Participating Site U10 from one 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 or relinquishing Group remains the responsibility of the U10 Participating Site.

In effecting the transition, the member U10 Participating Site (Institution) must submit an application (either Type 2 or Type 5) under the auspices of the receiving or acquiring Group. Also, the Participating Site must coordinate with CTEP, the NCI Grants Administration Branch and the Scientific Review Administrator to align its funding dates and review dates with those of the acquiring Group. The CTEP Program Specialist will be the NCI point of contact in helping to coordinate a smooth transition.

Responsibilities of the U10 Member Participating Site (Institution) and Principal Investigator include:

- Provide documentation that the Chairs of both the relinquishing and acquiring Groups are in support of the planned transfer.
- Work with CTEP to align the funding period and review date with those of the acquiring Group.
- Make an application under the auspices of the acquiring Group.
- Continue to send CDUS patient data to the relinquishing Group for patients already accrued to that Group as long as patients are on study or being followed.

Responsibilities of the Relinquishing Group include:

- Terminate member affiliation from the Clinical Trials Monitoring Branch Audit Information System (CTMB-AIS).
- Remove protocol Principal Investigators from the Regulatory Support System (RSS). Coordinate this action with the acquiring Group. Investigators with patients continuing on-study will have access to drug shipments for the relinquishing Group's protocols. These investigators must be flagged in the RSS on an individual basis.

Responsibilities of the Acquiring Group include:

- Add new member to Clinical Trials Monitoring Branch Audit Information System (CTMB-AIS).
- Add protocol Principal Investigators to Regulatory Support System (RSS) after they have been removed from relinquishing Group.
- Ensuring that the member Participating Site (Institution) is oriented to and in compliance with the guidelines of the acquiring Group.

F. Principal Investigator Not Employee of Awardee Organization

If the Principal Investigator (PI) is not an employee of the awardee organization for any Group component (e.g., Operations Center, the SDMC, Participating Site holding a U10 award), 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.

G. Funding Decisions on Group Components Not Receiving Meritorious Scores by Peer Review

If a Group component does not receive a meritorious score at the time of an interim review, future activity by this component is at the discretion of the responsible NCI Program Director. For example, a Scientific Committee that receives a non-meritorious score in two, sequential, peer review cycles may or may not continue future activities as a "Working Group" funded out of the Group Chair's Discretionary Funds after consultation with, and approval by, the responsible NCI Program Director. A Working Group, however, would not be in a position to launch a phase 3 trial, or any other major study, after failing peer review for a second time.

Participating Site U10 applications that receive non-meritorious scores in two, sequential, peer review cycles would not be re-funded. U10 applications for other Group component(s) that receive non-meritorious scores in two, sequential, peer review cycles would require re-competition for the Group component funded by that U10 application, if the component were vital to the Group's operations. If the component were not vital to the Group's operations, it would not be re-funded.

Likewise, the receipt of a non-meritorious score by a Statistics and Data Management Center application in two, sequential, peer review cycles would also require re-competition.

H. Miscellaneous Budgetary Considerations

1. Carryover Requests

Carry-over requests will be entertained in situations where circumstances prevented funding from being spent during the budget period for which it was provided and where funding is not replicated in the current budget year for an on-going expense.

2. Reporting Unexpended Balances

Following submission of the Financial Status Report (FSR) as required by NIH policy, the Group must report any major unexpended balance (\$25,000 or more) from the FSR to CTEP. Generally, such unexpended balances will exist in the Cooperative Agreements for the Operations Center and/or Statistics and Data Management Center.

Any major unexpended balance (\$25,000 or more) must be reported, according to the Common Budget Outline categories, and sent to the attention of the CTEP Program Specialist and responsible NCI Program Director within two weeks after the FSR is due. Email submission of this information is preferred. ([See Part 4 - Attachment #11.](#))

3. Requests for Non-competing Supplemental Funding

Informal discussions about the possibility of receiving non-competing supplemental funding for special needs may be initiated by the Group, however, formal requests must be made for funding to be received and must always be countersigned by the business official responsible for the Cooperative Agreement/grant and the Principal Investigator. Electronic facsimile signatures on documents transmitted via email are acceptable. Very simple requests (e.g., for capitation) may be handled by memorandum. Most requests, however, will require the use of a Form PHS 398/SF424 or PHS 2590 to capture the details of the requested budget. The original should be sent to the responsible NCI Program Director, in care of the CTEP Program Specialist.

PART 2: Guidelines Specific for Submission of Competing Applications

I. Pre-application Consultation/Letter of Intent and Application Submission Instructions

A. General Considerations and Receipt Dates

All new and competing continuation and competing supplemental applications (Types 1, 2, and 3, respectively) for support through the NCI Clinical Trials Cooperative Group Program must be prepared using the most currently revised PHS 398 research grant application instructions and forms – or SF424 (Research & Related [R&R]) application once this electronic application replaces the PHS 398 for this Cooperative Agreement. The major components of the PHS 398 as described in these Guidelines for the NCI-Sponsored Cooperative Group Clinical Trials Program are retained in the SF424. Hence, applicants should follow the same instructions provided in these Guidelines regardless of whether they are using the PHS 398 or SF424 (R&R) application. The PHS 398 is available at [[Website Reference 27\(a\)](#)] in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, **Email: GrantsInfo@nih.gov**. Once the SF424 application is required for all applications submitted under this Cooperative Agreement, applicants will be notified by the CTEP Program Specialist and applicants should use the appropriate NIH website references [[Website Reference 27\(b\)](#)] to access information regarding submission of the SF424.

It should be noted, however, that the standard instructions included in the PHS 398 and SF424 applications are designed primarily for individual research projects, and do not address the unique goals and policies of the NCI Clinical Trials Cooperative Group Program. **These Guidelines are only meant to supplement the PHS 398/SF424 instructions, except where it is explicitly noted that these Guidelines are replacing or supplanting instructions in the PHS 398/SF424 application (e.g., the format for the research plan is different for Group applications). If an issue is not explicitly included in these Guidelines, then Groups should follow the information and guidance given in the PHS 398/SF424.** United States (US) organizations submitting new or competing continuation applications for support through the NCI Clinical Trials Cooperative Group Program may apply for up to six (6) years of support. Non-US organizations may apply for up to five (5) years of support.

The receipt dates & review schedule for all applications, using 2007 as the sample year, are as follows:

(1) Visit by Group Leadership to CTEP	9 to 12 months prior to Application Receipt Date		
(2) Letter of Intent to NCI Referral Officer	6 weeks prior to Application Receipt Date		
(3) Draft Common Budget Outline to CTEP	4 weeks prior to Application Receipt Date		
(4) Submission of Appendix Material	10 weeks prior to Review by Subcommittee H-Clinical Groups		
(5) Application Receipt Date	Feb 1, 2007	Jun 1, 2007	Oct 1, 2007
(6) Site Visit (if applicable)	May/Jun 2007	Sep/Oct 2007	Jan/Feb 2008
(7) Subcommittee-H Review Meeting	Jun/Jul 2007	Oct/Nov 2007	Feb/Mar 2008
(8) National Cancer Advisory Board (NCAB) Meetings	Sep/Oct 2007	Jan/Feb 2008	May 2008
(9) Earliest Possible Funding Date	Dec 1, 2007	Apr 1, 2008	Aug 1, 2008
(10) Just-In-Time Information	Prior to Award		
(11) Revised (Final) Common Budget Outline	After final Award level is known		

Rationale for submission schedule and general information on funding decisions: **In general, because of the interrelatedness of the various components of a Group, all new and competing continuation applications from a particular Group should be submitted for review at the same time.** Funding recommendations for all of the Group’s components (including non-administrative components such as the Scientific Committees (e.g., Disease, Modality) rated by peer review as “Excellent to Outstanding” are usually of the same duration and period. Components rated as less than “Excellent” will receive funding recommendations for shorter durations than that for the Operations Center application. Competing supplement applications and applications from Participating Sites submitted out-of-sequence with the remainder of the Group will have adjustments made in the award such that funding periods coincide with those of the of the Group Operations Center.

The procedures for new and competing applications for Quality Assurance and Service Centers as well as International Groups funded under this Program are the same as those for US Groups except that a Common Budget Outline (described below) is not required. The information provided in the application or research plan, however, should focus on the specific activities of these entities (e.g., collection, transfer, and assessment of data collected or therapy delivered on a clinical trial and/or participation in trials rather than on the development of a specific scientific agenda and series of clinical trials).

B. Letter of Intent/Preliminary Budget Discussions

Nine (9) to twelve (12) months before application receipt date – Group visit to CTEP:

It is strongly recommended that Group leadership visit to CTEP 9 to 12 months before the receipt date for the application to discuss with Program, Grants Management, Grants Review staff, and the Scientific Review Administrator (SRA) for Subcommittee H-Clinical Groups all relevant aspects of the application including its organization, preparation, and expected budget, leadership changes, and any new changes that may be referenced in the application or review procedures.

Six (6) weeks before application receipt date – Approval of ARA:

For NCI budget planning purposes, applicants who plan to submit applications of \$500,000 or more in direct costs in any one year of the award must contact the NCI Referral Office to seek approval at least 6 weeks before the application is submitted in order that an internal “Awaiting Receipt of Application” (ARA) approval can be generated by the NCI. Without this approval, the application will not be accepted by the NIH Center for Scientific Review (CSR). **The request for approval must include the Cooperative Agreement number, the Principal Investigator’s name, the anticipated submission date, and an estimate of direct costs requested for the first year.** To facilitate and maintain a record of these actions, all communication regarding a request to exceed the \$500,000 direct cost level in any one year must be directed to the NCI Referral Office at the address below. **A copy must also be sent to the responsible NCI Program Director, in care of the CTEP Program Specialist.** For further information, contact:

NCI Referral Office
National Cancer Institute - Division of Extramural Activities
6116 Executive Boulevard, room 8041, MSC 8329, Bethesda, MD 20892-8329
PHONE: (301) 496-3428 **FAX:** (301) 402-0275 **E-MAIL:** ncirefof@dea.nci.nih.gov

With application – Draft Common Budget Outline:

The responsible NCI Program Director also requires that a draft Common Budget Outline for the entire Group application “package” be submitted with the application. (Based on the Group’s preference, the draft Common Budget Outline may be submitted with the ARA rather than with the application.) This draft Common Budget Outline should include expenses from all applications to be submitted from the various Group components. In addition, a list of committees requesting budget support should also be sent to SRA for Subcommittee H-Clinical Groups.

Three (3) copies of the items below should be sent directly to the responsible NCI Program Director at least four (4) weeks prior to the application due date, with electronic copy sent to the CTEP Program Specialist:

- A draft Common Budget Outline, organized as per the budget template provided in [Part 4 - Attachment #11](#), will need to be submitted which encompasses all of the direct costs that will be requested by all components of the Group’s application package. Only the first year of the award cycle need be presented. Although this draft Common Budget Outline does not have to contain the precise final numbers that will appear in the official application, it should present a reasonably close approximation for most or all major budget categories.
- A brief narrative justification for the main budgetary items in any category for which the requested budget is greater than 15 percent above current funding and for new categories or programs.

PART 2.I: Guidelines Specific for Submission of Competing Applications – Pre-application Instructions

- A listing of grant numbers and projected first year direct costs (and estimated indirect costs) for each separately awarded U10 in the Group package. Special notation should be made for any U10 application that will exceed \$500,000 direct costs in **any year** of the award cycle.

These items should be sent to:

Chief, Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division Cancer Treatment and Diagnosis
6130 Executive Boulevard - Room 7025
Bethesda, MD 20892-7436

EXPRESS MAIL ADDRESS:

Clinical Investigations Branch
Cancer Therapy Evaluation Program, DCTD
6130 Executive Boulevard - Room 7025
Rockville, MD 20852
PHONE: (301) 496-2522 **FAX:** (301) 402-0557

Rationale for time-lines for Letter of Intent and preliminary budget discussions and for the ARA: The peer review schedule for the large application packages that make up any Group submission must be organized well in advance. A refusal to accept a Group application (or any component application) would be very disruptive to both the Group's on-going functionality and to the NCI peer review committee system. Therefore, NCI believes it is essential for the Group to leave enough time to assure that any program issues that significantly impact the proposed budget can be analyzed, understood, and resolved in time to generate an internal "Awaiting Receipt of Application" (ARA) approval by the NCI and permit the main Group application and all component applications to be accepted on the planned date. Information on ARA approval is provided on the [previous page under the heading "Six \(6\) weeks before application receipt date."](#) For Group competing applications, the Operations Center and Statistics and Data Management Center applications will always require an ARA. Some Groups will also have other components for which they are submitting separate applications as part of the overall application package that also trigger this requirement. For those Groups that have a number of Participating Site U10 applications, some of these applications may also request budgets with direct costs over \$500,000 in any one year within the multi-year award cycle. These applications will also require an ARA.

C. Application Submission Procedures

SENDING AN APPLICATION TO THE NIH: Submit the original, including the Checklist, and 5 exact, legible, single-sided photocopies of each application, in one package to the Center for Scientific Review (CSR), according to the instructions in the Grant Application Form PHS 398/SF424. The original must be signed by the Principal Investigator and an authorized organizational or institutional official.

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710 (for regular or US Postal Service [USPS] Express or Regular mail)
Bethesda, MD 20817 (for Express/Courier Non-USPS Service)
Phone: 301-435-0715 TDY: 301-451-0088

At the time of submission, two additional copies of the application must be sent to NCI directly, to the address listed below, to assist NCI in scheduling reviews and requesting additional information, if needed.

NCI Referral Office
Division of Extramural Activities - National Cancer Institute
6116 Executive Blvd., Room 8041, MSC-8329
Rockville, MD 20852 (Express courier)
Bethesda MD 20892-8329
Phone: 301-496-3428 Fax: 301-402-2075

NOTE: All applications and other deliveries to the Center for Scientific Review must be delivered either via Courier or via the USPS. Application delivered by individuals to the Center for Scientific Review will not be accepted. C.O.D. applications will not be accepted. This policy does not apply to courier deliveries (e.g., FedEx, DHL, etc.) [[Website Reference 28](#)]. This policy for applications addressed to Centers for Scientific Review is published in the NIH Guide Notice at [[Website Reference 29](#)].

D. Appendix Material

1. Operations Center and SDMC Applications

After the applications have been submitted, the applicant should contact the Scientific Review Administrator (SRA) to discuss the inclusion of any Appendix material that is important to the peer review of the Operations Center and Statistics and Data Management Center applications. Groups may wish to contact the SRA to discuss what Appendix material would be useful to include in the application prior to the actual submission of the application. The Appendix material can be discussed with the SRA at any time prior to submission; however, Appendix material for Operations Center and SDMC applications should be **submitted to the SRA for Subcommittee H-Clinical Groups at least 10 weeks prior to the review of the Group’s full application package, so that the SRA may review the Appendix material to be submitted with the application.** It is useful for the Group to start discussions with the SRA on the Appendix material when the Group leadership visits CTEP about 9 to 12 months before the application receipt date to discuss its pending competitive application. (See [Letter of Intent/Preliminary Budget Discussions in Part 2.I., Section B on pages 54-55.](#))

The number of collated sets of Appendix material to be submitted will be negotiated with the SRA; Appendix material cannot be used to circumvent page limitations of the research plan. The information listed below, at a minimum, should be provided in the Appendix material for the Operations Center and SDMC applications. Copies of any required images can also be included as Appendix material.

- A table showing Data Quality and Timeliness (definitions of data timeliness should be provided with the table). (See [Attachment #3: Suggested Format for Summary of Data Quality & Timeliness.](#))
- A table showing total summary accrual for all studies from a Scientific Committee should be provided. Accrual should be categorized by type of study: (1) Group studies, (2) Group-led Intergroup studies, (3) endorsed/Intergroup studies, and (3) non-Group, non-endorsed, CTSU studies. Tables should also be provided showing accrual by specific study as well as summary accrual for all Group studies. In addition, the Group should provide summary accrual by Member Participating Sites. (See [Attachment #4: Suggested Format for Summary Accrual Tables.](#))
- A copy of the Policies and Procedures Manual for both the Operations Center and the SDMC (including Constitution & By-laws, Conflict of Interest Policy, Group DSMB Policy, Data and Safety Monitoring plan for phase 1 and phase 2 studies, Data Sharing Policy, etc.)
- A complete set of protocols for all studies that will be open at the time of review and all studies closed during the current funding period, with “up-date” material provided as appropriate (i.e., amended protocol information and other data obtained after submission of the application may be provided after submission of Appendix material, but prior to review, as “up-date” material). The Group should check with the SRA regarding appropriateness of submissions of “up-date” material.
- A copy of the most recent Group Report of Studies and Group Meeting Program Agenda
- One complete set of all key manuscripts published during the current funding period (i.e., manuscripts on the primary study findings and results). References can be provided for all other manuscripts published during this time period; however, the Group must provide a copy of any “non-key” manuscripts requested by reviewers on Subcommittee H-Clinical Groups. Submission of manuscripts/publications in Appendix material must follow NIH guidelines as described at [[Website Reference 43](#)]. If a Group has any problems adhering to the guidelines for submission of manuscripts, the Group must discuss this with the SRA for Subcommittee H-Clinical Groups. The relevant bibliography of these key manuscripts must be presented within each Committee write-up. At its discretion, the Group may also provide a complete bibliography of all key manuscripts and references in a separate listing in the Appendix material; however this is not necessary.
- Information on Non-U10 Member Institutions, if appropriate, including total accrual by institution

For more additional description of the type of information that should be provided in the Appendix Material for the Operations Center application, [see Part 2.II.C, Section 4 on page 67](#). For additional description of the type of information that should be provided in the Appendix Material for the SDMC application, [see Part 2.II.D., Section 4 on page 71](#).

Appendix material must be provided in a CD-ROM format or other electronic format acceptable to the SRA with a Table of Contents and bookmarks to improve readability of the CD-ROM or other electronic format in lieu of a paper format. **The applicant should contact the SRA to discuss the number of copies of the CD-ROM (or other electronic media) that should be submitted.**

With respect to submission of Appendix material for the Operations Center and SDMC applications for SRA review of the material that will be included in the application for Subcommittee H-Clinical Groups review, the Group should send this material to:

Scientific Review Administrator for Subcommittee H-Clinical Groups
National Cancer Institute
Division of Extramural Activities
Resources and Training Review Branch
6116 Executive Boulevard, MSC 8329
Bethesda, MD 20892-8329
Phone: 301-496-7721

2. Participating Site U10 & Other U10 Applications

Appendix material for Participating Site U10 applications as well as other U10 applications **should be included with the corresponding application according to the procedures outlined in [Part 2.I.D. on pages 56-57](#)**. The Appendix material should be placed after the Application Checklist. The Appendix material should be identified with the name of the Principal Investigator. The Appendix material should not be intermingled with the rest of the application. Three signed copies of the application along with three collated sets of Appendix material should be submitted to CSR, according to the Grant Application Form PHS 398/SF424. In addition, at the same time, two complete copies (application plus Appendix material) should be submitted to the NCI Referral Office. As with the Appendix material for the Operations Center and SDMC applications, the Appendix material cannot be used to circumvent the page limitations of the research plan and the material must be provided in a CD-ROM or other acceptable electronic format. For additional description of the type of information that should be provided in the Appendix Material for a Participating Site or other U10 application, [see Part 2.II.E, Section 4 on page 77](#).

E. Notification of International Involvement in Group Trials

The Group should alert the CTEP Program Specialist when a new or competing application involves any international (non-US) component. In such cases, advance clearance from the US Department of State is needed for each non-US component prior to the award. The information required by US Department of State is listed below (this information should also include all non-US subcontracts).

- Estimated annual Total Cost dollar award for the non-US component
- Name, organization, city, and country of the International (non-US) Principal or Collaborating Investigator(s)
- Biosketch and Curriculum Vitae (CV) for both the domestic Principal Investigator and the international Principal Investigator
- OHRP assurance number (i.e., Federalwide Assurance number) for the non-US component

II. New and Competing Applications Format and Budget Requests

A. General Guidelines

The application and formatting guidelines that follow are based upon an operational model of a Group in which there may be separate awards for the Operations Center, Statistics and Data Management Center, individual Participating Sites with the greatest academic contributions to Group activities and/or other important functional components of the Group. This structure is not required. An alternative model, in which there are no separate awards for individual Participating Sites through a U10 application (e.g., funds being provided to performance sites by the Operations Center via per-accrual reimbursement mechanisms) may provide more flexibility in placing resources where they are required.

It is recognized that available funding is not always adequate to offset research costs completely. While the goal of the NCI is to fully fund the cost of doing clinical research at peer review recommended levels, current budgetary constraints mandate that the systems employed by the Groups for allocating NCI funds be sufficiently flexible to permit shifting of financial resources during the multi-year funding period. To this end, it is strongly recommended that the Groups adopt or expand mechanisms that reimburse physician-participants on a per-accrual basis for the data-management and accrual-related costs they incur in participating in NCI-sponsored trials, while reducing the reimbursement for such costs in the context of the Participating Site U10 application. If individual Participating Site U10s are to be requested as separate U10 applications, they must be justified on the basis of scientific and administrative contributions to Group activities as well as on accrual.

Please Note:

- a. Community Oncologist Steering Committee.

- b. Participants in the Community Oncologist and Patient Advocate Steering Committees who are not participants in the Scientific Steering Committees will be selected by the community oncologists and patient advocates, respectively, who are Scientific Steering Committee participants.

All applications, including those of the Operations Center, the SDMC, U10 Participating Sites, etc., should describe the scientific and administrative experience of key personnel and should include and follow the PHS 398/SF424 instructions for Biographical Sketches and Other Support information (including support for clinical trials activities). In the section entitled "Key Personnel" in the PHS 398/SF424, it is **imperative** that applicants list all individuals participating in the scientific execution of Group activities in the format specified (i.e., name, organization [their institutional affiliation], and role on the project), including those with no requested salary support. Under "Role on the Project", indicate how the individual will function with regard to the Group.

A roster of Key Personnel should be included with the each application. Key Personnel for the Operations Center application will usually include the Group Chair, Group Vice-Chair, other significant administrative officers, and committee chairs and vice-chairs. Consultants should also be included if they meet the definition of "Key Personnel." Similarly, in the SDMC application, the Key Personnel would typically include Group Statistician, a number of additional senior biostatisticians, and leadership of the data management components of the SDMC. Applicants must ensure the list of Key Personnel is complete, and may use as many continuation pages as necessary. Although information on "Other support" is also required for all Key Personnel listed on all applications that are to receive grant awards; information on "Other Support" should NOT be submitted with the application. Rather, NIH will request complete and up to date "Other Support" information from applicants at an appropriate time following peer review. The NIH's scientific program and grants management staff will review this information prior to award. For information on NIH "Other Support" policy, [see Just-In Time Information in Part 2.II.C, Section 5.1 on pages 67-68](#).

For all competing applications (with exception of new competing applications), past problems should be frankly described, along with plans designed to address them in the next funding period.

B. Common Budget Outline

The Group is required to submit a draft Common Budget Outline ([See Attachment #11 in Part 4](#)) to the responsible NCI Program Director, with an electronic copy to the CTEP Program Specialist, at least four (4) weeks prior to the application receipt date. This draft Common Budget Outline should cover all components of the Group, including the Statistics and Data Management Center, Participating Sites with U10s, and other Group components funded by separate U10s. After completion of peer review, a “revised” or final Common Budget Outline based on the **actual** funding plan level granted must be submitted prior to the award of the Cooperative Agreement. The format for this revised Common Budget Outline should be the same as that used for the draft Common Budget Outline. An electronic copy of the revised or final Common Budget Outline should be sent to the CTEP Program Specialist.

Rationale for the Common Budget Outline: The Common Budget Outline was designed to provide budget information in a standard format that allows the responsible NCI Program Director, SRA, and CTEP Program Specialist to understand how the total Group budget is allocated among the various components of the Group to support its basic functions. The Common Budget Outline also allows comparisons to be made more easily from year to year for the Group as well as among the different Groups in order to provide a budget overview of the entire NCI Clinical Trials Cooperative Group Program. This budget overview also allows the responsible NCI Program Director to plan funding priorities across the Program.

C. Operations Center Application

In general except where noted below, all Group applications should conform to the instructions provided in the PHS 398/SF424 grant application kit. Specific instructions are provided on the following pages for the Operations Center application.

1. Detailed Budget for Initial Budget Period

1.1 General Information

Since the organizational framework of each Group may be different, the Operations Center budget should be presented in logical, discrete units, with specific budgets for each unit (e.g., capitation payments for Participating Sites as well as the total Operations Center request). A specific budget page covering the Group's quality control, study monitoring, on-site audit program, and independent Data and Safety Monitoring Boards must be included.

A separate budget page and item entitled "**Discretionary Fund**" may be included. The purpose of which is to provide the Group leadership with resources to support unanticipated needs, such as piloting innovative clinical proposals or providing limited funding for candidate members. The Group's process for allocating funds from this Discretionary Fund must be clearly described, as must be previous uses of the Fund since these constitute a major factor in peer review assessment of subsequent requests.

A separate budget page and item entitled "**Developmental Fund**" may be included. The purpose of which is to provide the Group leadership with resources to support the preliminary laboratory/clinical correlative studies preparatory to hypothesis-driven projects suitable for subsequent R01 or R21 funding consideration. The first year's plans for this Developmental Fund must be carefully justified, and the Group's process for allocating the funds clearly described. In future applications, previous uses of the Fund should be carefully described since these constitute a major factor in peer review assessment of subsequent requests. **NOTE:** Requests for Group Chair Discretionary Funds and Group Chair Development funds above \$500,000 in direct costs (for each type of fund) will not be entertained.

It is recommended that quality control services, including all research laboratories and Reference Laboratories of the Group, be funded via subcontract from, or consortium agreement with either the Operations Center or the SDMC. In this way, responsibility for resource management rests most clearly and appropriately with the executive leadership of the Group using these quality control services. The exception to this policy is for facilities providing services to the entire NCI Clinical Trials Cooperative Group Program that are funded under Participating Site U10 awards for these purposes. The Quality Assurance Review Center (QARC) and the Radiological Physics Center (RPC) are examples of such facilities.

The following budget guidelines apply specifically to the Operations Center budget. The categories listed below (with the exception of "Mechanisms for Per-Accrual Reimbursements") refer to those contained in the section of the PHS 398/SF424 pertaining to the detailed budget for initial budget period.

1.2 Personnel

Precise justification for the amount of effort requested for each position in the Operations Center application is essential, including the following:

- a) *Scientific effort and protocol development:* Research costs include the time and effort involved in developing the research agenda and entire repertoire of protocols for the Group as well as the analysis and publication of the results of Group research in peer reviewed journals in a timely manner.

- b) *Laboratory investigation efforts:* Research costs include the time and effort related to additional laboratory investigations specific to the research goals of a Group study (i.e., not associated with conventional patient care).
- c) *Administrative efforts:* 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.

1.3 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 Operations Center budget. Clear and quantifiable justification is required. These costs include travel, per-diem and consultant fees, if applicable and within institutional policy.

1.4 Equipment

Justification for equipment costs should include percent of time used for Group business as well as necessity for purchase. The amount of funds requested should be based on percent of use. Only those equipment items that are required to conduct Group protocols should be included.

1.5 Supplies

Research costs for appropriate supplies with quantitative justifications based on actual use should be provided.

1.6 Travel

The importance of meetings to the achievements of any Group's research objectives is obvious, as is the necessity to maintain careful control over the size of this budget item. The budget for travel must be itemized and justified. It should include the following:

- a) Trips by the Group's leadership and investigators on behalf of the Group to the NCI and other national organizations where the results of Group research must be presented or where Group research strategies are to be discussed;
- b) Travel for committee members to committee meetings held separately from the semi-annual Group meetings;
- c) Travel for protocol chairs and others who must perform quality control functions away from their home institution;
- d) Travel for persons on the Operations Center staff who must attend the Group's semi-annual meetings;
- e) Travel associated with on-site audit program; and
- f) A reasonable number of carefully justified trips is allowable for provisional or otherwise unfunded Group members to attend Group meetings in order to encourage participation and assure input from all relevant modalities.

1.7 Patient Care Costs

NCI will not support costs associated with routine patient care. Only in the most unusual circumstances would a Group clinical trial require interventions beyond those considered appropriate for the care of cancer patients. In those circumstances, a Group may make a case for reimbursement of patient care costs associated with the particular research element. The justification should be presented at the level of the Group Operations Center application with a specific request from each institution based upon likely accrual to the specific study.

Rationale for patient care cost policy: This policy is based on the observation that Group treatment trials always involve treatment that is administered with therapeutic intent to patients who require medical care, and always involves therapy that is either considered standard medical treatment or can reasonably be expected to be superior to it. Therefore all costs associated with standard patient care are legitimately borne by third party carriers.

1.8 Alterations and Renovations

Costs for alterations and renovations are not allowable under the NCI Clinical Trials Cooperative Group Program.

1.9 Other Expenses

Research costs due to other expenses include those related to communication and information dissemination among Group members. Also included are costs of equipment rental and maintenance (copiers, telephones, computers), postage, copying and printing, etc., justified quantitatively on the basis of previous experience, where relevant.

1.10 Consortium/Contractual Costs

Research costs include financial support to Group members who are responsible for committees or laboratory investigations and this financial support is usually provided through consortium/contractual arrangements. Groups are encouraged to structure their organization in a manner which minimizes the burden of indirect costs on the overall Group budget.

NOTE: The funds received by Participating Sites for patient accrual should be included in the consortium/contractual costs category of the Operations Center budget. These costs should be made subject to modification based on results of the Group's performance review. Also, third party costs requested for consortium/contractual participants require 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 Operations Center.

1.11 Mechanisms for Per-Accrual Reimbursement

A description of how the Group's formula for per-accrual reimbursement (e.g., treatment accrual, follow-up, accrual to ancillary trials, data management) was determined, including a line-item budget breakdown of the associated research costs, must be included in the application. In addition, the application must include a plan for disbursement of per-accrual reimbursement funds that includes consideration of performance and quality factors including eligibility and evaluability rates, data accuracy and completeness, quality of on-site audits, etc. As stated above, the funds received by Participating Sites for patient accrual should be made subject to modification based on results of the Group's performance reviews and these costs should be included in the consortium/contractual costs category of the Operations Center budget.

NOTE: For endorsed Intergroup studies, funds for the data management costs associated with patient follow-up should be provided by the enrolling Group even if the enrolling Group does not lead the study.

Rationale for the per-accrual reimbursement policy/formula: Per-accrual reimbursement is to be based on formulas that must relate to the actual time and effort required for enrolling new patients on a study and for managing data related to their participation on-study. In the event that a Participating Site serves as a center for affiliate sites and provides data management services to such affiliates, it is appropriate that the Operation Center's per-accrual reimbursement formula allocate the reimbursement between the affiliate site and the primary Participating Site or "Member Institution" on the basis of time and effort of the activities involved (e.g., allocate an appropriate percentage of the affiliate per-accrual reimbursement to the main Participating Site). In the absence of such a relationship (i.e., all Participating Sites, including affiliate sites, interact directly with the Group's Operations Center and SDMC), it is appropriate that the formula allocate the entire reimbursement to the Participating Site.

1.12 Consortium Arrangements

Consortium arrangements and all other contractual arrangements, including all mechanisms for reimbursement for patient accrual, must be formalized in writing in accordance with applicable NIH Grants Policy requirements, which are provided on the NIH website at [[Website Reference 30](#)]. 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.

2. Research Plan

In the “Research Plan” section of the Operation Center’s application, the essence of a Group’s program of clinical trials should be described in the application for support of its Operations Center. The application should characterize the Group’s mission and its plans to accomplish that mission as well as present the Group’s research accomplishments and its proposals for the upcoming funding period. It should outline the Group’s strategy for each of its Scientific and Administrative Committees. **Each Group Committee should be clearly identified as either a Scientific or an Administrative Committee in the application.**

As described earlier ([under Section 4 on Scientific and Administrative Committee Rights and Responsibilities in Part 1.V.A. on page 38](#)), Scientific Committees are defined as committees that develop and conduct clinical trials and studies and have a defined research agenda (e.g., Disease Committee such as a Breast Committee that conducts trials in breast cancer, Radiation Oncology Committee that conducts radiation-therapy trials in selected disease types, other Scientific Committee such as an Experimental Therapeutics Committee or a Correlative Science Committee).

Administrative Committees are defined as committees which function primarily by providing essential core service functions to other aspects of the Group’s research program (e.g., Patient Advocacy, Clinical Research Associates, Auditing, Pathology, Surgery).

The following format is suggested for completing the specific components of the PHS 398/SF424 Research Plan relating to “Specific Aims”, “Background and Significance”, “Preliminary Studies/Progress Reports”, and “Research Design and Methods.” All other components, however, requested in the Research Plan section of the PHS 398/SF424 must also be included in the application (including “Human Subjects Research”, “Inclusion of Women and Minorities”, “Inclusion of Children”, and “Data and Safety Monitoring”).

Although according to the PHS 398/SF424 instructions, the Research Plan must be limited to 25 pages; specific page-number allowances are made for the Operations Center applications, given the size and complexity of the NCI Clinical Trials Cooperative Group Program. **The page limit for the Research Plan of an Operations Center application for those components described in Sections 2.2 through 2.11 below, with the exception of Section 2.6 and Section 2.10 (for which specific additional page allowances are made) is extended to a total of 50 pages of text in 11-point Arial or Helvetica font size, exclusive of tables, graphs, diagrams, and charts.** The text in these 50 pages should include the Group’s response to the previous review of its application. Section 2.6 (“Scientific Committees”) describes specific page limitations for the discussion of each Scientific Committee. This discussion should include Reference Laboratories, which are considered Scientific Committees. Section 2.10 (“Accrual information”) relates to information on accrual that should be provided on Accrual in a tabular format, and these tables are not part of the 50-page limit.

2.1 Table of Contents

This is the table of contents for the entire application, including individual component applications such as the SDMC application and Participating Site U10 applications.

2.2 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 as outlined in the NIH policies available on its website at [\[Website Reference 15\]](#), [\[Website Reference 16\(a\)\]](#), and [\[Website Reference 16\(b\)\]](#). This section should also included plans for the inclusion of children (if applicable) as outlined in the NIH policies on its website at [\[Website Reference 17\]](#) and [\[Website Reference 31\]](#).

2.3 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 research objectives. The organizational structure will usually include a number of Scientific and Administrative Committees, in addition to the three major functional components (Operations Center, SDMC, and Participating Sites). The committees will have various research, quality control, and administrative mandates. Productive interaction among the organizational elements should be described and documented. The current members of the Group's Board of Directors or Executive Committee (i.e., oversight committee) should be named, along with their sub-specialty affiliations. Procedures for the selection of Group leadership should be described. Procedures for credentialing members (individuals and/or Participating Sites), for review of members' performance, and for ranking Participating Sites in terms of contributions to the Group should be described. In addition, a clear description of the Group's proposed financial structure, including a description of how funds are allocated to various Group operational components, should be provided. The Group should also provide justification for its policy regarding capitation payments for accrual to Participating Sites.

2.4 Research Strategies

It is essential for the Group and its Scientific Committees to develop and articulate comprehensive plans that summarize the Group's specific research objectives and lines of investigation for each disease chosen for study and to consider strategies for coordination with other Groups and other NCI-funded programs and investigators conducting clinical studies and trials (e.g., Cancer Centers, SPOREs, R01 and P01 investigators, etc.).

2.5 Group Administrative Functions and Administrative Committees

This section of the Operations Center application should address the major roles and responsibilities of the Group administrative staff 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 identify problems and proposed solutions. Applications should clearly document that the proposed Group Chair is experienced in dealing with the problems of cooperative clinical cancer research and that he/she has appropriate experience to qualify as the Group's leader. The Group should describe how its organization and facilities facilitate the complex task of protocol development, quality assurance/control, education, auditing, and compliance with NCI and federal regulations. This section should also address the roles, responsibilities, achievements, and future plans of the Group's Administrative Committees (e.g., Audit Committee, Membership Committee, Nursing and/or CRA Committee, Pharmacy Committee, International Liaison Committee, Minority Representation Committee, Patient Advocacy Committee). A report ([see Attachment #6 on the Suggested Format for Summary of Administrative Committee Activities](#)) may be used to provide information in tabular format on the activities of the Administrative Committees, if appropriate. A similar format may be used to summarize information on the publications associated with an Administrative Committee's work ([see Attachment #5 on the Suggested Format for Summary of Publications by Committee](#)).

2.6 Scientific Committees

In this section of the Operations Center application, the Group should describe how its Scientific Committees fulfill the tasks of protocol development, study monitoring, and quality assurance/control. Examples of these committees include the following: Disease Committees (e.g., Breast, Lung, and Gastrointestinal Committees), Developmental Therapeutics, Correlative Sciences, etc. The Scientific Committees section should include the following:

- a) An abstract, outlining accomplishments of the Scientific Committees during the current award period (interval since the last competing application) and plans for the next award period. This abstract must be limited in length to one page in **11-point Arial or Helvetica font size**.
- b) An abbreviated roster list, including dates of service, indicating the chair, co- or vice-chairs, and the number of committee members by specialty for each Scientific Committee.

- c) A table of studies (by protocol number) for each Scientific Committee describing those studies that were active or planned during the current funding period, using the suggested format in the Summary Accrual Tables ([Attachment #4](#)). For each study indicate: overall accrual by year, the date the study closed to accrual, and the date interim and/or the final study analyses were completed. The term year must be defined (e.g., calendar, grant, fiscal, etc.) and dates must be specified. The report should indicate if there are designated waiting periods (stated in the protocol) between when the study is closed to accrual and the time it is analyzed. For large Scientific Committees, two or more such tables may be appropriate. For instance, the Chair of a Lung Committee might wish to provide one table for non-small cell lung cancer studies and a second table for small cell lung cancer studies.
- d) A list of each Scientific Committee's relevant past studies, current studies and future studies. For each study in this list, a schema must be provided followed by a brief description of the study rationale, objectives, statistical endpoints, and where appropriate, results. Each study summary should occupy no more than two pages, including the study schema, using **11-point Arial or Helvetica font size**.
- e) A description of the encompassing vision of each Scientific Committee, that is, the rationale for the studies performed or services provided (e.g., pathology review) during the current award period and future directions, limiting the text to 10 pages in **11-point Arial or Helvetica font size**. This section should identify and discuss the major research questions or activities relevant to the purview of the committee, and discuss the Group's active and proposed studies in the context of these research questions. It should also identify and describe problems experienced by the committee during the current funding (award) period together with plans designed to address such problems during the next funding period.
- f) For each Scientific Committee, a bibliography for the current funding period for each protocol of the committee. This should include a list of manuscripts submitted for publication at the end of each protocol, with associated information on the study. ([See Attachment #5 on the Suggested Format for Summary of Publications by Committee](#).) A copy of each manuscript should be provided in the Appendix material submitted with the Operations Center application.
- g) For each Scientific Committee, a copy of each protocol active at the time of submission of the application. These protocols may be submitted in the Appendix material submitted with the Operations Center application.

NOTE: Since Reference Laboratories are considered Scientific Committees, the same information noted in sections "a" through "g" with the same page limitations should also be provided for Reference Laboratories, modified as appropriate. Although the NCI encourages incorporation of correlative science (biology) studies into Group clinical trials, there are distinctive funding mechanisms to support performance of laboratory tests on specimens from patients enrolled in Group clinical trials. One means of support is through funding Reference Laboratories. These Reference Laboratories should perform research that is integral to the conduct of a Group's clinical trials (i.e., in the absence of the testing performed by these laboratories, it would not be possible to either conduct the Group's clinical trials or alternatively to interpret results from these clinical trials). Examples would include laboratories performing tests required to assign patients to a particular protocol or to a specific arm on a protocol. The Group is required to explain in the application section on the Reference Laboratory why the test needed to be performed by the Reference Laboratory as opposed to a commercial laboratory. Research that is not integral to the conduct of the Group's clinical trials would be research for which other sources of funding should be sought. An example might include correlative science studies attached to a protocol that had the objective of identifying prognostic factors that might be used for risk factor prognostication in the future. NCI supports correlative science through other funding mechanisms that have their own peer review process. A Reference laboratory could be voted scientifically meritorious, but deemed inappropriate for funding through the NCI Clinical Trials Cooperative Group Program.

2.7 Cancer Control and Prevention Activities

Information on cancer control and prevention activities in the application for the Group should be included in the Operations Center application only for the purpose of demonstrating the Group's ability to conduct a breadth of research activities in cancer related clinical trials. This information could be used as advisory to the Division of Cancer Prevention (DCP), which funds Groups to perform this type of research under a separate grant as research bases for the Community Clinical Oncology Programs (CCOPs). However, peer review of a Group's Cancer Control and Prevention activities, including its Cancer Control and Prevention Committee, is performed separately from the peer review performed under the Cooperative Agreement for the NCI Clinical Trials Cooperative Group Program administered by CTEP.

2.8 Study Monitoring

This section should describe the Group's procedures for study monitoring including assessment of case eligibility and evaluability and the procedures for timely medical review and assessment of patient data. Measures used to ensure timely submission of study data should be described, including the Group's guidelines for data timeliness and its procedures for monitoring compliance with these guidelines by institution and by study. Data should be provided for data timeliness by study in the Study Summary reports submitted by the Group with the application. Groups should describe how the Operations Center and the Statistics and Data Management Center interact to ensure the study monitoring procedures are implemented appropriately.

2.9 Quality Assurance and On-site Auditing

This section of the Operations Center application should describe the Group's progress in and plans for its programs of quality control and on-site auditing. Information on the scope of the auditing program should be provided similar in a table similar to that described in [On-Site Auditing Activities in Part 2.II.C. Section 5.3 on page 68](#) and the suggested format for this table provided in [Part 4 – Attachment #9](#).

2.10 Overall Accrual Information & Accrual Information by Gender and Ethnicity/Race

This section should provide accrual data in tabular format as described below. This information may be provided as Appendix material as explained in [Part 2.I.D., Section 1 – Operations Center and SDMC Applications on pages 56-57](#). Tables should be provided that show accrual data for patients entered on studies during the current funding or award period broken down by (1) study type (i.e., phase 1, phase 2, phase 3 studies), (2) year, (3) Group studies vs Group-Led Intergroup studies vs Group-endorsed/Intergroup studies vs non-Group, non-endorsed CTSU studies, and (4) Scientific Committees. A table that reflects overall accrual to ALL studies conducted by the Group should also be provided. ([See Attachment #4 – Suggested Format for Summary Accrual Tables](#)). Patient follow-up should be reported as well, where appropriate. In the case of entries onto Group-led Intergroup studies, the application of the Group leading the study should include data displayed for all participating Groups. Applications of Groups participating in an endorsed Intergroup study should indicate only the Group's own accrual. The application should also include a table providing the number of patients accrued during the funding period to Group trials using standard sex/gender and ethnic/racial categories as described in the Inclusion Enrollment Report in the PHS 398/SF424.

NOTE: For Participating Site U10 applications, where relevant, the Group Operations Center and SDMC will provide the site with accrual data in tabular format. ([See Attachment #8 - Summary of U10 Participating Site Activities – Report #1: Accrual & Follow-Up](#).) Groups should also provide a table showing accrual data by member Participating Sites for all studies (and by study, if possible) even if they do not have Participating Sites with U10s in order to show the extent of their membership and robustness of accrual across all sites participating as Group members. ([See Attachment #4 – Summary Accrual Tables by Member Participating Sites – Report #4](#)).

2.11 Progress Report in the Current Funding Period

Since an Annual Progress Report (i.e., Type 5 Application) is required for the year in which a competing continuation application (i.e., Type 2 Application) is submitted, information on Group activities in the last year of the current funding period should be integrated into the body of the competing continuation application, as appropriate and relevant, given the time-frame in which the Type 2 Application must be submitted.

3. Human Subjects Research (Human Subjects Protection)

Applicants should consult the PHS 398/SF424 regarding general instructions on what types of information should be included in the application regarding human subjects research, including the protection of human subjects. The specific areas listed below must be addressed in the Operations Center application.

3.1 Inclusion of Women and Minority

For information on NCI policy for inclusion of women and members of minority groups in NIH-supported biomedical and behavioral clinical research projects involving human subjects, [see Part 1.V.A., Section 1.5 \(e\) on pages 25-26](#).

3.2 Inclusion of Children

For information on NCI policy for inclusion of children in all human subjects research, conducted or supported by the NIH, [see Part 1.V.A., Section 1.5 \(f\) on page 26](#).

3.3 Data and Safety Monitoring Board and Data and Safety Monitoring Plan

The application must describe the Group policies and procedures regarding its Data and Safety Monitoring Board (DSMB) policy for phase 3 studies, including its membership rosters for the DSMB and procedures for avoiding conflicts of interest (e.g., financial disclosure procedures). The application must also describe the Group's Data and Safety Monitoring Plan for phase 1 and phase 2 studies.

4. Appendix Material

Information on the Appendix material that should be provided in the Operations Center application, along with information on the timing of submission of this material and the format in which it should be provided is described in [Part 2.I.D., Section 1 – Appendix Material Operations Center and SDMC Applications on pages 56-57](#).

Although a copy of the Policies and Procedures Manual for the Operations Center (including Constitution & By-laws, Conflict of Interest Policy, Group DSMB Policy, Data and Safety Monitoring plan for phase 1 and phase 2 studies, Data Sharing Policy, etc.) should be provided in the Appendix material, the application itself should specifically describe Group policies regarding Conflict of Interest issues, the training of Group investigators, nurses, and data managers/clinical research associates regarding human subjects protection, ethics in the conduct of clinical research, and procedures in the event of scientific misconduct. The application should document on-going 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 CTEP Program Specialist may request an additional copy of the Group's Constitution and By-laws and a copy of the Group's Policies and Procedures Manual.

5. Just-in-Time Information

The following material must be submitted just prior to the award of this Cooperative Agreement.

5.1 Other Support for Key Personnel

NCI program staff will contact all applicants to be funded to request "Other Support" for Key Personnel, including consortium/contract personnel. "Other Support" includes all financial resources, whether federal, non-federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, Cooperative Agreements, contracts, and/or institutional awards. Training awards, prizes, or gifts are not

included. Percent effort should be specified as well as any support that is pending. Information on other support assists the awarding NCI staff in the identification and resolution of potential overlap of support. Overlap, whether scientific, budgetary, or commitment of an individual's effort greater than 100 percent, is not permitted. The goals in identifying and eliminating such overlap are to ensure that: (1) sufficient and appropriate levels of effort are committed to the project, (2) there is no duplication of funding for scientific aims, specific budgetary items, or an individual's level of effort, and (3) only funds necessary to the conduct of the approved project are included in the award.

5.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Group should also submit a roster of Key Personnel and indicate the type of training program on human subjects protection completed by each person listed. The NIH policy on Human Subjects Protection is available at [\[Website Reference 44\]](#).

5.3 On-site Auditing Activities

The NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the CTSU require all Participating Sites to be audited at least once every 36 months. In order for the NCI to review the Group's compliance with this requirement, each Group should conduct a comprehensive review of its membership and provide **updated** auditing information for all Participating Sites and affiliates to the CTEP Program Specialist two months prior to the anticipated award. This information should be provided in tabular format as part of Just-In-Time Information and should include the following: (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 or projected month/year of the next proposed audit. ([See the Suggested Format for Reporting On-Site Auditing Activities in Part 4 – Attachment #9.](#))

Rationale for on-site auditing activities: The Clinical Trials Monitoring Branch (CTMB) of CTEP provides direct oversight of each Group's monitoring program. This oversight includes auditing as one component. The main objective of the audit program used by the Groups is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documents. In addition, the auditing program provides an opportunity for the audit team to share with the Participating Site staff information concerning data quality, data management, and other aspects of quality assurance.

5.4 Provision of Funds to Participating Sites for Accrual

If the Operations Center provides funds to Participating Sites for accruals (including U10 holders, affiliates, or other unfunded Participating Sites) via per-accrual reimbursement mechanisms (e.g., purchased service agreements or subcontracts), the following information must be provided as Just-In-Time information:

- a) For the current budget period: (1) a list of Participating Sites that received funds to date in that year; (2) the total costs provided to each site (direct and indirect) to date in that year; (3) the number of patients accrued for each site to date in that year; and (4) total costs (direct and indirect) provided to all sites in that year and for all years.
- b) For the immediately preceding budget period: (1) a list of Participating Sites that received funds to date in that year; (2) the total costs provided to each site (direct and indirect) to date in that year; (3) the total number of patients accrued in that year for each site, and (4) total costs (direct and indirect) provided to all sites in that year and for all years.
- c) For the upcoming budget period: (1) the estimated number of accruals and (2) the estimated total costs (direct and indirect) for each Participating Site.

The above information may be provided in a format of the Group's choosing.

5.5 Common Budget Outline

A “revised” or final Common Budget Outline, as well as a standard PHS 398/SF424 budget, based on the **actual** funding plan level awarded by the NCI must be submitted prior to the Cooperative Agreement Award as Just-In-Time Information. The format for this revised Common Budget Outline should be the same as that used for the draft Common Budget Outline. (See [Part 4 – Attachment #11](#).) The revised Common Budget Outline should sum to the total of all budget requests made by **all** components of the Group (i.e., the Operations Center, the Statistics and Data Management Center, Participating Site U10s, and other Group components funded by U10 applications such as a Group Chair’s Office).

D. Statistics and Data Management Center Application

Specific instructions are provided on the following pages for the Statistics and Data Management Center (SDMC) application. In general, except where noted below, all applications should conform to the instructions in the PHS 398/SF424.

1. Detailed Budget for Initial Budget Period

The following budget guidelines apply specifically to the SDMC budget. The categories listed below refer to those contained in the section of the PHS 398/SF424 entitled "Detailed Budget for Initial Budget Period." It should be noted that requests for computer systems or other major equipment must be very carefully documented with supporting justification and cost analysis.

- *Personnel:* Precise justification for the amount of effort requested for each position is essential.
- *Data management:* Time and effort involved in the central collection, computerization, and analysis of primary patient data, as well as in determining patient eligibility, providing for registration and randomization of patients, developing Case Report Forms for studies, etc.
- *Administrative efforts:* Time and effort involved in the overall management of the SDMC's resources, compliance with regulatory activities, quality assurance, and study monitoring procedures.
- *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 Operations Center budget. Clear and quantifiable justification is required. These costs include travel, per-diem, and consultant fees, if applicable and within institutional policy.
- *Equipment:* Justification for equipment costs 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. Only those equipment items that are required to conduct Group protocols should be included.
- *Supplies:* Research costs for appropriate supplies with quantitative justifications based on actual use should be provided.
- *Travel:* The importance of meetings to the achievements of any Group's research objectives is obvious, as is the necessity to maintain careful control over the size of this budget item. The budget for travel must be itemized and justified. It should include:
 - a) Trips by the SDMC's leadership and investigators on behalf of the Group to the NCI and other national organizations where the results of Group research must be presented or where Group research strategies are to be discussed.
 - b) Travel for SDMC members to committee meetings held separately from the semi-annual Group meetings.
 - c) Travel for persons on the SDMC staff who must attend the Group's semi-annual meetings.
- *Other expenses:* Research costs due to other expenses include those related to communication and information dissemination among Group members. Also included are costs of equipment rental and maintenance (copiers, telephones, computers), postage, copying and printing, etc., justified quantitatively on the basis of previous experience, where relevant.

PART 2.II.D: New and Competing Applications Format and Budget Requests
Statistics and Data Management Center

- *Consortium/contractual costs:* Groups are encourage to structure their organization in a manner that minimizes the burden of indirect costs on the overall Group budget. 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 SDMC.

2. Research Plan

In most Groups, the SDMC is funded via a separate Cooperative Agreement. This arrangement is encouraged by NCI. Occasionally, a single Operations Center Cooperative Agreement is awarded that funds both operations and statistics/data management. In any event, even if a single Cooperative Agreement cover both operations and statistics/data management, the roles and responsibilities discussed under SDMC Rights and Responsibilities should be addressed in a separate application or a separate section of the Operations Center application. (See Part 1.V.A., Section 2 on pages 31-34.)

If the SDMC is submitting a separate application for a Cooperative Agreement under the NCI Clinical Trials Cooperative Group Program, the general instructions described below and on the following pages should be followed for the SDMC Research Plan.

An abstract (limited in length to one page in **11-point Arial or Helvetica font size**) outlining SDMC accomplishments during the current award period (interval since the last competing application) and plans for the next award period should be provided. The separate SDMC application (or separate SDMC section within an Operations Center application) 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.

The following format is suggested for completing the sections in the PHS 398/SF424 Research Plan relating to "Specific Aims", "Background and Significance", "Preliminary Studies/Progress Reports", and "Research Design and Methods." All other components requested in the Research Plan section of the PHS 398/SF424, however, should also be included in the application. The term year must be defined (e.g., calendar, grant, fiscal, etc.) and all dates must be specified. Wherever appropriate, narrative should supplement, rather than duplicate or replace, standard manuals that should be supplied as part of the application.

According to the PHS 398/SF424 instructions, the Research Plan must be limited to 25 pages; specific page-number allowances are made for the SDMC applications, given the size and complexity of the NCI Clinical Trials Cooperative Group Program. **The page limit for the Research Plan of a SDMC application is extended to a total of 75 pages of text in 11-point Arial or Helvetica font size for the bulleted items listed below and on the next page, exclusive of tables, graphs, diagrams, and charts.** The text in these 75 pages should include the SDMC's response to the previous review of its application. If statistics and data management are supported by two separate applications, the Research Plan page limitation for each of these applications should be set so that their total represents 75 pages. The actual distribution of the 75 pages of text between the two applications can be varied (e.g., 45 pages for statistics and 30 pages for data management).

- *Roles and responsibilities:* The major objectives of the Group's statistical and central data management staff should be listed.
- *Organization and facilities:* The organization and facilities involved in accomplishing the complex tasks of central data management, quality control, study monitoring, and data analysis for the Group should be described.
- *Data management policies and practices:* The flow of data following submission from the individual investigator should be described.

PART 2.II.D: New and Competing Applications Format and Budget Requests
Statistics and Data Management Center

- *Quality control:* The procedures for quality control and accuracy verification should be described.
- *Study monitoring procedures:* The Group's standard methods for on-going study monitoring, including procedures for assessing case eligibility and evaluability, timely medical review and assessment of patient data, monitoring of data timeliness, and SDMC staff interactions with Study Chairs should be described. The application should also address the questions: 1) are the Group's guidelines for data timeliness appropriate?, and 2) are they implemented in a way that results in acceptable data timeliness, for the Group's clinical trials?
- *Study design and data analysis:* The Group's routine methodological practices should be described (e.g., methods of sample size calculations, choice of testing and estimation procedures, interim analysis policies, early stopping procedures for studies, etc.). Plans for the inclusion of women and minorities as research subjects in Group studies (also required in Operations Center application) should also be included.
- *Partnership in Group research:* The role and contributions of the Group's statisticians to Group research, including their involvement in designing studies, should be documented.
- *Independent research:* Research being conducted by the SDMC staff that use Group resources, including the Group databases, should be described.

3. Human Subjects Research (Human Subjects Protection)

Applicants should consult the PHS 398/SF424 regarding general instructions on what types of information should be included in the application regarding human subjects research, including the protection of human subjects. The specific areas listed below must be addressed in the SDMC application.

3.1 Inclusion of Women and Minority

For information on NCI policy for inclusion of women and members of minority groups in NIH-supported biomedical and behavioral clinical research projects involving human subjects, [see Part 1.V.A., Section 1.5 \(e\) on pages 25-26.](#)

3.2 Inclusion of Children

For information on NCI policy for inclusion of children in all human subjects research, conducted or supported by the NIH, [see Part 1.V.A., Section 1.5 \(f\) on page 26.](#)

4. Appendix Material

Information on the Appendix material that should be provided in the SDMC application, along with information on the timing of submission of this material and the format in which it must be provided is described in [Part 2.II.D., Section 1 – Appendix Material Operations Center and SDMC Applications on pages 56-57.](#) The Appendix material should include general information on the SDMC's Policies and Procedures and SDMC activities. In addition, information should be provided estimating data quality as well as the timeliness of data submission from Participating Sites. **A copy of the most recent Report of Studies should be submitted in the Appendix material for the Operations Center application, rather than in the Appendix material for SDMC application.**

5. Just-in-Time Information

Information on "Other Support" for Key Personnel in the SDMC may be submitted just prior to the award of the Cooperative Agreement. This information should be submitted with the "Other Support" material being submitted as Just-in-Time Information by the Operations Center. In addition, the SDMC should submit a list of Key Personnel along with the type of training course/program on human subjects protection completed by each person listed.

E. Participating Site U10 Applications & Other U10 Applications

1. Detailed Budget for the Initial Budget Period

The following budget guidelines apply specifically to Participating Site U10 and other U10 applications; the categories listed below refer to the items contained in the "Detailed Budget for Initial Budget Period" section of the PHS 398/SF424. The budget guidelines provided below are general and should be modified to address the unique aspects of the particular U10 application. In particular, for Participating Site U10s, the appropriate categories of costs should be clearly related to the per-accrual formula for that Participating Site to aid in review by Subcommittee H-Clinical Groups.

- *Personnel:* Precise justification for the percent effort requested for each position is essential, and should include the following:
 - a) Investigator efforts: Research costs include the time and effort involved in developing the research agenda and repertoire of protocols for the Group, investigator chairing of Group trials, and preparing the results of the Group's research for publication. This may also include the time and effort involved in direct interactions of investigators with patients due to the participation of the patient in the research, and the time and effort related to investigator intellectual activities required for development, implementation, and conduct of clinical trials.
 - b) Data management: Research costs include the time and effort involved in accurate data collection and submission at the Participating Site.
 - c) Other consultant costs: Consultant costs related to specific services such as pathology and radiology.
 - d) Laboratory investigations: These costs are not usually requested in a Participating Site U10 application budget. Most Groups request these funds in the Operations Center application; however, in certain circumstances, they can be included in a Participating Site or Other U10 application,
 - e) Administrative efforts: 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. If a Participating Site serves as a center for affiliates, it must have the resources to assure proper monitoring of these sites.
- *Consultant costs:* Consultant costs are not usually appropriate in a Participating Site or Other U10 application budget, so requests should be justified in detail. These costs include travel, per-diem, and consultant fees, if applicable and within institutional policy.
- *Supplies/Equipment/Other:* Research costs for appropriate supplies, with quantitative justifications based on actual use, should be provided. Significant equipment costs are unusual in a Participating Site or Other U10 application budget, and such costs must be carefully justified. The amount of funds requested for equipment should be based on the percent of usage. Research costs due to other expenses include those associated with communication with the Group office, 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).
- *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 Operations Center or SDMC award, rather than the Participating Site U10 award.
- *Patient care costs:* NCI will **not** support the costs associated with routine patient care. Only in the most unusual circumstances would a Group clinical trial require interventions beyond those considered appropriate for the care of cancer patients. In those circumstances, a Group may make a case for reimbursement of patient care costs associated with the particular research element.

PART 2.II.E: New and Competing Applications Format and Budget Requests
Participating Site U10 Applications & Other U10 Applications

The justification should be presented at the level of the Group Operations Center application with a specific request from each Participating Site U10 application based upon likely accrual to the specific study at that Site.

Rationale for patient care cost policy: This policy is based on the observation that Group treatment trials always involve treatment that is administered with therapeutic intent to patients who require medical care, and always involves therapy that is either considered standard medical treatment or can reasonably be expected to be superior to it. Therefore all costs associated with standard patient care are legitimately borne by third party carriers.

- *Consortium/Contractual costs:* Separate budget pages with detailed justification of all requested items should be submitted for each consortium agreement and applicable indirect costs should be included.
- *Consortium/Contract arrangements:* 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. 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.

Funding of accrual exceeding Participating Site U10 accrual targets: Once expected therapeutic accrual targets have been established and approved for each U10 Participating Site, the Group can make payments from its own capitation funds to its U10 Participating Site as long as the targets have been met and the Group informs the involved Participating Sites that these funds should be reported to each U10 Participating Site's Grants Office as additional Program Income. Two important components must also be considered:

- a) *Accruals to Group studies* – Accrual from U10 Participating Sites to Group studies (i.e., Group only, Group-led Intergroup, and Group-endorsed/Intergroup studies) will count toward meeting the annual accrual target assigned to the U10 Participating Site by the Group. Once the target is exceeded, additional such accruals are reimbursable from the Groups' capitation funds. **NOTE:** It is the responsibility of the Group to monitor these accrual figures for its U10 Participating Sites.
- b) *Accruals to non-Group studies* – Accrual from U10 Participating Sites to non-Group, non-endorsed studies in the CTSU will be reimbursed using capitation funds available from the CTSU. **NOTE:** No accrual target level needs to be met before accruals to non-Group, non-endorsed studies in the CTSU can be reimbursed. The CTSU will send these payments to the Group for transfer to its U10 Participating Site.

Rationale for and detailed information on the budget policy for Participating Site U10 applications & Other U10 applications: Participating Sites with U10 applications perform two primary activities - they contribute scientific expertise to the Group and they accrue patients to Group clinical trials. Participating Site U10 budgets should request those costs required for scientific/administrative contributions to Group activities and for attendance of a reasonable number of investigators at Group meetings. The budget of a typical U10 Participating Site application should be largely devoted to personnel, reflecting investigator support and the costs associated with patient accrual and treatment at the U10 Participating Site (and its affiliates, if appropriate).

Data management support and other costs related specifically to accrual at affiliate sites, including costs of follow-up of previously accrued patients, and data management costs associated with ancillary/correlative studies should not be requested in the Participating Site U10 application. Instead, these costs should be provided by the Operations Center through a per-accrual reimbursement mechanism. This is because, in most Groups with U10 Participating Sites, the Participating Site provides data management services for an affiliate of the Participating Site, and therefore, in most cases, the Operations Center should allocate an appropriate percentage of the affiliate per-accrual reimbursement to the main Participating Site to cover those services. Only data management costs associated accrual at the Participating Site should be included in the Participating Site U10 application

PART 2.II.E: New and Competing Applications Format and Budget Requests
Participating Site U10 Applications & Other U10 Applications

based on an annual target accrual level set by the Group. **NOTE:** These targets will be subject to negotiation following review by Sub-committee H and prior to award.

Participating Site per-accrual budget: For each U10 Participating Site, the Operations Center should calculate the allowable **per-accrual site expenses** in accordance with current Group policies/payment for per-capita funding and provide this figure to the U10 Participating Site. The Operations Center should provide to each U10 Participating Site the annual target accrual that forms the basis for determining an appropriate U10 budget. The target accrual for each U10 Participating Site should be based on the average **therapeutic** trial accrual for the U10 Participating Site (including only affiliates counted as part of the U10 which do not receive capitation payments directly from the Group) over the past three (3) years. The figures supporting the assigning of these baselines need to be submitted to the responsible NCI Program Director before the plan is implemented (and as noted above, these targets are subject to negotiation following review and prior to award). Also, each U10 Participating Site Annual Progress Report to the NCI should include the updated track record for the previous three (3) and the new assigned target for each U10 Participating Site. When the Group carries out non-competing (Type 5) redistributions, the new target accrual levels needs to be justified in relation to the re-calculated new award level.

Each U10 Participating Site should provide a budget that requests up to the per accrual formula times the number of target accrual for those categories included in the per-accrual formula (e.g., oncologist time, nurse clinician time, data management time, regulatory and pharmacy services, and protocol-related supplies postage/phone/photocopying). The per-accrual formula budgets should specifically not include travel, and the PI's salary, or Group or protocol leadership roles (these belong in the Operations Center application). All of the expense categories that relate to the allowable per-accrual U10 Participating Site expenses should be flagged in the budget as such, that is, they should be labeled "included in allowable per-accrual Participating Site expenses."

If a U10 Participating Site has a reason to want to allocate a larger proportion of the allowable per-accrual U10 Participating Site expenses to a specific category (e.g., CRAs), a clear justification for this should be provided to reviewers. However, the total for all of the categories should sum to the total of the per-accrual formula time the target level of patients to be accrued. U10 Participating Site should be aware that requests for CRAs generally never exceed a Group average of about 35 patients per CRA.

After the allocation of those expenses covered within the allowable per-accrual Participating Site formula, each U10 budget can add other justified and allowable fixed expenses such as PI time, travel, and affiliate management costs.

To assist reviewers, a table listing the three-year average accrual, personnel costs, supply costs, travel costs, other costs and total direct costs requested by the U10 Participating Site should also be included in the U10 Participating Site application.

U10 Participating Sites may receive additional payment for accrual once they have exceeded the annual target accrual number. ([See the sub-section on Funding of accrual exceeding Participating Site U10 accrual targets in this section on page 73.](#))

Each U10 Participating Site (or other U10 Group component) must develop its U10 application budget request based upon its unique requirements. The importance of meticulous justification for all budget items should be apparent. The Group Chair should provide each Participating Site and/or other Group component submitting a U10 application 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 the travel budgets. As indicated above, the Group Chair will have been provided guidance on the Group's aggregate budget by CTEP staff. Any specific fiscal or administrative questions should be addressed to the CTEP Program Specialist.

2. Research Plan

Rationale for U10 Participating Site applications & other U10 applications: If the Group chooses to seek U10 support for Participating Sites or for another component of the Group (e.g., Group Chair's office), each Participating Site or other U10 application should concentrate on the scientific and administrative contributions of the Group component (as well as accrual for Participating Site U10 applications). Specifically, applications should focus on the roles and responsibilities as defined in Part 1 of these guidelines. The clinical trials and research strategies of the Group are described in the Operations Center application and should not be repeated in the U10 Participating Site or other component's U10 application. In general, Participating Sites seeking U10 support need to supply information on patient accrual and follow-up, data quality, and Group publications in their applications along with information on the following: scientific leadership, administrative leadership, additional participation in Group activities, and sex/gender and ethnic/racial composition of patients entered on Group studies. This information should also be supplied in the U10 applications for other Group components, as appropriate (e.g., components such as a Group Chair's U10 application will stress administrative and research capabilities while a data management U10 will stress functions usually contained in the SDMC application).

Each U10 Participating Site application should include the information listed below in its research plan. (U10 applications for other Group components should modify this information, as appropriate, in their applications). The format provided below and on the following page is suggested for completing the sections in the PHS 398/SF424 Research Plan relating to "Specific Aims", "Background and Significance", "Preliminary Studies/Progress Reports", and "Research Design and Methods." All other components requested in the Research Plan section of the PHS 398/SF424, however, should also be included in the application. For suggested report formats for the forms/reports referenced in the sub-sections below, [see Attachment # 8 on the Suggested Format for Summary of Participating Site Activities in Part 4](#). The term year must be defined (e.g., calendar, grant, fiscal, etc.) and all dates must be specified.

The Research Plan for all Participating Site or other U10 applications should be limited to 25 pages of text in **11-point Arial or Helvetica font size**, exclusive of tables, graphs, diagrams, and charts. The text in these 25 pages should include the response of the U10 Participating Site or other U10 entity to the previous review of its application. If data management is being funded through a U10 application, see the page limitation information for the SDMC research plan in [Section 2 of Part 2.II.D. on pages 70-71](#).

2.1 Major Research Interests/Capabilities

The application should summarize, **in no more than 10 pages of narrative in 11-point Arial or Helvetica font size**, the institution's cancer research interest and capabilities, contributions to the Group during the current award period (interval since the last competing application) and plans for the next award period. This section should describe the following:

- a) The organization employed for institutional Group participation. Documentation should be provided of adequate participation by, and interactions among, all modalities and disciplines required for conduct of Group studies;
- b) Institutional pilot studies preparatory to Group-wide studies and other clinical research contributions to the Group, indicating how many institutional studies have progressed to Group-wide protocols;
- c) The process for prioritizing intra-institutional versus Group protocols; and
- d) Problems with past institutional participation together with concrete plans for addressing such problems during the next funding period.

2.2 Accrual

The Group Operations Center and SDMC are responsible for providing each Participating Site that is submitting a U10 application with a standard report of accrual activity by the Site (and its affiliates, if applicable). The Participating Site must include this table in its U10 application. ([See the Suggested Format for Summary Accrual Tables in Attachment #8, including Report #1: Accrual and Follow-Up.](#)) Patient follow-up should be delineated for those patients who have

been on study for more than one year, who are not known to be dead, and for whom at least annual follow-up is required. Unless otherwise specified, accrual refers to the current funding period, or in the case of new applications, to the period of time since first affiliation with the Group. Updated material should be requested by the U10 Participating from the Group Operations Center prior to the review of the application.

Specific assets of the U10 Participating Site regarding access to particular patient populations or unusual problems related to patient accrual should also be included in the application.

2.3 Scientific Leadership

In tabular format, the application should provide evidence of scientific leadership contributions of the institution's investigators to the Group, including chairmanship of protocols. (See the [Suggested Format for Summary of U10 Participating Site Activities in Attachment #8 – Report #2: Scientific and Administrative Leadership Activities.](#))

2.4 Administrative Leadership

In tabular format, the application should provide evidence of administrative leadership contributions of the institution's investigators to the Group. (See the [Suggested Format for Summary of U10 Participating Site Activities in Attachment #8 – Report #2: Scientific and Administrative Leadership Activities.](#))

2.5 Publications

In tabular format, the application should a listing of manuscripts and abstracts (organized by Group committee) relating to studies on which individuals from the U10 Participating Site were authors or co-authors. In addition, the application should provide a bibliography of Group publications (organized by Group committee) listing U10 Participating Site investigator authorship by status (primary, senior, and co-authors), with designation of publication status (published, in press, and in preparation). For all publications, the following dates should also be listed: (1) date the final analysis was scheduled, (2) date the SDMC completed the analysis, and (3) date the data were published. The event to which any date is assigned must be defined and used consistently. (See the [Suggested Format for Summary of U10 Participating Site Activities in Attachment #8 – Report #3: Publications.](#))

2.6 Data Quality and Timeliness

In tabular format, the application should provide information regarding U10 Participating Site timelines for data management and data submission to the Group, including Adverse Event Reporting. Data timelines, by study, for the U10 Participating Site should be provided in a tabular format using data provided by the Group's SDMC. Any unsatisfactory data audit reports should be addressed. Any probation/suspensions handed out due to poor data quality during the current funding period should be listed. (See the [Suggested Format for Summary of U10 Participating Site Activities in Attachment #8 – Report #4: Data Quality and Data Timeliness.](#))

2.7 Additional Contributions

In narrative format, the application should describe the important additional services or contributions made by the U10 Participating Site to the Group. Additional important services include activities such as laboratory studies and assays for particular protocols, service on site-visit teams for audits, etc. Also, the application should indicate any disciplinary actions imposed by the Group on the U10 Participating Site during the current funding period.

2.8 Gender and Ethnic/Racial Composition of Human Subjects

Using the PHS 398/SF424 "Inclusion Enrollment Report", the application should describe the sex/gender and ethnic/racial composition of patients entered on Group studies during the current funding period. The following three accrual tables should be provided in the application: one for the main U10 Participating Site accrual only, one for affiliate site accrual only, and a combined enrollment table for both the main U10 Participating Site and its affiliate sites. Each of these

tables should present the sex/gender and ethnic/racial composition of enrolled patients by year and summarized for the entire previous funding period. Below the tables, a description of proposed outreach programs for recruiting women and minorities as participants in Group studies should be provided.

3. Human Subjects Research (Human Subjects Protection)

Applicants should consult the PHS 398/SF424 regarding general instructions on what types of information should be included in the application regarding human subjects research, including the protection of human subjects. The specific areas listed below must be addressed in the SDMC application.

3.1 Inclusion of Women and Minority

For information on NCI policy for inclusion of women and members of minority groups in NIH-supported biomedical and behavioral clinical research projects involving human subjects, [see Part 1.V.A., Section 1.5 \(e\) on pages 25-26.](#)

3.2 Inclusion of Children

For information on NCI policy for inclusion of children in all human subjects research, conducted or supported by the NIH, [see Part 1.V.A., Section 1.5 \(f\) on page 26.](#)

4. Appendix Material

The Appendix material should contain general information on the policies and procedures specific to the U10 Participating Site or other U10 component of the Group. This information should not duplicate what is provided in the Appendix material for the Operations Center and SDMC applications as described in [Part 2.I.D., Section 1 – Appendix Material Operations Center and SDMC Applications on pages 56-57.](#) This section also provides information on the timing of the submission of Appendix material and the format in which it must be provided.

5. Just-in-Time Information

“Other Support” for Key Personnel at U10 Participating Sites or located at other U10 Group components may be submitted just prior to award of the Cooperative Agreement for the Participating Site and/or other Group component. This information should be submitted with the “Other Support” material being submitted as Just-in-Time Information by the Operations Center. In addition, U10 Participating Sites and other U10 Group components submitting U10 applications should submit a list of Key Personnel, indicating the type of training course/program on human subjects protection completed by each person listed.

F. Competing Supplemental Applications (Interim Review)

Supplemental applications include applications for components not completely funded at the time of initial Award (e.g., “Interim Review” application for a Scientific Committee that received only three years of funding when the entire Operations Center application received 6 years of funding). Competing supplemental applications should follow the basic format as for new, competing continuation applications, and should include the following sections: (1) Detailed budget for initial budget period; (2) Research plan; (3) Human Subjects Protection; (4) Appendix material, (5) Just-In-Time Information; and (6) “Awaiting Receipt of Application” (ARA) information for components with over \$500,000 direct costs in any given year. Budget data submitted with a competing supplemental application should be limited to those elements of the total Group budget that are specifically tied to the application for the specific Group component(s) included in the application. (See Attachment #10 in Part 4 for a suggested outline of the information to be provided in an “interim review” application.)

G. Applications for New Groups and New U10 Applications

An organization that chooses to apply to the NCI to establish a new Group must consult with CTEP staff at the earliest stage of the planning process and must obtain permission from the responsible NCI Program Director, in writing, to submit an application for a Cooperative Agreement for a new Group. In this way, CTEP staff has maximum opportunity to advise the Group on the practicality of a new Group application and help with the preparation of its application(s). While these Guidelines are written specifically for currently funded Groups, the principles set forth should be followed in planning any new (i.e., first-time) competing application.

A Group may also submit a new U10 application to support a Group component (e.g., U10 application for a Participating Site, Group Chair’s Office, etc.). **In general, however, new U10 applications are discouraged unless there are exceptional circumstances that support such an application.** Before a new U10 application can be submitted to CTEP, the Group must obtain permission from the responsible NCI Program Director for such a submission. CTEP staff members then have the maximum opportunity to advise the Group regarding preparation of the new U10 application, if the application is deemed appropriate and feasible and does not duplicate existing resources.

III. Review Criteria for New and Competing Applications

A. General Policies and Procedures

1. Role of Peer review

The role of peer review is to assess the extent to which the Group has and/or is likely to promote excellence in research that may lead to a reduction in the incidence, morbidity and mortality attributable to cancer. The focus of the review will be the ability of the Group to implement meritorious clinical trials and the overall quality of the Group's clinical and associated translational scientific efforts. It is considered important for each Group to optimize its organizational structure and the processes to be utilized.

Peer review is an essential component of the Group program and process. Peer review provides the NCI with a critical assessment of the Group's research capabilities and plans. It also provides important feedback regarding the functioning of the Cooperative Agreement relationship between CTEP and the Group. Peer reviewers identify meritorious activities of the Group, as well as deficiencies that require correction. Examples of deficiencies which peer review might identify may include the following:

- Avenues of research that may be inappropriate or unimportant;
- Ineffective leadership of a particular Committee;
- Operating procedures that may be flawed, limiting the Group's ability to conduct research;
- Insufficient productivity of a particular Committee; or poor accrual of patients from minority or other underrepresented populations.

2. General Review Procedures

Because of their interrelatedness, all applications from all components of a particular Group are reviewed simultaneously, except for competing supplement applications and Participating Site U10 applications submitted out-of-sequence with the Group's Operations Center application. Upon receipt, applications will be reviewed for completeness and for responsiveness by the NCI.

Incomplete and/or 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 Initial Review Group (IRG), NCI Subcommittee H-Clinical Groups, in accordance with the review criteria stated below. NCI Subcommittee H-Clinical Groups (also referred to as "Subcommittee H") is a chartered multi-disciplinary peer review subcommittee with representation from all oncology specialties, cancer control, statistics, patient advocacy, and Group administration. A current roster for Subcommittee H-Clinical Groups can be obtained from the NCI Division of Extramural Activities website at [[Website Reference 32](#)]. Ad hoc reviewers are recruited for Subcommittee H-Clinical Groups activities as needed.

The Scientific Review Administrator (SRA) of Subcommittee H-Clinical Groups is responsible for all aspects of the peer review process, and will contact the Group Chair regarding the date, duration and content of the review activities. The SRA will request information from the applicant to facilitate the review process. Such information may include complete patient accrual records for each institution, performance evaluations based on data quality, etc. Some of this information may be best supplied in the form of tables.

The Subcommittee H review of a Group's Statistics and Data Management Center (SDMC) may consist of either an **on-site visit** to the SDMC facilities, or a thorough presentation on the SDMC at the Group's Operations Center review. An on-site visit may be preferable if previous Type 2 or Type 5 application reviews have raised concerns regarding the appropriate operation of the SDMC and/or other information is provided that raises concerns. If a decision is made to conduct an on-site visit to the SDMC, the review team generally consists of Subcommittee H-Clinical Groups members plus ad hoc reviewers, as appropriate, for the proposed Group research plan. The decision regarding

whether the SDMC will be reviewed by an on-site visit is usually made when the Group representatives visit CTEP to discuss the submission of a Type 2 application (usually 9 months prior to the Type 2 application receipt date). The findings of any on-site review are provided to all Subcommittee H-Clinical Groups members during consideration of the application at the full Subcommittee H review meeting.

Standard NIH numerical priority scores will be applied to all submitted applications. For individual reviewers, the NIH numerical scoring scale ranges from 1.0 (best) to 5.0 (worst). Adjectives, such as Outstanding, Excellent, Very Good, Good, and Acceptable, which correspond to defined ranges of the numerical scoring scale, are also often referenced. After the scores of individual reviewers are averaged, the result is multiplied by 100 to derive the overall NIH numerical priority score for an application, which can range from 100 (best) to 500 (worst). The score of NRFC (Not Recommended for Further Consideration) is also available to the committee. Individual components or sections of applications, such as Scientific Committees, are often assigned a merit score by Subcommittee H in a similar way.

A Chair of a Cooperative Group Scientific Committee cannot serve as reviewer of the same category of Scientific Committee for another Cooperative Group (i.e., a Chair of the Breast Committee for Cooperative Group "A" cannot serve as a reviewer for the Breast Committee of Cooperative Group "B"). The applicant may request that potential reviewers, who have a conflict of interest with regard to the submitted application, be excluded from the review of that application. Such requests must be made to the SRA far in advance of the review meeting (at least 4 months prior to the date of the review meeting). The SRA will carefully consider all such requests, but as the overall responsibility of the SRA is to coordinate a thorough and fair review of the submitted application, the SRA is under no obligation to comply with specific requests for the exclusion of individual reviewers.

3. Review Order for Group Applications

The content of the Operations Center application is usually evaluated first (except at the discretion of the responsible NCI Program Director acting in conjunction with the SRA of Subcommittee H-Clinical Groups). Review of the Operations Center application includes evaluation of the Group's Administrative and Scientific Committees. The Subcommittee H review team then votes either to: (1) recommend the application for scoring, or (2) not recommend the application for further consideration. **If the Operations Center application is NOT recommended for further consideration, any separate applications from individual components of the Group (including Participating Site U10s) are not reviewed.**

If the Operations Center application is recommended for scoring, Subcommittee H proceeds to assign individual merit scores to each Scientific Committee. After merit scores are given to the Scientific Committees, each reviewer assigns a priority score to the Operations Center application as a whole. Administrative Committees are considered an integral part of Operations Center and thus are not assigned individual merit scores.

Group peer review occurs at a maximum of 6-year intervals and the review team makes a recommendation regarding the number of years of funding as part of the Operations Center review. Funding for Groups in the USA may be recommended for no more than 6 years. Funding for non-US Groups may be recommended for no more than 5 years.

After the scoring of an Operations Center application, Subcommittee H evaluates and scores the applications from additional individual components of the Group (e.g., SDMC, Participating Site U10s, etc.). The team also develops separate budgetary recommendations for each scored application and makes a recommendation regarding the number of years of funding for each of these applications.

B. Review Criteria for the Operations Center Application

1. Group Structure, By-Laws, Procedures, and Administrative Committees

Specific review criteria for the Operations Center Application are provided below and on the following pages by general review categories.

1.1 General Issues

Is the Group well administered by the Chair and the Operations Center staff? Does its organization and infrastructure allow it to meet its major objectives and goals? Does the Group's organizational structure conform to the policies and procedures described in its Constitution and By-laws? Does the Group have up-dated Standard Operating Procedures (SOPs) that cover the organizational structure and all administrative functions? Are these SOPs updated on a regular basis?

1.2 Group Chair

Subcommittee H reviewers will evaluate how well the Group's leadership, organization, and processes for development and evaluation of research ideas have facilitated scientific productivity, strengthened the Group's research capabilities, and enabled its investigators to take advantage of scientific opportunities. It is up to the Group Chair to provide evidence in support of the effectiveness of the Group. Are the scientific and administrative qualifications and experience of the Group Chair in relation to the Group's research activities and objectives appropriate? Is the Chair's time commitment to the Group's research activities appropriate? Is the Chair's authority over and effectiveness of the Chair's management of Group resources adequate? When appropriate, are there detailed plans in place for transfer of leadership to a new Group Chair?

1.3 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? Does the Group deal with deficiencies of members in a timely manner and in compliance with Group policies and procedures?

1.4 Key Personnel

Are the qualifications and effectiveness of each of the senior leaders in relation to his/her role in the activities of the Group effective and appropriate? Does the expertise of the senior leaders reflect the appropriate disciplines for modern, multi-disciplinary cancer research?

1.5 Staff

Are the roles of the Operations Center staff adequately defined to accomplish the goals of the Group? Is there an adequately defined staff to cover the multiple tasks that are the responsibility of the Operations Center?

1.6 Patient Accrual

Is the membership of the Group adequate for the volume of patient enrollment needed to mount multiple, concurrent, large-scale clinical trials?

1.7 Overall Group Priorities

Are the priorities of the Group appropriate? Are its resources well directed?

1.8 Major Research Objectives/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?

1.9 Group Cohesiveness

Does the Group function as a cohesive research team? Do all committees have appropriate resources?

1.10 Interdisciplinary Coordination

Is there adequate interdisciplinary participation in protocol development and design? Does the expertise of protocol investigators reflect the modalities used in study therapies?

1.11 Mentoring Junior Investigators

Does the Group have an effective plan for mentoring junior investigators in Group research? Are junior investigators adequately represented across the Group's activities?

1.12 Oversight Committees (Board of Directors, Executive Committee)

What are the responsibilities of the Group's Oversight Committees? How is information communicated to these bodies and what type of information is provided to them? Do these Oversight Committees meet often enough to be truly knowledgeable about the Group? Can they overturn decisions made by the Scientific Committees, including Disease Committees, or the Group Chair? What mechanisms are in place for these Oversight Committees to prioritize Group science? Are the performances of key leaders within the Group reviewed on a periodic basis by these Oversight Committees?

1.13 Administrative Committees

Are the organizational structures and specific responsibilities of the administrative committees described in a clear manner? Do the committees appear to function according to the descriptions provided? Are the research experience and qualifications of the committee chair and other committee members appropriate for the committee goals? Is the committee well administered by the committee chair? Does its organization and infrastructure allow it to meet its major objectives and goals? Do the committees have distinct roles and responsibilities that aid Group in the achievement of its research goals and objectives?

2. Study/Protocol Development and Study Monitoring

2.1 Study/Protocol Development

Does the Group have a well-defined process for protocol development, including SOPs? Does the Group have processes for communicating decisions made regarding protocol development to committee chairs and Group members?

2.2 Research Methodology

How well-designed are the Group's planned clinical trials? Will their design allow clinically important conclusions to be drawn?

2.3 Efficiency of Protocol Development and Study Monitoring

Does the process of study development proceed in an efficient and timely manner? Are important studies rapidly developed and implemented? Are the Group's procedures for study monitoring appropriate for assessing case eligibility and for providing timely medical review and assessment of patient data? Are the Group's guidelines for data timeliness appropriate? Are these guidelines implemented in a way that results in acceptable data timeliness for the Group's clinical trials?

2.4 Timeliness of Study Completion

Is the Group able to carry out its planned studies in a reasonable period of time? Is Intergroup collaboration used when necessary to satisfy the requirement for timely completion? **NOTE:** The NCI is specifically directing Subcommittee H reviewers to consider Group endorsement of and

participation in Intergroup studies being led by another Group to be equivalent in scientific merit to Group-led studies.

3. Quality Control of Group Clinical Trials

3.1 Participating Site Performance Evaluations

Are the Group's mechanisms of quality control adequate and functioning in a manner that ensures accurate and reliable data? Does the Group provide Participating Site performance evaluations? Are these evaluations provided for all Participating Sites with patient accrual (as reported in the application) during the current funding period? If performance is not adequate for a Participating Site, does the Group have policies and procedures in place to put the site on probation? Are these policies and procedures adequate?

3.2 Educational Functions

Does the Group have educational functions, including training for Clinical Research Associates (CRAs)?

3.3 Central Review of Major Elements of Clinical Trials

Does the Group have committees that provide central review of the major elements in its clinical trials, including pathology, radiation therapy, chemotherapy, surgery, diagnostic imaging, etc., where appropriate?

4. On-Site Auditing Program

Does the Group's auditing program conform to the NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases and the Cancer Trials Support Unit (CTSUS)? How well do Participating Sites meet these guidelines? What is the percentage breakdown of each Participating Site's audit ratings ("Acceptable", "Acceptable with follow-up", and "Unacceptable") during the current funding period? What is the percentage breakdown of audit ratings ("Acceptable", "Acceptable with follow-up", and "Unacceptable") across all audits performed for Group Participating Sites during the current funding period? Is the Group completing all audits and re-audits on a timely basis? What are the Group's policies and procedures regarding suspension and probation of Participating Sites and how do these policies and procedures relate to unacceptable audits?

5. Compliance with Federal Regulations

5.1 OHRP and IRB Regulations

Does the Group ensure that Participating Sites have adequate Office of Human Research Protection (OHRP) Assurances and Institutional Review Board (IRB) approval for its protocols via the CTSUS's Regulatory Support System (RSS)? Does the Group have OHRP and IRB review of its Operations Center?

5.2 Adequacy of Plans to Include Minorities and Both Genders

Does the Group have plans for the recruitment and retention of patients from minority and ethnic sub-groups and both genders? How well have these plans been implemented? Does the Group have appropriate scientific research goals related to these patient population sub-groups? Do Group's protocols include plans for appropriate analyses for these patient sub-groups?

5.3 Data and Safety Monitoring Boards

What are Group's policies & procedures regarding Data and Safety Monitoring Boards (DSMBs)? Are its policies & procedures in compliance with NCI/CTEP, NIH, and federal regulations?

5.4 Data Sharing

Does the Group have a data sharing policy that is robust (i.e., applicable to most clinical trials/situations) and in compliance with NCI and NIH policies?

5.5 NCI Clinical Trials Policy

Does the Group adhere to the NCI Clinical Trials Policy for all clinical studies and trials?

6. Adverse Event Reporting

Does the Group have a system for ensuring that there is timely reporting of serious and/or unexpected adverse events, including the use of the NCI/CTEP's system for the expedited reporting of adverse events (i.e., AdEERS)? Does it appear that the Group's internal systems work well and that the Group is using the NCI/CTEP AdEERS appropriately?

7. Biological Specimen Collection and Banking

Does the Group have policies and procedures with SOPs related to specimen collection and tracking? Does it appear that these systems work well? Has the Group provided information on the numbers, types, and quality of the specimens collected during the current funding period? Has the Group provided a breakdown of the percentage of biological specimens collected by study?

8. Correlative Science, Reference Laboratory Support, and Adjunct Studies

8.1 Correlative Science Studies/Reference Laboratories

Does the Group have appropriate correlative science studies associated with its Scientific Committee treatment protocols? Is there a well-defined plan to integrate correlative studies into the overall research effort? Does the Group identify and use appropriate Reference Laboratories to perform the correlative science studies? Does the Group have policies related to how correlative studies (including the use of Reference Laboratories) are coordinated and prioritized? While not required, the capacity and expertise within the Group to develop innovative research ideas based on laboratory models and pilot studies in limited institution trials with an eye to their potential use as experimental arms in phase 3 trials is considered a strength. Certain of these types of studies associated with a Scientific Committee treatment trial, may be eligible for inclusion in a Group application for financial support in certain circumstances, particularly when the laboratory/clinical efforts are integral/critical to the clinical treatment trials proposed. Has the Group collaborated with other NCI-funded programs and investigators conducting clinical research (e.g., Cancer Centers, SPOREs, R01 and P01 investigators) in the development and conduct of correlative science studies? This type of collaboration should be considered positively at the time of peer review.

8.2 Adjunct Studies

While not required, Group involvement in diagnostic, cancer control, and quality of life, and prevention research, especially as it relates to or follows logically from the Group's prime therapeutic mission, is considered a strength. If these studies are included in the Group's research portfolio, are they appropriate to the Group's overall research goals and objectives and are they conducted well? Certain of these studies may be eligible for inclusion in a Group application for financial support, particularly when the efforts are integral to the clinical treatment trials being proposed.

9. Publications

Is the Group's research published in a timely manner and in quality, peer reviewed journals? Does the Group have policies and procedures with respect to time-lines for the development of abstracts and manuscripts as well as the systems to track adherence to these time-lines?

10. Group Meetings and Group Communications

Does the Group have regular (usually at least semi-annual) meetings to review Group progress and establish Group priorities and future activities? Do the agenda materials and Report of Studies provided at the meeting contain appropriate and timely information/data? Are the Group meetings well attended? Is there broad representation at the meetings from the oncologic disciplines, and from investigators, nurses, CRAs, patient advocates, etc. Are there defined plans and roles for patient advocates in the Group? Has attendance of patient advocates at Group meetings been included in the

budget? Does the Group have adequate systems in place to communicate effectively with its members, especially about time-sensitive information related to patient safety?

11. Cross-Group CTSU Accrual & Collaboration with Other NCI-funded Programs/Investigators

Most Group members will participate in Group studies, which include Group only, Group-led Intergroup studies, or Group endorsed/Intergroup studies; however, Group members may also elect to enroll patients in non-Group, non-endorsed studies offered in the CTSU for a variety of reasons. These reasons include a gap in the trials offered by the member's Group at a particular point in time or in the Group's disease portfolio, relevance of a particular trial to the patients whom the physician member treats, and eligibility criteria that may allow a patient to be treated on one trial but not another. A Group, therefore, should be given credit for accrual to trials by its members even if the trial is not being led or endorsed by the Group. Review criteria should include consideration of whether the record of patient accrual to non-Group, non-endorsed CTSU studies is significant. While failure to accrue to non-Group, non-endorsed studies should not necessarily reflect poorly on a Group, NCI believes Subcommittee H reviewers should consider such participation positively since it is a reflection of the Group's membership actively seeking trials for patients. For the review criteria for endorsed, Intergroup trials, [see Section 13.3 on pages 86-87 in this section \(Intergroup Trial Accrual & Collaboration with Other NCI-funded Programs/Investigators\)](#).

In addition to cross-Group accrual in phase 3 studies and selected phase 2 studies via the CTSU, collaborative activities of the Groups with other NCI-funded programs and investigators conducting clinical studies and trials (e.g., Cancer Centers, SPOREs, R01 and P01 investigators, etc.) should be considered positively at the time of peer review. The Group should describe the degree of cooperation and interaction with other NCI-funded programs by detailing these activities as they relate to its clinical research agenda.

12. Conflict of Interest

Does the Group have an adequate Conflict of Interest Policy? Is this policy consistent with NCI and NIH policies?

13. Scientific Committees

13.1 Organizational Structure

Are the organizational structures and specific responsibilities of the committees described in a clear manner in the Constitution and By-laws of the Group? Do the committees appear to function according to the descriptions provided? Are the research experience and qualifications of the committee chair and other committee members appropriate for the committee goals? Is the committee well administered by the committee chair? Does its organization and infrastructure allow it to meet its major objectives and goals? Do the committees have distinct roles and responsibilities that aid Group in the achievement of its research goals and objectives?

13.2 Major Research Objectives

In general, Subcommittee H reviewers should determine the accomplishments of the Group's Scientific Committees during the current funding period (interval since the last competing application, both for pilot/early phase studies and phase 3 studies) and evaluate how the Scientific Committee adds value to the Group's overall research agenda. General NIH review criteria related to the significance of the Committee's scientific research/clinical trials, the conceptual / clinical approach taken, the innovative aspects of the research/clinical trials, the ability of the Committee's investigators to carry out the Committee's research/clinical trials, the scientific environment, and compliance with federal regulations related to the protection of human subjects from research risk in the Committee's trials should all be evaluated. In particular, how meritorious are the research plans and strategies for each of the major areas of study of the Scientific Committees for the next award period? Are they appropriate in the context of national priorities? Do the Group and the leadership of its Scientific Committees encourage input from new/young investigators and provide mentoring and research opportunities for them? Do the

Scientific Committees' operating policies address issues related to change in leadership, such that representation and leadership opportunities for new/young investigators?

The NCI also recognizes that the research agenda of a Scientific Committee will be based on a mix of pilot, phase 1, phase 2, and phase 3 studies, with appropriate correlative research. Given the collaborative requirements and national priorities of the NCI Clinical Trials Cooperative Group Program, and the NCI approval process, it is unlikely that each Group will be able to lead a phase 3 trial in every cancer, or in every clinical stage within a cancer, at all times. Groups are encouraged, therefore, to contribute meaningful phase 2 or pilot studies in order to replenish the pipeline for new phase 3 concepts.

The overall output from a Scientific Committee should be based on a combination of Group-led pilot and early-phase studies and strong support of and active, meaningful participation in Intergroup phase 3 studies, whether or not the Group leads the phase 3 study. While the primary basis for review of this Cooperative Agreement should be based on the overall value of a Group's scientific agenda, **the emphasis should be placed on active, meaningful participation in phase 3 studies**, both from a scientific and accrual standpoint. Pilot studies in the Group may provide the basis from which new phase 3 trials may evolve and thus provide evidence of the direction and strategies being evolved by the committee. Group collaborations with other NCI-funded programs and investigators (e.g., Cancer Centers, Specialized Programs of Research Excellence [SPOREs], R01 and P01 investigators, etc.) on the development of phase 3 studies based on pilot studies conducted by these other NCI-funded programs and investigators should be considered positively at the time of peer review. Contribution to phase 3 trials in the national Program, in the form of scientific leadership and/or accrual, should be considered of paramount importance for a Group's Scientific Committee, no matter which Group leads a phase 3 trial.

The NCI/CTEP may provide additional review criteria in the future to address Group Scientific Committees in disease sites that have oversight by NCI Scientific Steering Committees, if necessary. The current review criteria provide scientific credit for active participation in and endorsement of studies led by other Cooperative Groups and for working with other NCI-funded programs and investigators (e.g., Cancer Centers, SPOREs, R01 and P01 investigators, etc.) to develop appropriate phase 3 trials.

In summary, a Cooperative Group's research objectives should be characterized, optimally, by a mix of creative, individual clinical initiatives focused on providing definitive scientific evidence and strong commitment to active, meaningful participation in NCI phase 3 treatment trials.

13.3 Intergroup Trial Accrual & Collaboration with Other NCI-funded Programs/Investigators

Most Intergroup trials are large phase 3 trials open to accrual from any Group via the CTSU. On rare occasions, a phase 3 trial will not be open in the CTSU, usually because the trial's total accrual target is not large or participation is limited due to special requirements. Since Intergroup trials require enrollment from multiple Groups and participation from multiple co-Principal Investigators in order to be successful, the NCI is specifically directing Subcommittee H reviewers to consider Group endorsement of, coupled with its active, meaningful participation in, Intergroup studies being led by another Group to be equivalent in merit to Group-led studies. This is an especially important consideration in disease areas where accrual to Group studies has been poor or the Group has not led many trials. Subcommittee H reviewers should determine whether or not the Group contributed significant accrual to Intergroup studies. While it is true that only the Lead Group will perform administrative and data management of an Intergroup study, co-PIs on the trials should contribute intellectual leadership, assist in study development, help promote and monitor the trial, and have an important role in study authorship. **Based on these considerations, endorsement of Intergroup studies, coupled with active, meaningful participation in these studies, should be considered by Subcommittee H reviewers to be as important as the scientific contribution the Group provides through development and accrual to its own studies.** In addition, Group collaborations with other NCI-

funded programs and investigators conducting clinical studies and trials (e.g., Cancer Centers, SPORes, R01 and P01 investigators, etc.) should be considered positively at the time of peer review.

13.4 Protocol Development

Does the Group have clear guidelines related to protocol development and are the Scientific Committees' roles and responsibilities related to this development clear? Does protocol development by the Scientific Committees proceed in an efficient and timely manner? Have the Scientific Committees received appropriate support for protocol development? Are important studies rapidly developed and implemented? How well designed are the Scientific Committees' planned clinical trials? Will their design allow clinically important conclusions to be drawn? Are patients accrued to Scientific Committees trials in a timely manner? Are the Scientific Committees able to carry out their planned studies in a reasonable period of time? Is there adequate interdisciplinary participation in protocol development and design? Is Intergroup collaboration used when necessary to satisfy the requirement for timely completion? Does expertise of study investigators reflect the disciplines used in the trial? Do Administrative (or Scientific) Committees provide appropriate discipline expertise in the development of protocols?

13.5 Study Monitoring and Quality Control

Are the roles and responsibilities of the Study Committees for protocols clearly defined? Do the Study Committees for Scientific Committee protocols satisfactorily meet their responsibilities with respect to study monitoring? Are the Study Committees' mechanisms of quality control adequate and do they function in a manner that ensures accurate data? Is modality-specific expertise provided by modality-oriented Administrative (or Scientific) Committees in the quality control of data collected where applicable?

13.6 Publications

Is the Scientific Committees' research published in a timely manner and in quality peer reviewed journals?

14. Cancer Control and Prevention Committee

Information on cancer control and prevention activities in the application for the Group should be included **only** for purposes of demonstrating the Group's ability to conduct a breadth of research activities in cancer related clinical trials. The Division of Cancer Prevention (DCP) funds Groups to perform this type of research under a separate grant mechanism as Research Bases for the Community Clinical Oncology Programs (CCOPs). Peer review of the Cancer Control and Prevention activities of a Group (or its Cancer Control and Prevention Committee), however, is performed separately from the peer review performed under the Cooperative Agreement for the NCI Clinical Trials Cooperative Group Program administered by CTEP. Subcommittee H reviewers do not perform scientific review of a Group's cancer control and prevention activities or its Cancer Control and Prevention Committee; information on these activities is presented in the Group application simply to demonstrate the scope of Group activities.

15. Budget

Has sufficient capitation funding been included for site participation in Group-led and Group-endorsed trials? Have costs for travel, office supplies, equipment and data management been adequately justified? Have costs for the on-site audit plan been accurately detailed (if this activity is performed by the Operations Center)? Is there sufficient funding allotted to carry-out the proposed study/protocol development and study monitoring, handle Group communications, and coordinate Group activities, especially with respect to the Scientific and Administrative Committees as well as Intergroup activities? Has sufficient funding for the participation of Group representatives on NCI disease-specific Scientific Steering Committees been included?

16. Cancer Trials Support Unit (CTSU) Integration

The CTSU is viewed by NCI as an integral part of the Cooperative Group system. The CTSU was instituted to provide a mechanism to foster intergroup participation by assuring consistency and uniform procedures for these collaborations and to reduce the duplicative regulatory burdens on investigators and their staffs that occur with cross-Group participation and/or membership in more than one Group. Thus, the NCI deems it essential that the Groups demonstrate that they are taking optimal advantage of the CTSU's mechanism for promoting accrual, streamlining regulatory information, and cost sharing in the conduct of Group trials.

16.1 Regulatory Support System

How well has the Group integrated its collection of regulatory information for clinical trial participation with the Regulatory Support System (RSS) of the CTSU? Has duplicative collection of regulatory information from Group members been eliminated or significantly reduced? Is the Group's membership roster well integrated into RSS and kept up-to-date? Has the Group complied with RSS requirements for electronic submission of regulatory documents? Does the Group maintain up-to-date information on its protocols, protocol specific requirements, and processing instructions for trials open in the CTSU?

16.2 Communication

What processes does the Group have in place to ensure that appropriate and timely information is transmitted to the CTSU regarding the conduct of any Group trial that is open in the CTSU (e.g., study amendments, study closure, and other related information on the trial as well as Group-specific information that is important for participating investigators or local IRBs to know such as Data and Safety Monitoring Board Committee Reports)? How well do these procedures work? If the Group has encountered problems, how have they resolved the specific issues?

16.3 Data Management and Information Technology Initiatives

How well does the Group integrate its data management operations with the CTSU when a Group trial is open in the CTSU? How well do these processes work? Has the Group integrated its operations with other Information Technology Initiatives of the CTSU? If yes, the Group should provide details on this experience. If no, the Group should explain why this has not happened.

16.4 Supportive Functions

Does the Group provide accurate and timely information to the CTSU from the Group's specimen tracking system as needed for studies open in the CTSU? Does the Group provide this type of information to the CTSU on all ancillary studies associated with Group studies open in the CTSU? What procedures does the Group have in place to ensure the CTSU is aware of additional financial support for non-Group sites participating in Group studies open in the CTSU? How does the Group work with the CTSU to ensure this information is communicated to the non-Group sites and appropriate payments are made?

16.5 Promotion, Education, and Training

How well does the Group work with the CTSU to provide educational and other promotional materials on Group trials open in the CTSU? What procedures and processes does the Group have in place to inform its membership of CTSU policies and procedures? Does the Group provide training at its Group meeting on CTSU procedures? What processes does the Group have in place to promote participation in trials open in the CTSU?

16.6 Auditing

How well does the Group interact with the CTSU to conduct audits of CTSU-enrolled sites (i.e., audits of Group members participating on non-Group led trials via the CTSU)? Are required audits conducted in a timely manner and per CTMB guidelines?

C. Review Criteria for the Statistics and Data Management Center (SDMC) Application

1. SDMC Organization and Facilities

Does the SDMC have a well-defined organizational structure and clearly defined roles and responsibilities for its staff? Do the research experience and qualifications of the head of the SDMC (or Principal Investigator of the SDMC application) demonstrate understanding of design and analysis of multi-institutional clinical trials and relevant laboratory studies? Does the SMDC have clear Standard Operating Procedures (SOPs) that are regularly updated for its major functions, including data management, study monitoring, and data analyses for Group trials? Do the SOPs include training for Group investigators, CRAs, and Study Chairs? Does the SDMC abide by the Group's Constitution and By-laws? Are the SDMC offices, computer hardware, and overall facilities 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?

2. Study/Protocol Development

2.1 Study Design and Analysis

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? Are analytical techniques, procedures, and policies adequate, appropriate, and consistent with accepted standards? Is there evidence that past publications of the Group demonstrate thorough and state-of-the-art methodology, awareness of problems of multiple analyses, and sufficient independence and lack of bias of statistical collaborators? Are the Case Report Forms appropriately designed?

2.2 Collaboration with the Operations Center

Is there adequate collaboration between the statistical and data management functional components of the Group in the development and conduct of the Group's research?

3. Data Management

Are data management procedures adequate, appropriate, and consistent with accepted standards? Are central registration and randomization provided for all study subjects? Are there central storage, security, analysis, and retrieval processes for study results? Are these processes secure and reliable? Is patient confidentiality protected? 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? Are data management policies and practices in compliance with the Group's policy on data sharing? Can true copies of data files be provided in a timely manner?

4. Study Monitoring

Are data monitoring procedures adequate, appropriate, and consistent with accepted standards? Is there timely and precise tracking of patient accrual, including eligible and ineligible patients, and adherence to protocol-defined accrual goals? Does the SDMC have adequate measures in place to ensure timely submission of study data? Are performance measures provided by the Group for monitoring compliance with Group guidelines for data timeliness by Participating Site and study? Are summary reports of performance review/evaluation of Participating Sites provided in the progress report for the current funding period? Are adequate measures in place to ensure timely medical review of patient data? Are summary reports detailing the adequacy of medical review provided by study? Does the Group have a rapid reporting system for communication adverse events to Participating Sites and Group investigators, as well as to CTEP, the NCI Central IRB, and FDA? Does this system function well? Does the SDMC provide interim evaluations in its protocols for review of outcome

measures and patient safety information? Does the SDMC provide study monitoring reports describing patient accrual, demographics, adverse events, etc. on a routine basis to Study Chairs, Group members, and CTEP, as appropriate? Does the SDMC have adequate policies and procedures in place for closure of studies, unblinding of treatment, etc.

5. Publications

Does the SDMC conduct final study analyses at the appropriate times, as specified in the protocols, and to allow timely publication of study results?

6. Independent Research

While independent research is not required (or funded by this Cooperative Agreement), involvement in research related to the design, conduct, and analysis of cancer clinical trials should be considered a strength. What research, if any, is being conducted by the SDMC using Group resources, including the Group databases?

7. Support for On-Site Auditing Program, Participating Site Evaluation, Data Submission

Does the SDMC provide adequate support for the on-site auditing program in compliance with the NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases and the Cancer Trials Support Unit (CTSU)? Does the SDMC provide data to allow timely reporting and evaluation of Participating Site performance on a regular basis? Is this information communicated to the Participating Sites effectively? Does the SDMC report data from clinical trials to CTEP using the Clinical Data Update System (CDUS) in a timely manner on a regular basis?

8. Compliance with Federal Regulations

Is the SDMC in compliance with federal regulations related to confidentiality of patient data, including Health Insurance Portability and Accountability Act (HIPAA) regulations? Does the SDMC have adequate safeguard in place to ensure the technical integrity and confidentiality of patient data in compliance with federal regulations?

9. Adverse Event Reporting

Does the SDMC assist the Group in ensuring that all serious and/or unexpected adverse events are reported in a timely manner to CTEP, the FDA, other entities with oversight responsibilities (e.g., IRBs) and investigators, as appropriate?

10. CTSU Interactions & Collaboration with Other NCI-funded Programs/Investigators

Does the SDMC interact well with the CTSU to ensure that all data collected for Group studies are transmitted to the Group appropriately and in a timely fashion? Does the SDMC interact well with other NCI-funded programs and investigators (e.g., Cancer Centers, SPOREs, R01 and P01 investigators, etc.) when the Group is collaborating with these programs and investigators in the conduct of clinical research?

11. Group Meetings

Does the SDMC provide a Report of Studies at the Group's biannual meetings? Does the Report include appropriate and timely data and study analyses?

12. Budget

Have costs for travel, office supplies, equipment and data management been adequately justified? Have costs for the on-site audit plan been accurately detailed (if the SDMC handles this activity)? Is there sufficient funding allotted for the SDMC to carry-out the multiple quality control tasks required, including adverse event reporting, study monitoring, biological specimen collection, study/protocol development for Group and Intergroup studies, and preparation of publications?

D. Review Criteria for Participating Site U10 Applications and Other U10 Applications

The review of Participating Site U10 applications focuses on the scientific and administrative contributions of the Participating Site to the Group. Patient accrual and data quality are also given significant weight in the evaluation of a Participating Site's U10 application. The reviews for other U10 applications submitted for other Group components are tailored to focus on the particular contributions of the components, as appropriate, and the review criteria described below should be interpreted with respect to the particular needs of the other U10 application.

1. Participation in Group Activities and Contribution to Group Science

Do the research experience and qualifications of the Principal Investigator of the U10 application demonstrate understanding of the conduct of multi-institutional clinical trials in cancer treatment and relevant laboratory studies? What are the contributions of the investigators at the U10 Participating Site to the Group's research strategies and plans? Do the investigators chair Scientific Committees and studies (or Administrative Committees)? Do the institution's investigators contribute to publication of Group studies? Although correlative science research is not required, the ability to conduct pilot trials, which can then serve to foster the Group's research goals, should be considered a strength. Do the institution's investigators participate in other Group activities, including Group meetings? Does the Participating Site provide adequate interdisciplinary cooperation and coordination, as appropriate given the Group's research agenda? Are all appropriate oncologic disciplines represented among Participating Site representatives at Group meetings and other Group activities? Does the Participating Site have an effective plan to mentor junior faculty in the Group's research activities?

2. Patient Accrual and Intergroup Participation

Is the record of patient accrual appropriate in the context of Group standards? Are projections for the future reasonable and adequate? Has the Participating Site been effective in recruiting under-represented populations such as minorities to clinical trials? Is the record of patient accrual to CTSU and Intergroup studies from the U10 Participating Site significant? The NCI is specifically directing Subcommittee H reviewers to consider Group endorsement of, coupled with active, meaningful participation in, Intergroup studies being led by another Group to be equivalent in merit to Group-led studies.

3. Data Collection, Data Quality & Timeliness, and Data Management

Are patient data complete, accurate, and submitted in a timely fashion by the U10 Participating Site? What is the site's record with respect to the quality of data submitted during the current funding period? Are the relationships between affiliates and the primary Participating Site carefully explained, including the responsibilities of the Principal Investigator at the U10 Participating Site and with respect to the affiliates? Does the site provide data management oversight of affiliate sites? If so, are the site's data management practices and procedures adequate and appropriate? Does the site provide adequate oversight of affiliates participation in protocols and data quality? Is there adequate data management to meet the data submission needs required by clinical trials? Is there high-quality nursing support to meet the patient care needs required for clinical trials? Does the U10 Participating Site comply with Group procedures related to adverse event reporting and submission of patient biospecimens, as well as general Group policies such as the Conflict of Interest policy?

4. Human Subjects Protection

Are the U10 Participating Site and its affiliates in compliance with federal regulations regarding the protection of human subjects in clinical trials, including review of protocols by the Institutional Review Boards at the sites and ensuring that sites have an approved OHRP Assurance on file.

5. Budget

Have costs for personnel, travel, office supplies, equipment, and data management been adequately justified? Have costs for Intergroup activities and participation in other Group activities been accurately detailed? Is there sufficient funding allotted to carry out responsibilities related to chairing Scientific Committees, study development, and other scientific leadership activities?

E. Review Criteria for Quality Assurance and Service Centers

The review of applications from Quality Assurance and Service Centers which provide quality assessment and support services for Groups conducting treatment trials focuses on the content and quality of the assessments provided, the timeliness of the information, and the overall value of the services provided. Review of these entities should be tailored to the mission of the organization, but should address the main review criteria expected of all NIH applications for research-related grant applications. General and specific review criteria for the Quality Assurance Review Center (QARC) and the Radiological Physics Center (RPC) are provided below.

1. General Review Criteria for Quality Assurance and Service Centers

- 1.1 **Significance:** Does the quality assurance program and services provided address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, and services that drive clinical oncology practice? How do the assessments and services provided differ from what Groups could provide on their own?
- 1.2 **Approach:** Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the quality assessment being provided? Does the Quality Assessment and Service Center acknowledge potential problem areas and consider alternative tactics?
- 1.3 **Innovation:** Does the Quality Assessment and Service Center provide state-of-the art services as well as innovative approaches? For example: Does the Quality Assessment and Service Center employ novel concepts, approaches, methodologies, tools, or technologies for this area when needed?
- 1.4 **Investigators:** Are the investigators appropriately trained and well suited to carry out the quality assessment and services? Is the experience level of the principal investigator and other researchers appropriate to the work proposed? Does the quality assessment and services team bring complementary and integrated expertise to the services provided?
- 1.5 **Environment:** Does the scientific environment in which the quality assessments are performed contribute to the probability of success? Do Group clinical trials benefit from unique features of the scientific environment of the Quality Assessment and Service Center? Is there evidence of institutional support? Are the quality assessments and services provided to the Groups in a timely fashion? How are deficiencies noted and corrected with respect to both the assessments and services provided?
- 1.6 **Protection of Human Subjects from Research Risk:** Is the Quality Assessment and Service Center in compliance with federal regulations regarding the protection of human subjects in clinical trials? Is the Center in compliance with federal regulations related to confidentiality of patient data, including Health Insurance Portability and Accountability Act (HIPAA) regulations? Does the Center have adequate safe-guards in place to ensure the technical integrity and confidentiality of patient data in compliance with federal regulations?

2. Specific Objectives for Consideration in Review of the Radiological Physics Center

How well does Radiological Physics Center (RPC) meet the following stated objectives:

- Ensure institutions participating in Cooperative Group clinical trials deliver prescribed radiation doses that are clinically comparable and consistent.
- Operate and enhance systems and procedures to assess radiotherapy programs at institutions, help institutions implement remedial actions, assist the Cooperative Groups in

developing protocols and quality assessment procedures, and inform the community of its findings.

- Ensure appropriate credentialing of institutions participating in Cooperative Group clinical trials with respect to new technologies or treatment techniques (i.e., assessing adequate knowledge of the protocol, treatment planning system, and quality assessment procedures at the institution).
- Work with the Advanced Technology Radiation Therapy Clinical Trials Support (ATC) consortium, QARC, the Cancer Trials Support Unit (CTSU) and other organizations to ensure that services are provided in a timely manner and to create new processes to improve the overall conduct of the cancer clinical trials of the Groups

3. Specific Objectives for Consideration in Review of Quality Assurance Research Center

How well does the Quality Assurance Research Center (QARC) meet the following stated objectives:

- Ensure radiation therapy compliance with protocols through data collection and rapid comprehensive case reviews of target volumes and treatment plans;
- Educate radiotherapy professionals, thus increasing participation in protocols and compliance with guidelines;
- Assist clinical research participants in following data submission guidelines via personal contact and/or the QARC website;
- Standardize and improve radiation and diagnostic imaging protocol guidelines and provide leadership in developing clinical guidelines to incorporate new technologies and techniques into multi-institutional clinical trials;
- Provide a database of radiotherapy details of each protocol case which is adequate for protocol analysis and clinical research;
- Develop systems at to receive, review, and archive imaging studies, data, and treatment plans electronically while ensuring patient confidentiality; and
- Work with the Advanced Technology Radiation Therapy Clinical Trials Support (ATC) consortium; the Radiological Physics Center; and the Cancer Trials Support Unit (CTSU) in developing new processes to improve the overall conduct of the cancer clinical trials of the Cooperative Groups supported by the NCI.

4. Review Criteria for Budgets for Quality Assurance and Service Centers

Have costs for travel, office supplies, equipment and data management been adequately justified? Is there sufficient funding allotted for the Quality Assessment and Service Centers to carry-out the multiple quality control tasks required, including quality assessment and credentialing as well as costs associated with the Centers providing assistant to the Cooperative Groups with respect to protocol development and development of quality assurance programs within the Groups?

F. Review Criteria for International Groups

The review of applications from International Groups located outside the United States that conduct large-scale, randomized clinical treatment trials in a multi-institutional setting such as the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) and the European Organization for Research and Treatment of Cancer (EORTC) focuses on the statistical and data management services provided by the International Group’s Statistical and Data Management Center and/or Operations Center that are used to facilitate collection and analysis of clinical data on trials in which both US Groups and International Groups participate and, in some instances, for trials run solely in the international group’s member sites without US Group participation.

1. General Review Criteria for International Groups

Review of applications from International Groups should follow the general review criteria provided for evaluation of the Statistics and Data Management Center for US Groups as outlined in [Part 2.III.C. \(see pages 89-90\)](#), including compliance with required federal regulations. The review should focus on the ability of the International Groups to collaborate with US Groups to ensure that collaborative clinical trials and associated correlative science studies have robust international participation. This collaboration should include participation of US Groups in clinical trials led by International Groups as well as participation of International Groups in clinical trials led by US Groups. Although the NCI does not support the full scientific agenda of International Groups, these Groups should demonstrate the strength of their research portfolio in their application because this provides the rationale for NCI administrative support. This is particularly relevant when funds are requested to support trials led by the International Group in which US Groups do not participate.

2. Review Criteria for Budgets for International Groups

Have costs for data management related to international collaboration and participation in clinical trials been adequately justified? Is there sufficient funding allotted to carry-out the proposed study/protocol development and study monitoring for international collaborations as well as communications between the International Group and collaborating US Groups? If appropriate, has sufficient capitation funding been included for international site participation in Group trials.

G. Review Criteria for Competing Supplemental Applications (Interim Review)

The focus of the review of competing supplemental applications is the same as for new and competing applications. The only difference is that the review is limited to those Group components that did not receive meritorious scores at the time of initial review, and the type of review (paper-based review of the application by Subcommittee H versus a Group presentation in-person before the Subcommittee H review team) is at the discretion of the responsible NCI Program Director, after consultation with appropriate NCI and CTEP staff.

PART 3: Guidelines Specific for Submission of Non-Competing Continuation Applications (Annual Progress Reports)

I. General Policies and Procedures

The following sections include instructions on the types of information that should be included in the non-competing continuation applications (Type 5 Applications) submitted by the Group – i.e., the Group’s annual Progress Reports. Applicants should consult the PHS 2590 [[Website Reference 33](#)] for up-to-date information on NIH requirements for completing the annual Progress Report or Type 5 Application. The annual Progress Report (Type 5 Application) is required for every year of award, including the year in which a competing continuation application (Type 2 Application) is submitted.

The Progress Report should contain the basic information needed to allow the responsible NCI Program Director to monitor the progress and performance of the Group and all its components.

The submission procedures for non-competing continuation applications are described below.

SENDING A NON-COMPETING APPLICATION TO THE NIH: Two months before the start of the budget period, submit the original application, signed by the Principal Investigator and the authorized business official, and one copy of the application to the address below, according to the instructions in the PHS 2590.

Division of Extramural Activities Support, OER
National Institutes of Health
6705 Rockledge Drive, Room 2207, MSC 7987
Bethesda, MD 20892-7987 (for US Postal Service [USPS] Express or Regular mail)
Bethesda, MD 20817 (for Express/courier Non-USPS Service)
Phone: 301-594-6584

NOTE: All applications and other deliveries must be delivered either via courier or via USPS. Applications delivered by individuals will not be accepted. C.O.D. applications will not be accepted. This policy does not apply to courier deliveries (e.g., FedEx, DHL, etc.).

The procedures for non-competing continuation applications for Quality Assurance and Service Centers as well as International Groups funded under this Program are the same as for US Groups. The information provided in the application or annual report, however, should be focused on the specific activities of these entities (e.g., collection, transfer, and assessment of data collected or therapy delivered on a clinical trial and/or participation in trials rather than on the development of a specific scientific agenda and series of clinical trials).

II. Non-Competing Continuation Applications Format and Budget Requests

The information included in a non-competing continuation application (also called an annual progress reports or Type 5 Application) should be provided in formats similar to the ones presented in this Part of the Guidelines. Providing the information in a standard format will allow both the Group and the responsible NCI Program Director to evaluate the progress of the Group more easily and to identify areas that need attention. The format may be varied somewhat, depending on the Group component submitting the application (Operations Center, Statistics and Data Management Center, U10 Participating Site, or other Group component funded by a U10); however, it should be similar to what is presented here. The instructions on the following pages cover application formats for all Group components. The non-competing continuation application must specify the 12-month period for which data are being reported, and this same 12-month period should be used for all information presented.

A. Application for all Group Components (Ops Center, SDMC, Participating Sites, & Other)

1. Research Plan (Annual Progress Report – Type 5 Application)

The Research Plan for each Type 5 application should be limited to 25 pages of text in **11-point Arial or Helvetica font size**, exclusive of tables, graphs, diagrams, and charts.

1.1 Accrual Performance & Accrual by Gender and Ethnicity/Race

The Group Operations Center and SDMC should provide a summary table that lists the number of patients accrued during the current funding period (i.e., the three [3] most recently completed quarters during the funding period plus a projection for the current fourth quarter) with the exact calendar dates/time-periods used to provide the actual and projected accrual noted at the top of the table. For the entire Group, accrual for all studies should be reported by Scientific Committee, by study type for a Scientific Committee, and for all Scientific Committees ([See Reports #1, #2, #3, respectively, on pages 97-99](#)). Summary accrual information should include patient enrollment data for all studies sponsored or endorsed via the Intergroup mechanism by a specific Scientific Committee as well as accrual to non-Group, non-endorsed CTSU studies. Total Group accrual broken down by sex/gender and ethnicity/race should also be presented using the standard Inclusion Enrollment Report format provided in the PHS 2590 [[Website Reference 33](#)]. This table should be modified to show sex/gender and ethnicity/race breakdown in accrual for the previous 3 years in addition to the current funding period. A suggested format for this modification of the Inclusion Enrollment Report covering these time period for U10 Participating Site progress reports is described in the next paragraph and the same modified format could be used to provide this information for the total Group accrual as well.

For a U10 Participating site progress reports, a summary table that lists the number of patients accrued during the current funding period (i.e., the three [3] most recently completed quarters during the funding period plus a projection for the current fourth quarter) with the exact calendar dates/time-periods used to provide the actual and projected accrual noted at the top of the table ([See Report #4 on page 100](#)), so that trends can be appreciated by the staff reviewing the progress reports. This summary accrual table should list all studies with U10 Participating Site accrual by study type, and it should include the annual accrual targets from the U10 Participating Site since the annual targets are revised following Type 5 redistributions. Also, U10 Participating Site accrual tables should include affiliate accrual only if the affiliate is part of the U10 application and does not receive capitation payments directly from the Group. The U10 Participating Site annual progress report may also include a table that reports accrual by Scientific Committee. Information should also be provided in the U10 Participating site progress reports on accrual by sex/gender and ethnicity/race for the previous 3 years in addition to the current funding period as described in [Section 1.2 on page 101](#). **NOTE:** The Groups Operations Center should provide accrual information to U10 Participating Sites submitting non-competing continuation applications (i.e., annual progress reports or Type 5 Applications) so that they have the necessary information to include in these reports.

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

Report # 1: Summary Accrual Table for ALL Studies by a Scientific Committee by Annual Funding Period (Annual Grant Year)

Please Note: This report format can also be used to present accrual for ALL studies by ALL Committees)

Scientific Committee (e.g., Disease Committee): _____ Committee Chair: _____

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Actual Non-Group Accrual (if different): _____

Time Period (Calendar Dates) for Projected Group Accrual: _____

TYPE OF STUDY	PILOT Treatment Studies	PHASE 1 Treatment Studies	PHASE 2 Treatment Studies	PHASE 3 Treatment Studies	OTHER Studies (Non-Treatment)	ALL STUDIES
Pts enrolled in current period by Group Participating Sites on Group only studies: Actual (projected) Accrual	10 (3)	20 (5)	55 (15)	300 (50)	0 (0)	385 (73)
Pts enrolled in current period by Group Participating Sites on Group-Led Intergroup studies: Actual (projected)	Not Applicable	Not Applicable	15 (2)	200 (40)	Not Applicable	215 (42)
Pts enrolled in current period by Group Participating Sites on Group-endorsed/Intergroup studies: Actual (projected)	Not Applicable	Not Applicable	Not Applicable	40 (5)	Not Applicable	40 (5)
Pts enrolled in current period by Group Participating Sites on non-Group, non-endorsed, CTSU studies: Actual (projected)	Not Applicable	Not Applicable	Not Applicable	10 (5)	Not Applicable	10 (5)
Total Patients Enrolled by Group Participating Sites on all Group and non-Group studies: Actual (projected)	10 (3)	20 (5)	70 (17)	550 (100)	0 (0)	650 (125)
Total Patients in Follow-Up by Group Participating Sites on all Group-only, Group-Led Intergroup, or Group-endorsed/Intergroup studies: Actual (projected)	0 (0)	0 (0)	80 (26)	2000 (140)	0 (0)	2080 (166)

- Accrual figures should include both eligible and ineligible patients. Follow-up figures should include any patients in follow-up at any time during the current funding period being reported in the application
- Pilot studies refer to studies testing the feasibility of administration of the therapeutic intervention/approach.
- Actual data should usually be available for the 3 most recently completed quarters of the annual grant year (funding period) and data should be projected for the current quarter; however, the Group should list the specific calendar dates for actual data and the specific calendar dates for the projected data supplied in the heading information for the table so that it is clear to reviewers what is being presented. If a Group does not make projections by certain categories (e.g., the Group projects data only by "all studies" not by specific categories of studies, the Group should designate that this information is "Not Available" in the appropriate location in the table. The designation of "Not Applicable" should be used to indicate that that category is not appropriate for the Group and no data will be forthcoming for that category.
- A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.
- For the "Other Study" category, the Group should select the Committee under which it wishes to provide information on embedded and stand-alone non-therapeutic studies. The Group should ensure that this information is presented in a clear and consistent manner and is not double-counted (e.g., the same non-therapeutic study should not be listed under the Breast Committee and the Cancer Control Committee).
- **Please Note:** If Group Participating Sites accrue to non-Group, non-endorsed CTSU studies that are conducted in a disease site that is not supported by any of the Group's Scientific Committees or if the number of patients enrolled is particularly significant, the accrual should be presented and described in a separate table (e.g., present accrual figures by study #/protocol).

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

Report # 2: Summary Annual Accrual Table by Study for a Scientific Committee
 (i.e., for all Group-only and Group-Led Intergroup Studies open at any time during the annual funding period):

Please Note: The time period for this table should be the 3 most recently completed quarters of the funding period plus projection for current quarter; however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

Scientific Committee (e.g., Disease Committee): _____ **Committee Chair:** _____

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Actual Non-Group Accrual (if different): _____

Time Period (Calendar Dates) for Projected Group Accrual: _____

Group Study Type Study # / Title	Actual Group Accrual (Projected Group Accrual)	Actual Non-Group Accrual	Total Actual Accrual (Cumulative Accrual Since Activation)	Total Annual Target Accrual	Projected Study Completion Date (Total Study Protocol Sample Size)
Therapeutic Studies					
Phase 1					
Study #1: Title, etc.					
SubTotal					N/A
Phase 2					
Study #2: Title, etc.					
SubTotal					N/A
Phase 3					
Study #1: Title	100 (25)	20 (Non-endorsed - CTSU)	120 (700)	150	Projected Date: --/-- (900)
Study #2: Title *	150 (25)	100 (Endorsed & Non-endorsed - CTSU)	250 (1400)	250	Actual Date: ** 1/1/07 (1400)
SubTotal	250 (50)	120	370 (N/A)	400	N/A (N/A)
Total Therapeutic Studies:					N/A
Non-Therapeutic					
Correlative Science					
Study #1/Title, etc.	40 (10)	N/A	40 (120)	60	Projected Date: --/-- (300)
SubTotal					N/A
QOL					
Study #1/Title *, etc. (Phase 3 – Intergroup Study)	100 (30)	60	160 (600)	170	Projected Date: --/-- (1200)
SubTotal					N/A
Other					
Study #1/Title, etc.					
SubTotal					N/A
Total Non-Therapeutic Studies					N/A

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (no asterisk next to the Study Title means it is a Group-only study).

** Indicates study is closed. Comment should be provided if study closed for reason other than reaching its protocol-specified accrual target.

N/A = Not Applicable.

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

Report # 3: Summary Annual Accrual Table for ALL Studies by Study Type for ALL Scientific Committees
 (i.e., for all Group-only and Group-Led Intergroup Studies open at any time during the annual funding period):

Please Note: The time period for the current year in this table should be the 3 most recently completed quarters of the funding period plus projection for current quarter; however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Actual Non-Group Accrual (if different): _____

Time Period (Calendar Dates) for Projected Group Accrual: _____

Group Studies - Type	Previous Year Accrual (-3)	Previous Year Accrual (-2)	Previous Year Accrual (-1)	Actual Accrual for Current Year	Projected Accrual For Remaining Part of Year
Therapeutic Studies					
Phase 1					
Study #1					
Study #2, etc.					
SubTotal					
Phase 2					
Study #1/Title					
Study #2, etc.					
SubTotal					
Phase 3					
Study #1/Title *					
Study #2					
Study #3/Title *, etc.					
SubTotal					
Total Therapeutic Studies					
Non-Therapeutic					
Correlative Science					
Study #1/Title * (Phase 3 Intergrp Study)					
Study #2/Title, etc.					
SubTotal					
QOL					
Study #1/Title, etc.					
SubTotal					
Other					
Study #1/Title, etc.					
SubTotal					
Total Non-Therapeutic Studies					

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (actual non-Group accrual should be noted in parentheses). No asterisk next to the Study Title means it is a Group-only study.

If study closed during annual funding period, please indicate this in the "Projected Accrual" Column.

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

Report #4: U10 Participating Site Annual Accrual & Follow-Up Table for ALL Studies by Study Type

Please Note: The time period for the current year in this table should be the 3 most recently completed quarters of the funding period plus projection for current quarter; however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

U10 Participating Site: _____ **Principal Investigator:** _____ **Cooperative Agreement #:** _____

Time Period (Calendar Dates) for Actual U10 Accrual: _____

Time Period (Calendar Dates) for Projected U10 Accrual (if available): _____

Group Studies – Type	Lead Group (Group Endorsed Intergroup Studies Only)	Previous Yr Accrual (-3)	Previous Yr Accrual (-2)	Previous Yr Accrual (-1)	Actual Accrual for Current Year	Projected Accrual For Remaining Part of Year	Total in Follow-Up ¥	Annual U10 Accrual Target €
Therapeutic Studies								
Phase 1								
Study #1/Title, etc.								
SubTotal								
Phase 2								
Study #1/Title								
Study #2/Title §	Group A							
SubTotal								
Phase 3								
Study #1/Title								
Study #2/Title *								
Study #3/Title **								
Study #4/Title §	Group B							
Study #5/Title Φ	Group C							
SubTotal								
Total Therapeutic:								
Non-Therapeutic								
Correlative Science								
Study #1, etc.								
SubTotal								
QOL								
Study #1, etc.								
SubTotal								
Other								
Study #1, etc.								
SubTotal								
Total Non-Therapeutic:								

¥ The total in follow-up # should reflect the total # patients in follow-up at the time the application is submitted. A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.

€ Annual U10 accrual targets for Group only, Group-led Intergroup, and Group-endorsed Intergroup trials should be listed where appropriate in the last column (e.g., in last column of totals row for all treatment studies).

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (no symbol next to a Study Title means it is a Group-only study).

** Indicates study is closed. Comment should be provided if study closed for reason other than reaching its protocol-specified accrual target.

§ Study is a Group-endorsed/Intergroup trial.

Φ Study is a non-Group, non-endorsed CTSU trial.

N/A = Not Applicable.

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

1.2 **U10 Participating Site Performance & Accrual by Gender and Ethnicity/Race**

In addition to the summary accrual table on the previous page, the annual progress report should include summarize key aspects of U10 Participating Site's performance (e.g., timeliness of data submission, timeliness of AdEERS reports submission, the date of the last audit for the site [and its affiliates, if appropriate], compliance with specimen submission, etc.). Tables providing this information can be organized in a manner similar to those required for the U10 Participating Site competing applications (Type 2 applications), as outlined in [Attachment #8 in Part 4](#) of these Guidelines. For U10 Participating Sites whose performance was considered unacceptable at some point during the past 12 months, the annual progress report should indicate the corrective measures taken.

Accrual broken down by sex/gender and ethnicity/race should be presented using the standard Inclusion Enrollment Report format provided in the PHS 2590 [[Website Reference 33](#)]. This table should be modified to show sex/gender and ethnicity/race breakdown in accrual for the previous 3 years in addition to the current funding period. A suggested format for this modification of the Inclusion Enrollment Report is provided on the next page (i.e., Report #5).

In addition, information provided in the annual progress report for U10 Participating Sites should provide the same general information that is provided to justify the U10 at the time of competitive renewal (i.e., information on how the U10 Participating Site contributes to the mission of the Group via leadership activities, core services to the Group, as well as accrual, with emphasis on what the U10 Participating Site has accomplished in the current funding period.

1.3 **Overall Group Performance for Study Conduct**

The annual progress report should summarize the overall performance of the Group in terms of data timeliness, timeliness of AdEERS report submissions, compliance with specimen submission, and auditing, etc.

1.4 **Protocol Development and Submission**

The annual progress report should list protocol development activities during the current funding period, in terms of approved Letters of Intent (LOIs) and Concepts submitted, as well as protocols submitted and activated. This table should be organized by Scientific Committee, as appropriate. A suggested format for this table is provided below.

Group Study/Protocol Development Timelines

Scientific Committee: _____ **Time Period (Calendar Dates):** _____

Study #/Title	Approved LOIs, Concepts & Protocols	Date LOI or Concept Submitted to CTEP ** (Date Approved by CTEP)	Date Protocol Submitted to CTEP (Date Approved by CTEP)	Date Protocol Activated
Study #1: Title	LOI	--/--/-- (--/--/--)	--/--/-- (--/--/--)	--/--/--
Study #2: Title	Concept	--/--/--	Pending	N/A
Study #3: Title *	Concept	--/--/-- (--/--/--)	--/--/-- (--/--/--)	--/--/--
Study #5: Title	Protocol (e.g. Phase 2 study)	N/A	--/--/-- (--/--/--)	--/--/--

* Indicates the study is a Group-led Intergroup trial. No asterisk next to a Study Title indicates it is a Group-only study.
 N/A = Not Applicable.

** For concepts submitted to NCI disease-specific Steering Committees, please provide the date the concept was submitted to the Steering Committee. The date of approval should remain the date CTEP approves the concept since

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

concepts approved by Steering Committees will subsequently receive either full or expedited review by CTEP prior to final approval.

Report #5: U10 Participating Site Modified Inclusion Enrollment Table for the Annual Progress Report

Please Note: Calendar dates should be provided showing the exact dates for the accrual reported in this table for the Current Funding Period. This table should include only actual accrual numbers.

U10 Participating Site: _____ **Principal Investigator:** _____ **Cooperative Agreement #:** _____

	Previous Year Accrual (-3) Calendar Dates for Period:				Previous Year Accrual (-2) Calendar Dates for Period:				Previous Year Accrual (-1) Calendar Dates for Period:				Current Funding Period Calendar Dates for Period:			
	Females	Males	Unknown or Not Reported	Total	Females	Males	Unknown or Not Reported	Total	Females	Males	Unknown or Not Reported	Total	Females	Males	Unknown or Not Reported	Total
Part A. Total Enrollment Report: # of Subjects Enrolled by Ethnicity & Race																
Ethnic Category				**				**				**				**
Hispanic or Latino																
Not Hispanic or Latino																
Unknown (individuals not reporting ethnicity)																
Ethnic Category: Total of All Subjects *				*				*				*				*
Racial Categories																
American Indian/Alaskan Native																
Asian																
Native Hawaiian or Other Pacific Islander																
Black or African American																
White																
More Than One Race																
Unknown or Not Reported																
Racial Categories: Total of All Subjects *				*				*				*				*
Part B. Hispanic Enrollment: # of Hispanics or Latinos Enrolled																
Racial Categories																
American Indian/Alaskan Native																
Asian																
Native Hawaiian or Other Pacific Islander																
Black or African American																
White																
More Than One Race																
Unknown or Not Reported																
Racial Categories: Total of Hispanics or Latinos **				**				**				**				**

* These totals must agree in each annual period. ** These totals must agree in each annual period.

1.5 Summary of Research Accomplishments

The application should provide a brief, narrative description of protocols that have been completed during this reporting period/funding period by Scientific Committee and any other

studies for which significant research findings are available (i.e., 1 to 2 page narrative for summary of all protocols completed for the Scientific Committee during this funding period), as well as update information on other significant accomplishments by the Scientific Committee. This summary narrative on the completed protocols should be adequate to convey the important facets of the studies (e.g., schedule, target patient population) and the significant findings of the studies (e.g., patients accrued, open dose level, important toxicities observed, pharmacokinetic findings, anti-tumor activity observed, etc.).

1.6 Research Plans

The annual progress report should provide a brief narrative description of important, new trials in development in the current funding period and other Group initiatives.

1.7 Auditing Activities

The NCI-Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) require all institutions to be audited at least once every 36 months. In order for NCI to review the Group's compliance with this requirement, each Group should conduct an annual review of its membership and provide in the non-competing continuation application an accounting similar to the table provided for competing applications that is described in [On-site Auditing Activities in Part 2.II.C. Section 5.3 on page 68.](#) (See the [Suggested Format for Reporting On-Site Auditing Activities in Part 4 – Attachment #9.](#)) Any significant audit problems encountered during the preceding year should be fully described and the corrective action(s) taken explained.

1.8 Publications

The annual progress report should list the titles and complete references of all publications not previously reported. This includes manuscripts submitted or accepted for publication. One copy of each publication not previously submitted should be provided. Only those publications resulting directly from Group activities funded by the Cooperative Agreement should be reported.

1.9 Training on Human Subjects Protection for Key Personnel

The Group should submit a list of Key Personnel, indicating the type of training course/program on human subjects protection completed by each person listed.

2. Budget

2.1 General Budget Information

The budget included in the non-competing application should be similar to that provided in the new, competing continuation application, except limited to a 12-month period for the current funding period. A Common Budget Outline, similar to that required for a competing continuation application (Type 2 Application), should also be provided after the Group's funding level is known along with any revised budget pages. (See [Attachment #11 in Part 4.](#))

2.2 Non-Competing Budget Adjustments/Redistributions

- a) *General comments:* Out-year budget commitments, as reflected in each Notice of Grant Award, are based upon the funding level for the competing year; however, 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.

Adjustments in the relative funding of the various U10 Participating Sites or other Group components funded by a U10 at the time of a 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

PART 3.II.A: Non-Competing Continuation Applications Format and Budgets
Applications for all Group Components (Ops Ctr, SDMC, Participating Sites & Other

adjustments are initiated by the leadership of the Group, and are based on such factors as increased or decreased level of activity at an institution. The effect of any such adjustment

PART 3.II.A & B: Non-Competing Continuation Applications Format and Budgets
Applications all Group Components & Notification of International Involvement

will be reflected in revised out-year commitments. Authority to effect an adjustment rests with NCI Grants Management Officer in the NCI Office of Grants Administration (OGA) on the recommendation of the responsible NCI Program Director. Funding adjustments are facilitated by the CTEP Program Specialist.

- b) *Process:* Informal administrative discussions about a contemplated redistribution may take place between the CTEP Program Specialist and Group Administrator, and may be initiated by either party. The CTEP Program Specialist is responsible for providing an estimate of available budget for the Group as a whole, based on discussions with the responsible NCI Program Director. Similarly, the responsible NCI Program Director and CIB scientific/administrative liaisons are typically in on-going discussions with the Group on their budgetary needs and scientific priorities.

The Group Administrator will transmit to the CTEP Program Specialist an electronic spreadsheet detailing the planned redistribution of funds among the Group's U10 components. It will include direct costs and estimated indirect costs for each component. At that time, scientific justifications may also be transmitted and provided by the Group for review by the responsible NCI Program Director. In this way, questions can be addressed prior to the Chair forwarding a formal request and justification for approval to the NCI.

The timing of such discussions vary. Type 5 Applications are due at the NCI eight (8) weeks prior to the award date, so sufficient time should be allotted to permit timely receipt of applications in line with the redistribution. In connection with this time-line, it should be noted that OGA generally requires a formal, updated budget when changes of more than 25 per cent are requested.

2.3 Budget Adjustments by CTEP for Groups and their Components

Adjustments may be made in the funding of the Group's Cooperative Agreement at the time of a non-competing continuation award. Such adjustments provide the NCI with a program that ensures that available funds are put to their best use. Authority to effect adjustments in funding rests with the responsible NCI Program Director, who works in conjunction with the CTEP Program Specialist.

Budget commitments for the non-competing 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 competing application or in the previous year. The actual monies awarded 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.

B. Notification of International Involvement in Group Trials

The Group should alert the CTEP Program Specialist when a non-competing application involves any new international (non-US) component. In such cases, advance clearance from the US Department of State is needed for each non-US component prior to the award. The information required by US Department of State is listed below (this information should also include all non-US subcontracts).

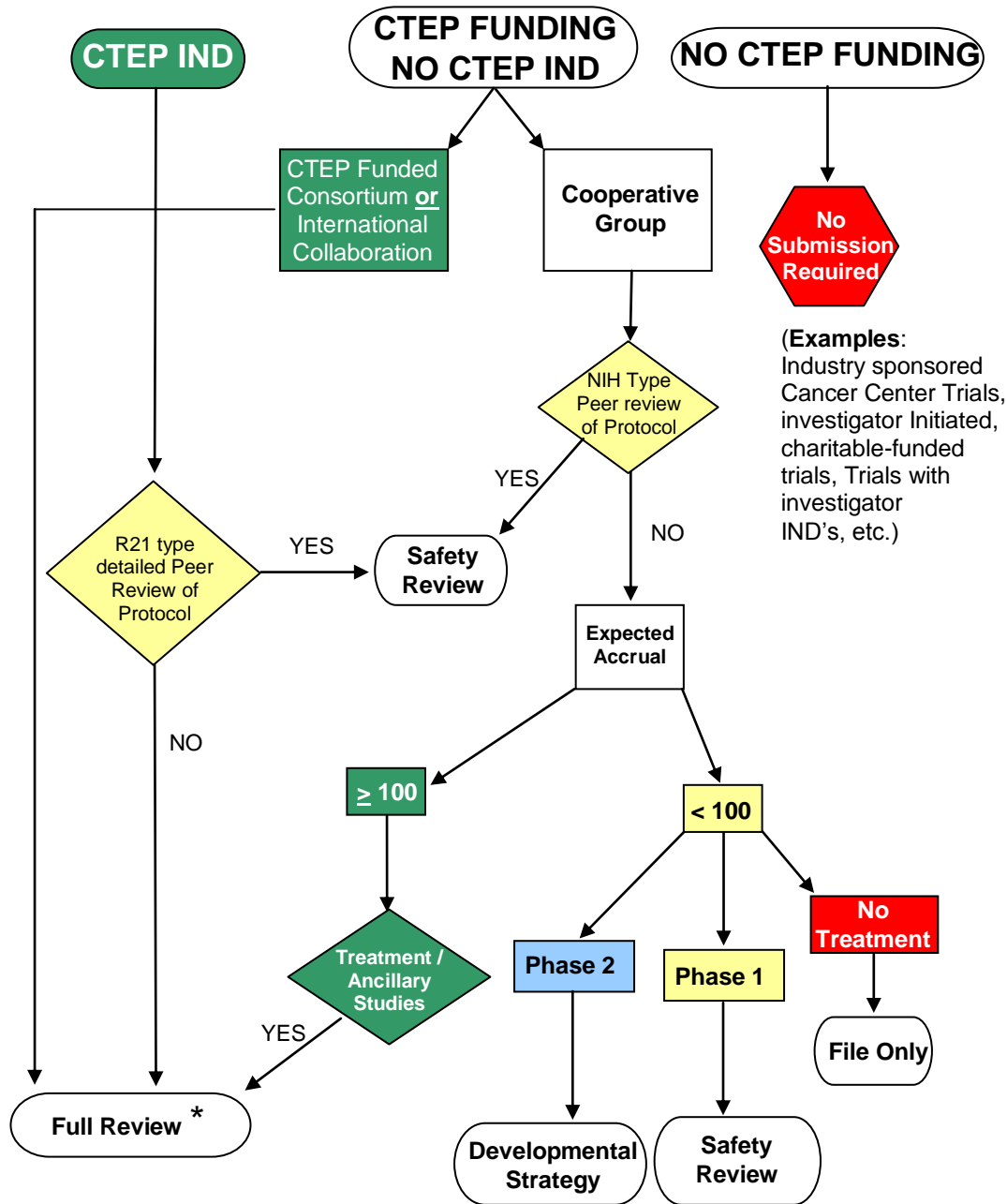
- Estimated annual Total Cost dollar award for the non-US component
- Name, organization, city, and country of the International (non-US) Principal or Collaborating Investigator(s)
- Biosketch and Curriculum Vitae (CV) for both the domestic Principal Investigator and the international Principal Investigator
- OHRP assurance number (i.e., Federalwide Assurance number) for the non-US component

PART 4: Attachments

- [Attachment # 1:](#) Protocol and Information Office Schema for CTEP Review by Study Type
- [Attachment # 2:](#) Protocol and Information Office Summary of CTEP Review by Study Type
- [Attachment # 3:](#) Suggested Format for Summary of Data Quality and Data Timeliness
- [Attachment # 4:](#) Suggested Format for Summary Accrual Tables
- [Attachment # 5:](#) Suggested Format for Summary of Publications By Committee
- [Attachment # 6:](#) Suggested Format for Summary of Administrative Committee Activities
- [Attachment # 7:](#) NCI/CTEP and Group Policy on Contract Review
- [Attachment # 8:](#) Suggested Format for Summary of U10 Participating Site Activities
- [Attachment # 9:](#) Suggested Format for Reporting On-Site Auditing Activities
- [Attachment # 10:](#) Suggested Outline for an “Interim Review” Application (Budget and Research Plan)
- [Attachment # 11:](#) Cooperative Group Common Budget Outline
- [Attachment # 12:](#) Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies
- [Attachment # 13:](#) NCI Clinical Trials: Prioritization/Scientific Quality Initiative
- [Attachment # 14:](#) List of Abbreviations
- [Attachment # 15:](#) Website References

Attachment # 1: Protocol and Information Office Schema for CTEP Review by Study Type

CTEP REVIEW TYPES DIAGRAM



Green – for items getting 'Full Review'
 Yellow – for item getting 'Safety Review'
 Blue – for item getting 'Developmental Strategy Review'
 Red – for item **not reviewed** by CTEP

* Concepts for Phase 3 trials approved by NCI disease-specific Scientific Steering Committees will receive either a Full or an Expedited Review by CTEP.

Please Note: A "No Treatment" study must also be sent to CTEP/PIO even if the study does not involve an official protocol document. If these studies involve < 100 patients or < 100 specimens banked from a Group study, these studies or research plans will be processed as "File Only" studies by CTEP/PIO. If these studies involve ≥ 100 patients or ≥ 100 specimens, then full CTEP review is required. For correlative study proposals requesting use of specimens from Intergroup trials in

PART 4: Attachment #1: Protocol and Information Office Schema for CTEP Review by Study Type

which specimens were banked, PRC review can be substituted by review by an Intergroup Correlative Sciences Committee or Steering Committee consisting of Group representatives and NCI/CTEP representatives according to an agreement between the particular Intergroup and NCI/CTEP.

Attachment # 2: Protocol and Information Office Summary CTEP Review by Study Type

CTEP's Protocol Review Committee (which includes staff of other DCTD programs, plus ad hoc reviewers) must review the following categories of protocols:

- studies involving CTEP supplied investigational agents;
- all CTEP funded Cooperative Group and Consortium (NABTT, NABTC, PBTC, AMC, etc.) trials;
- CCOP research base treatment; and
- ACRIN protocols that involve treatment interventions.

The type of review is dependent on whether the study:

- utilizes a CTEP IND agent;
- is from a CTEP funded trial organization and which type (e.g., Cooperative Groups vs. UO1 funded Consortia);
- has already received NIH-type peer review for the specific protocol (e.g. R21)
- focus is on treatment vs. correlative science;
- involves collaboration in an ongoing international trial;
- is expected to accrue ≥ 100 patients; and
- is a phase 1, phase 2, or phase 3 trial.

A summary of the review types follows:

- **Full Review** –
 - Types of studies: All studies that utilize a CTEP IND agent and are not specifically peer reviewed; OR CTEP funded treatment trials with an expected accrual ≥ 100 patients; OR all consortia trials funded by a cooperative agreement or contract.
 - Focus of NCI review: The protocol is reviewed for completeness and clarity; scientific merit risk: benefit ratio; optimal design; accrual rate; patient safety; pharmaceutical accuracy; adequacy of regulatory and human subject's protection aspects; and agent availability and duplication with existing studies.
 - NCI Reviewer comments: Reviewers may provide 'comments requiring a response' and/or 'recommendations' to modify any aspect of the trial.
 - Typical assignment of NCI reviewers: IDB; BRB; PMB; CTMB; CIB (if disease specific, phase 2 trial or phase 3 trial; or Group involvement); and other specialists as appropriate (e.g. imaging; bio-markers; quality-of-life; etc.).
- **Safety Review** –
 - Types of trials: Group phase 1 treatment trial without a CTEP IND agent AND an expected accrual < 100 patients; OR the study has received funding after specific NIH-type peer review.
 - Focus of NCI review: The protocol is reviewed for patient safety; pharmaceutical accuracy; and adequacy of regulatory and human subject's protection aspects.
 - NCI Reviewer comments: Reviewers may provide 'recommendations' and/or 'comments requiring a response' to modify the study within the focus area of the review. Recommendation maybe made in other areas for CTEP IND agent studies.
 - Typical assignment of NCI reviewers: CIB; CTMB; & PMB (if a treatment trial). Other reviewers with specialized expertise may be assigned as appropriate.

- **International Collaboration** –
 - Types of Trials: When CTEP-funded organizations, typically Cooperative Groups, wish to join a new trial or a study already under way under the sponsorship of another major international clinical trials organization (e.g. EORTC).
 - Focus of NCI review: It is assumed that as a result of the prior international review, that there would be limited ability to reconsider major design issues. In this case the protocol is reviewed first with regard to whether the scientific question merits commitment of funded CTEP resources, and if so it is reviewed for patient safety; pharmaceutical accuracy; and adequacy of regulatory and human subject's protection aspects.
 - NCI Reviewer comments: Will focus on whether to commit Group resources towards the trial. Other comments will be limited to recommendations within the focus area of the review.
 - Typical assignment of NCI reviewers: CIB; PMB; BRB & CTMB. Other reviewers with specialized expertise may be assigned as appropriate.

- **Developmental Strategy Review** –
 - Types of Trials: These are Cooperative Group phase 2 treatment trials without a CTEP IND agent AND an expected accrual < 100 patients that are undertaken as preliminary to an eventual large randomized phase 3 trial (with its attendant commitment of substantial resources and funds); or a definitive correlative science (non-treatment) trial with expected accrual of \geq 100 patients.
 - Focus of NCI review: Review at this stage provides the Group with an early indication of the potential scientific value of an eventual phase 3 question. Particularly in the context of other potential trials.
 - NCI reviewer Comments: This category of protocol receives a limited review. In general NCI comments will be limited to "recommendations only" regarding the scientific merit of the protocol. These studies are not reviewed by NCI for human subject protection or for pharmaceutical and regulatory accuracy/compliance. The submitting organization assumes full responsibility for assuring compliance with all federal or NCI-specific regulations regarding these regulatory and safety issues for this category of trials. In the event that a NCI scientific reviewer finds a regulatory or safety issue that is incorrect or non-compliant in the course of this limited review, this will be indicated to the Group as "comments requiring a response."
 - Typical assignment of NCI reviewers: CIB and BRB (and CDP for non-treatment trials).

- **File Only** –
 - Types of Trials/Studies: All non-treatment trials or studies with expected accrual < 100.
 - Focus of NCI review: No review required.
 - NCI reviewer comments: None provided. The submitting organization assumes full responsibility for assuring compliance with all federal or NCI-specific regulations regarding these regulatory and safety issues for any file-only study.
 - Typical assignment of NCI reviewers: None required.

Please note: Trials without NIH funding, trials with commercial agent or industry sponsored INDs, without CTEP IND agents, (e.g. SPORE or cancer center trials using industry or locally supplied agents) do not receive any CTEP review. The investigator and institution are entirely responsible for compliance with federal and local regulations.

Attachment # 3: Suggested Format for Summary of Data Quality and Data Timeliness

This is a suggested format only. Groups may use any report format that provides information on data timeliness for reviewers that is accurate and easy to comprehend.

Institution Name: _____ (NCI Site ID #: _____; Group Site ID #: _____)

Year	Accrual	%Eligible Patients	ADR/SAE Reporting % Timeliness	ADR/SAE Reporting % Accuracy	% Follow-up Forms Submitted on Time	Date of Site Visit Audit	Result of Site Visit Audit
1	0	N/A	N/A	N/A	N/A		
2	12	0.0%	85.0%	88.0%	88.0%		
3	24	1.1%	90.0%	90.0%	90.0%	1/6/2002	Unacceptable
4	13	2.0%	98.2%	99.0%	99.0%	1/23/2003	Acceptable
5	19	1.0%	100.0%	98.0%	98.0%		
6	N/A	N/A	N/A	N/A	N/A		

Institution Name: _____ (NCI Site ID #: _____; Group Site ID #: _____)

Year	Accrual	%Eligible Patients	ADR/SAE Reporting % Timeliness	ADR/SAE Reporting % Accuracy	% Follow-up Forms Submitted on Time	Date of Site Visit Audit	Result of Site Visit Audit
1							
2							
3							
4							
5							
6							

etc.

Summary Statistics for All Institutions

Year	Accrual	%Eligible Patients	ADR/SAE Reporting % Timeliness	ADR/SAE Reporting % Accuracy	% Follow-up Forms Submitted on Time	Date of Site Visit Audit	Result of Site Visit Audit
1						N/A	N/A
2						N/A	N/A
3						N/A	N/A
4						N/A	N/A
5						N/A	N/A
6						N/A	N/A

Definitions:

- Accrual data is for Group studies (i.e., Group-only and Group-Led Intergroup studies).
- ADR = AdEERS; SAE = Serious Adverse Event.
- Accuracy percentage for ADR/SAE Reporting is the percent of ADR forms amended for a change in toxicity Grade or addition of a toxicity Grade 3+. For example, if the total number of ADR forms received during the time-period covered by the report is 1,000, and out of those 1,000 ADR reports, 45 of them required a change in toxicity Grade or the addition of a grade 3+ or higher AE, then the accuracy percentage would be calculated as: $((1000 - 45) / 1000) = 95.5\%$. Groups should provide the exact definition that they use to calculate their accuracy percentage with this report.
- Timeliness percentage for ADR/SAE Reporting is the percent of follow-up data submitted as of January 31 of the project year (December 31 for project year 5) with a 6-month grace period.
- Disciplinary actions imposed by the Group during the current funding period should be described and explained.

Attachment # 4: Suggested Format for Summary Accrual Tables

Report # 1: Summary Accrual Table for All Studies by a Scientific Committee Over Entire Funding Period

(This report format can also be used to present accrual for ALL studies by ALL Committees)

Scientific Committee (e.g., Disease Committee): _____ Committee Chair: _____

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Actual Non-Group Accrual: _____

Time Period (Calendar Dates) for Projected Group Accrual: _____

TYPE OF STUDY	PILOT Treatment Studies	PHASE 1 Treatment Studies	PHASE 2 Treatment Studies	PHASE 3 Treatment Studies	OTHER Studies (Non-Treatment)	ALL STUDIES
Pts enrolled in current period by Group Participating Sites on Group only studies: Actual (projected) Accrual	10 (3)	20 (5)	55 (15)	300 (50)	0 (0)	385 (73)
Pts enrolled in current period by Group Participating Sites on Group-Led Intergroup studies: Actual (projected)	Not Applicable	Not Applicable	15 (2)	200 (40)	Not Applicable	215 (42)
Pts enrolled in current period by Group Participating Sites on Group-endorsed/Intergroup studies: Actual (projected)	Not Applicable	Not Applicable	Not Applicable	40 (5)	Not Applicable	40 (5)
Pts enrolled in current period by Group Participating Sites on non-Group, non-endorsed, CTSU studies: Actual (projected)	Not Applicable	Not Applicable	Not Applicable	10 (5)	Not Applicable	10 (5)
Total Patients Enrolled by Group Participating Sites on all Group and non-Group studies: Actual (projected)	10 (3)	20 (5)	70 (17)	550 (100)	0 (0)	650 (125)
Total Patients in Follow-Up by Group Participating Sites on all Group-only, Group-Led Intergroup, or Group-endorsed/Intergroup studies: Actual (projected)	0 (0)	0 (0)	80 (26)	2000 (140)	0 (0)	2080 (166)

- Accrual figures should include eligible and ineligible patients; Follow-up figures should include any patients in follow-up at any time during the current funding period being reported in the application.
- Pilot studies refer to studies testing the feasibility of administration of the therapeutic intervention/approach.
- Actual data should usually be available for the most recent 4 ½ years with a projection for part of year 5 and for year 6 for Type 2 applications; however, the Group should list the specific calendar dates for actual data and the specific calendar dates for projected data supplied in the heading information for the table so that it is clear to reviewers what is being presented. If a Group does not make projections by certain categories (e.g., the Group projects data only by "all studies" and not by specific categories of studies, the Group should designate that this information is "Not Available" in the appropriate table location. "Not Applicable" should be used to indicate that a category is not appropriate for the Group and no data will be forthcoming for that category.
- A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.
- For the "Other Study" category, the Group should select the Committee under which it wishes to provide information on embedded and stand-alone non-therapeutic studies. The Group should ensure that this information is presented in a clear and consistent manner and is not double-counted (e.g., the same non-therapeutic study should not be listed under the Breast Committee and the Cancer Control Committee).
- **Please Note:** If Group Participating Sites accrue to non-Group, non-endorsed CTSU studies that are conducted in a disease site that is not supported by any of the Group's Scientific Committees or if the number of patients enrolled is particularly significant, the accrual should be presented and described in a separate table (e.g., present accrual figures by study #/protocol).

Report # 2: Summary Accrual Table by Study Sponsored for a Scientific Committee Over Entire Funding Period (i.e., for all Group-only and Group-Led Intergroup Studies open at any time during entire funding period):

Please Note: The time period for this table should be the 4 1/2 most recently completed years of the funding period plus projection for part of year 5 and for year 6 for Type 2 applications; however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

Scientific Committee (e.g., Disease Committee): _____ **Committee Chair:** _____

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Actual Non-Group Accrual (if different): _____

Time Period (Calendar Dates) for Projected Group Accrual: _____

Group Study Type Study # / Title	Actual Group Accrual (Projected Group Accrual)	Actual Non-Group Accrual	Total Actual Accrual (Cumulative Study Accrual)	Total in Follow-Up †	Projected Study Completion Date (Total Study Protocol Sample Size)
Therapeutic Studies					
Phase 1					
Study #1: Title, etc.					
SubTotal					N/A
Phase 2					
Study #2: Title, etc.					
SubTotal					N/A
Phase 3					
Study #1: Title	400 (100)	80 (Non-endorsed - CTSU)	480 (700)	575	Projected Date: --/-- (900)
Study #2: Title *	600 (100)	100 (Endorsed & Non-endorsed - CTSU)	700 (1400)	1000	Actual Date: ** 1/1/07 (1400)
SubTotal	1000 (200)	180	1180 (N/A)	1575	N/A (N/A)
Total Therapeutic Studies:					
					N/A
Non-Therapeutic					
Correlative Science					
Study #1/Title, etc.	40 (10)	N/A	40 (120)	60	Projected Date: --/-- (300)
SubTotal					N/A
QOL					
Study #1/Title *, etc. (Phase 3 – Intergroup Study)	100 (30)	60	160 (600)	170	Projected Date: --/-- (1200)
SubTotal					N/A
Other					
Study #1/Title, etc.					
SubTotal					N/A
Total Non-Therapeutic Studies					
					N/A

† The total in follow-up # should reflect the total # patients in follow-up at the time the application is submitted. A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (no symbol next to the Study Title means it is a Group-only study).

** Indicates study is closed. Comment should be provided if study closed for reason other than reaching its protocol-specified accrual target.
N/A = Not Applicable.

PART 4: Attachment # 4: Suggested Format for Summary Accrual Tables

Report # 3: Summary Accrual Table for ALL Studies by Study Type for the Group Over Funding Period

Please Note: The time period for this table should be the 4 1/2 most recently completed years of the funding period plus projection for part of year 5 and for year 6 for Type 2 applications; however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Actual Non-Group Accrual (if different): _____

Time Period (Calendar Dates) for Projected Group Accrual: _____

Group Studies - Type	Lead Group	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Total Accrual	Total in Follow-Up ¶	Target Accrual	Closed to Accrual Date	Date of Analysis £
	(Group Endorsed Intergroup Studies Only)											
Therapeutic Studies												
Phase 1												
Study #1/Title												
Study #2/Title, etc.												
SubTotal												
Phase 2												
Study #1/Title §	Group A									Not Available	Not Available	Not Available
Study #3/Title, etc.												
SubTotal												
Phase 3												
Study #1/Title												
Study #2/Title *												
Study #3/Title **												
Study #4/Title §	Group B									Not Available	Not Available	Not Available
Study #5/Title ¶	Group C									Not Available	Not Available	Not Available
SubTotal												
Total Therapeutic:												
Non-Therapeutic												
Correlative Science												
Study #1												
Study #2, etc.												
SubTotal												
QOL												
Study #1, etc.												
SubTotal												
Other												
Study #1, etc.												
SubTotal												
Total Non-Therapeutic:												

¶ The total in follow-up # should reflect the total # patients in follow-up at the time the application is submitted. A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (no symbol next to a Study Title means it is a Group-only study).

** Indicates study is closed. Comment should be provided if study closed for reason other than reaching its protocol-specified accrual target.

§ Study is a Group-endorsed/Intergroup trial.

¶ Study is a non-Group, non-endorsed CTSU trial.
N/A = Not Applicable.

£ This date should correspond to that of the technical report produced by the Group Statistical Center with the expectation of the development of the primary manuscript draft.

PART 4: Attachment # 4: Suggested Format for Summary Accrual Tables

Report # 4: Summary Accrual Table by Member Participating Sites for ALL Group-Led Studies Over Entire Funding Period (i.e., for all Group-only and Group-Led Intergroup Studies open at any time during entire funding period):

Please Note: The time period for this table should be the 4 1/2 most recently completed years of the funding period plus projection for part of year 5 and for year 6 for Type 2 applications (if available); however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Projected Group Accrual (if available): _____

If a Group has U10 Participating Sites, a column should be provided in the Table to designate these sites as illustrated below.

Participating Sites	U10 Site?	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total Accrual	Total in Follow-Up *
Participating Site #1									
Participating Site #2	Yes								
Participating Site #3									
Participating Site #4, etc.									
Total – Participating Sites									

* The total in follow-up # should reflect the total # patients in follow-up at the time the application is submitted. A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.

This report can also be provided by Study by Scientific Committee.

Report # 5: Summary Accrual Table by Member Participating Sites for ALL Non-Group Studies Over Entire Funding Period (i.e., for Group-endorsed/Intergroup Studies or non-Group, non-endorsed CTSU studies open at any time during the entire funding period):

Please Note: The time period for this table should be the 4 1/2 most recently completed years of the funding period plus projection for part of year 5 and for year 6 for Type 2 applications (if available); however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

Time Period (Calendar Dates) for Actual Group Accrual: _____

Time Period (Calendar Dates) for Projected Group Accrual (if available): _____

If a Group has U10 Participating Sites, a column should be provided in the Table to designate these sites as illustrated below.

Participating Sites	U10 Site?	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total Accrual	Total in Follow-Up *
Participating Site #1									
Participating Site #2	Yes								
Participating Site #3									
Participating Site #4, etc.									
Total – Participating Sites									

* The total in follow-up # should reflect the total # patients in follow-up at the time the application is submitted. A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.

This report can also be provided by Study by Scientific Committee.

Attachment # 6: Suggested Format for Summary of Administrative Committee Activities

Administrative Committee: _____

Committee Chair: _____

Time Period (Calendar Dates): _____

Group Studies in Which Administrative Committee Discipline is a Primary Component - Study Type	Total Accrual	Target Accrual	Closed to Accrual Date	Date of Analysis £
Therapeutic Studies				
Phase 1				
Study #1/Title				
Study #2/Title, etc.				
SubTotal				
Phase 2				
Study #1/Title				
Study #2/Title, etc.				
SubTotal				
Phase 3				
Study #1/Title *				
Study #1/Title				
Study #2/Title, etc.				
SubTotal				
Total Therapeutic:				
Non-Therapeutic				
Correlative Science				
Study #1				
Study #2, etc.				
SubTotal				
QOL				
Study #1, etc.				
SubTotal				
Other				
Study #1, etc.				
SubTotal				
Total Non-Therapeutic:				

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (no asterisk next to the Study Title means it is a Group-only study).

£ This date should correspond to that of the technical report produced by the Group Statistical Center with the expectation of the development of the primary manuscript draft.

Attachment # 7: NCI/CTEP and Group Policy on Contract Review

NCI/CTEP uses 3 main mechanisms available for entering into binding collaborative agreements with pharmaceutical and biotechnology companies: CRADAs (Cooperative Research and Development Agreements), CTAs (Clinical Trials Agreements) and CSAs (Clinical Supply Agreements). Of these, only CRADAs allow the government to receive funding directly. NCI/CTEP shares with the Groups all terms of these collaborative agreements that might apply to Group trials. The language for these terms is non-negotiable and is readily available to the Groups. NCI/CTEP is unable to share the complete agreements with the Groups because the pharmaceutical/biotechnology companies require them to be kept confidential. CRADAs and CTAs are almost always executed for fairly broad development plans and generally include multiple trials in addition to the particular one being conducted by a Group.

The CRADAs/CTAs provide specific and limited access to Group data sets to the pharmaceutical and biotechnology companies. For phase 1 and phase 2 studies under a CTEP IND, CDUS complete reporting data are made available to the pharmaceutical/biotechnology company. For phase 3 trials, only CDUS abbreviated data and ADEERS reports are provided. NCI/CTEP has informed companies that they must negotiate with the Group leading the trial for access to any additional data other than the CDUS data.

NCI/CTEP policy described below reflects the agreement between NCI/CTEP and the Groups on how Group contracts should be handled by the Groups when CTEP holds the IND or provides agent distribution for a Group study.

1. The Regulatory Affairs Branch at CTEP will provide Groups with the non-negotiable terms that appear in all NCI/CTEP collaborative agreements.
2. Groups agree to utilize this language as the minimum requirement when they contract with companies. Proposed changes to the standard terms **must be discussed with the Regulatory Affairs Branch in NCI/CTEP prior to finalizing any contract for any study where CTEP is involved with the IND or agent distribution.**
3. Single Company Involvement: NCI/CTEP does not need to review each and every contract between a Group and a single company if there are no changes to the minimum requirements as long as the Group agrees to provide any proposed changes to this language (i.e., the minimum requirements) to NCI/CTEP before finalizing a Group contract. Likewise, NCI/CTEP would be required to inform the Group if NCI/CTEP “non-negotiable” terms were changed, either as an individual exception or in general.
4. Multiple Company Involvement: When multiple companies are involved in the same trial, then NCI/CTEP requires that it **review all agreements in their entirety before approving the study.**
5. NCI/CTEP requires a letter annually, at the time of the Type 5 non-competitive renewal, stating that all Group contracts with companies respect the agreed upon NCI/CTEP terms, noting in the letter, any exceptions to NCI/CTEP terms in specific contracts and documenting that these have been approved by NCI/CTEP,
6. NCI/CTEP is always willing to review or be involved in contract negotiations, if requested by a Group.
7. NCI/CTEP reserves the right to request a copy of any Group contract associated with a study for which CTEP holds the IND and/or provides agent distribution.

Attachment # 8: Suggested Format for Summary of U10 Participating Site Activities

Report #1: U10 Participating Site Accrual & Follow-Up Table for ALL Studies by Study Type Over Entire Funding Period

Please Note: The time period for this table should be the 4 1/2 most recently completed years of the funding period plus projection for part of year 5 and for year 6 for Type 2 applications (if available); however, calendar dates should be provided detailing the exact dates used for the actual accrual reported and the projected accrual reported in the table.

U10 Participating Site: _____ Principal Investigator: _____ Cooperative Agreement #: _____

Time Period (Calendar Dates) for Actual U10 Accrual: _____

Time Period (Calendar Dates) for Projected U10 Accrual (if available): _____

Group Studies – Type	Coordinating Group (Endorsed Intergroup Studies Only)	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Total Accrual	Total in Follow-Up †	Target Accrual
Therapeutic Studies										
Phase 1										
Study #1/Title, etc.										
SubTotal										
Phase 2										
Study #1/Title §	Group A									Not Available
Study #2/Title, etc.										
SubTotal										
Phase 3										
Study #1/Title										
Study #2/Title *										
Study #3/Title **										
Study #4/Title §	Group B									Not Available
Study #5/Title ¶	Group C									Not Available
SubTotal										
Total Therapeutic:										
Non-Therapeutic										
Correlative Science										
Study #1, etc.										
SubTotal										
QOL										
Study #1, etc.										
SubTotal										
Other										
Study #1, etc.										
SubTotal										
Total Non-Therapeutic:										

† The total in follow-up # should reflect the total # patients in follow-up at the time the application is submitted. A patient in follow-up is defined as a patient who is 1 year from his/her effective on-study date, who is not known to be dead, and for whom at least annual follow-up is required. If the Group uses a different definition for follow-up, that definition should be supplied with this table.

* Indicates Group-Led Intergroup study that has official endorsements from one or more Groups (no symbol next to a Study Title means it is a Group-only study).

** Indicates study is closed. Comment should be provided if study closed for reason other than reaching its protocol-specified accrual target.

§ Study is a Group-endorsed/Intergroup trial.

¶ Study is a non-Group, non-endorsed CTSU trial.

N/A = Not Applicable.

Report #2: U10 Participating Site Scientific and Administrative Leadership Activities

Investigator Name	Committee	Activity

Study Chairs

Open Study #/Title	Investigator Name
Studies in Follow-up (Study #/Title)	Investigator Name

Report #3: U10 Participating Site Publications

Time Period (Calendar Dates): _____

Scientific Committee (or Administrative Committee)	Study #/Title	Publication (Title, Citation, Date)	Authorship (Author ¹ , Status ²)	Date Study Activated	Date Study Closed to Accrual	Date Final Analysis £	Additional Information

* Indicates Group-Led Intergroup study. No asterisk next to a study title indicates it is a Group-only study.
 ** Indicates Group-endorsed/Intergroup study.
 £ This date should correspond to that of the technical report produced by the Group Statistical Center with the expectation of the development of the primary manuscript draft.

¹ U10 Participating Site Author
² Status of U10 Participating Site Author on the Publication (e.g., Primary Author, Co-Author)

Report #4: U10 Participating Site (and Affiliate) Data Quality and Data Timeliness

U10 Participating Site Name: _____ (NCI Site ID #: _____; Group Site ID #: _____)
Time Period (Calendar Dates): _____

Year	Accrual	%Eligible Patients	<u>ADR/SAE Reporting % Timeliness</u>	<u>ADR/SAE Reporting % Accuracy</u>	% Follow-up Forms Submitted on Time	Date of Site Visit Audit	Result of Site Visit Audit
1	0	N/A	N/A	N/A	N/A		
2	12	0.0%	85.0%	88.0%	88.0%		
3	24	1.1%	90.0%	90.0%	90.0%	1/6/2002	Unacceptable
4	13	2.0%	98.2%	99.0%	99.0%	1/23/2003	Acceptable
5	19	1.0%	100.0%	98.0%	98.0%		
6	N/A	N/A	N/A	N/A	N/A		

Definitions:

- Accrual data is for Group studies (i.e., Group-only and Group-Led Intergroup studies).
- ADR = AdEERS; SAE = Serious Adverse Event.
- Accuracy percentage for ADR/SAE Reporting is the percent of ADR forms amended for a change in toxicity Grade or addition of a toxicity Grade 3+. For example, if the total number of ADR forms received during the time-period covered by the report is 1,000, and out of those 1,000 ADR reports, 45 of them required a change in toxicity Grade or the addition of a grade 3+ or higher AE, then the accuracy percentage would be calculated as: $((1000 - 45) / 1000) = 95.5\%$. Groups should provide the exact definition that they use to calculate their accuracy percentage with this report.
- Timeliness percentage for ADR/SAE Reporting is the percent of follow-up data submitted as of January 31 of the project year (December 31 for project year 5) with a 6-month grace period.
- Disciplinary actions imposed by the Group during the current funding period should be described and explained.

Attachment # 9: Suggested Format for Reporting On-Site Auditing Activities

The NCI-CTMB Guidelines for On-Site Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) require all Participating Sites to be audited at least once every 36 months. Each Group should conduct a comprehensive review of its membership and provide in its competing continuation and non-competing applications (i.e., Type 2 and Type 5 applications) an accounting for all Participating Sites in tabular format that includes the following information: (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 or projected month/year of the next proposed audit.

Participating Site Name (Inst NCI Code)	Site Type	Current Site Status	Status Date	Accrual _____*	Accrual _____*	Accrual _____*	Accrual Projected for upcoming year _____*	Date Last Audit	Date Next Proposed Audit
Name	Main Member	Active	2007						
Name	Affiliate	Active	2007						
Name	Affiliate	Terminated	2006						
Name	NIA	Active	2007						
Name	CCOP	Active	2007						
Name	CCOP component	Withdrawn	2006						
Name	CCOP component	Active	2007						
Name	Main Member	Active	2007						
Name	Main Member	Active	2007						

* Fill in accrual blank with year (this should cover the preceding 36 months, e.g. 2004, 2005, 2006)

Please Note: The actual "Date of Last Audit" for any Participating Site listed as "Active" on the Group roster should be provided, even if the Participating Site has not been audited in the past 3 years.

Attachment # 10: Suggested Outline for "Interim Review" Application (Budget/Research Plan)

Competing supplemental applications include "Interim Review" applications for Group components that were not completely funded at the time of initial Award (e.g., a specific Scientific Committee may have received only three years of funding based on peer review recommendation, while the Operations Center application received 6 years of funding). Interim Review applications should follow the basic format as that used for new, competing continuation applications, and the focus of the review of an Interim Review application is the same with the exception that the review is limited to those Group components that did not receive fundable scores at the time of initial review.

Budgetary Considerations for Interim Review Application

Since activities are usually highly integrated in a Group and may not be easily disaggregated across specific committees, it may be difficult to prepare budgets for both the Operations Center and the Statistical and Data Management Center (SDMC) that attempt to parse out the precise level of effort allocated to support only the activities of the specific committees under Interim Review. Therefore, in lieu of this, a Group may provide budgets in similar in format to the one suggested below in its Interim Review application. Such budgets should describe how specific activities of the committees under evaluation (i.e., support of chairpersons' salaries, support for travel, etc.) should be funded as well as the approximate resources that the Group devotes to these committees (broken down into key program areas such as data management, regulatory affairs, statistical support, etc.).

**Group Budget Support for Specific Committees
(Fiscal Year ____)**

	<u>Disease Site Committee</u>	<u>Other Scientific Committee</u>
<u>Operations Center Personnel</u>		
Administration	X.X FTE	X.X FTE
Regulatory Affairs	X.X FTE	X.X FTE
Communication	X.X FTE	X.X FTE
Clinical Coordination	X.X FTE	X.X FTE
Membership Affairs	X.X FTE	X.X FTE
Fiscal	X.X FTE	X.X FTE
<u>Biostatistical Center Personnel</u>		
Administration	X.X FTE	X.X FTE
Data Management	X.X FTE	X.X FTE
Clerical Support	X.X FTE	X.X FTE
Medical Review	X.X FTE	X.X FTE
Quality Assurance	X.X FTE	X.X FTE
Statistics	X.X FTE	X.X FTE
Applications Programming	X.X FTE	X.X FTE
Systems Support	X.X FTE	X.X FTE
<u>Hardware, Software, Equipment and Supplies</u>	(Prorated based on number of full-time equivalents)	(Prorated based on number of full-time equivalents)
<u>Additional Per-Case Reimbursement</u>	\$XXXX	Not Applicable

Outline of Research Plan for Interim Review Application

An example of a modified outline for the research plan to be submitted as part of the application for Interim Review is presented below. **This is an example only and may be modified per the specific needs of the committees or other Group component under review.** Since this is a PHS 398/SF424 application to the National Institutes of Health (NIH) in request for funds, all components contained in the Research Plan section of the PHS 398/SF424 must be included, including those listed under "Human Subjects Research" (e.g., "Protection of Human Subjects", "Inclusion of Women and Minorities", and "Inclusion of Children). The Group bibliography section should include only abstracts and manuscripts pertaining to the specific committees under review.

Although the PHS 398/SF424 instructions state that the Research Plan must be limited to 25 pages, the page limit for the Research Plan for an Interim Review application may be extended to 50 pages of text in **11-point Arial or Helvetica font size**, exclusive of tables, graphs, diagrams, and charts. The text in these 50 pages should include the Group's response to the previous review of its application. The page limit extension is provided in order to allow detailed discussion of the major research questions and activities relevant to the purview of the specific committees to be evaluated as part of the Interim Review. Even though the page limitation for the Research Plan may be extended to 50 pages, the Research Plan should be concise and only as long as necessary, and should emphasize how the Group's functions pertain to the specific committees and/or other Group components under review.

Proposed Outline of Research Plan

1. Introduction and Background (general information on background/reason for Interim Review and summary of the major activities taken to correct deficiencies identified)
2. Format and Content of Application (description of guidelines used to prepare the Interim Review application and explanation of format/content of the application)
3. Group Overview and History Relevant to this Application (this should be a brief overview just to emphasize how the specific committees under Interim Review fit into the overall organization of the Group)
4. Organizational Structure of the Group
 - 4.1 Structure of the Group
 - 4.2 Organization and structure of the Operations Center
 - 4.3 Role of Operations Center in protocol development, implementation, management
 - 4.4 Organization and responsibilities of the Statistics and Data Management Center (SDMC)
 - 4.5 Role of SDMC in protocol development, implementation, management)

All further descriptions of components of Group structure may be placed in an appendix

5. Response to the Critiques on the Specific Committees
 - Specific Committee # 1 (Disease Committee)
 - Specific Committee # 2 (Other Scientific Committee)
 - etc.
6. Specific Committee # 1 (Disease Committee)
 - History and significance of this committee's program
 - Development and implementation of research in this disease site
 - Interim report of progress achieved by this disease site committee
 - Current plans and future research directions for committee
7. Specific Committee # 2 (Other Scientific Committee)
 - Introduction of this committee's program and significance
 - Interaction with other committees in the Group
 - Active and recently closed trials which included this Scientific Committee's expertise
 - Protocols and concepts in development with this Scientific Committee's expertise as a component
 - Quality control and assurance activities
 - Current plans and future research activities for committee

8. Human Subjects Research
 - Investigator training in human subjects research
 - Human subjects involvement/characteristics
 - Sources of research material
 - Recruitment of human subjects/informed consent
 - Potential risks and protection against risk
 - Potential benefits of proposed research to subjects and others
9. Gender and Ethnic/Racial Minority Representation for the specific committees under Interim Review
 - Inclusion of women
 - Inclusion of minorities
 - Planned enrollment
10. Inclusion of Children
11. Data and Safety Monitoring Plan
12. Vertebral Animals
13. Literature Cited/References
14. Consortium/Contractual Arrangements
15. Consultants
16. Group Bibliography as it pertains to the committees and/or other Group components under Interim Review (Published manuscripts, abstracts, accepted/submitted manuscripts)
17. Patient Accrual for the specific committees under Interim Review (the application should show several prior years of accrual for these committees; at a minimum, the time interval should cover all accrual since the previous review)
18. Letters of Support and Collaboration

TABLES/FIGURES

APPENDICES

(Procedural details not directly related to the specific committees & Group components under Interim Review do not need to be put in the application, but can be included in the appendices).

Note: Sections devoted to Group function and description of the application (i.e., sections 1.0, 2.0, 3.0, and 4.0 in the outline above) should be kept brief and concise and should emphasize how the Group's functions pertain to the committees and/or other Group components under Interim Review.

Attachment #11: Cooperative Group Common Budget Outline

Common Budget Outline – Direct Costs¹

Operational Functions

Include both personnel costs and other costs in support of these functions

Exclude salaries for Group leadership – these are under the *Scientific Leadership* category.

1. Administrative
 - a. General
 - b. Financial Management
 - c. Contracting
 - d. Administrative Operations Database, Web and IT Support
2. Regulatory Functions (including IRB)
3. Protocol Development, Preparation, Revision and Management
4. Audits Organization (excluding travel)
5. Quality Assurance and Training (include all personnel and other costs except those related to Statistics and Data Management Functions)
6. Routine Office Costs associated with support of #'s 1 - 5 above, e.g.,
 - Supplies
 - Phone/Fax; Postage/Shipping; Printing, etc.
 - PCs/Workstations and Software
 - Furniture
 - Office Equipment (non-IT)
7. Chair's Office, if separate
8. Chair's Development Fund (primarily for pilot lab projects)
9. Discretionary Fund (for support of working groups, etc.)
10. Honoraria (but not travel) for consultants, speakers, etc.

Statistics and Data Management Functions

1. Data Management
 - a. Data Entry Personnel
 - b. Data Coordination Personnel
 - c. Equipment
 - d. Other (split out major categories)
2. Statistics
 - a. Statistical Personnel
 - b. Database and Informatics Personnel
 - i. Database
 - ii. Network & PC Support
 - iii. Website Maintenance & Helpdesk
 - iv. Applications Development
 - v. Other
 - c. Administrative personnel

¹ This format captures estimated costs associated with all CTEP-funded Group functions. No CCOP costs are included. The totals should correspond to the grant totals across the package of Group awards. Costs should not be accounted in more than one place. A total should be provided for each category and subcategory. Cost detail is optional below the lettered items (at the roman numeral level). Please use the Excel format provided on the CTEP website at [[Website Reference 42](#)]. Please do not alter existing categories; but feel free to footnote and to add additional categories below the lettered level. It is acceptable to show zero costs in categories.

- d. Major Hardware & Software
 - i. Capital Equipment
 - ii. Non-capital Equipment
 - iii. Data Processing Supplies
 - iv. Hardware Maintenance
 - v. Software Costs
 - vi. Network/Internet Support
 - vii. Voice Support
3. Routine Office Costs associated with support of #'s 1-2 above, e.g.
 - Supplies
 - Phone/Fax; Postage/Shipping; Printing, etc.
 - PCs/Workstations and Software
 - Furniture
 - Office Equipment (non-IT)
4. Quality Assurance (other than included in the category above under Operational functions)

Scientific Leadership (Personnel Costs)

1. Group Leadership
2. Scientific Committee Leadership (e.g., Disease Committee, Developmental Therapeutics Committee, etc.)
3. Protocol Chairs
4. Principal Investigators of Non-U10 Main Participating Site Members

Biological Specimen Banks, Laboratories and Other Core Support Services

1. Pathology Coordinating Office (including pathology reviews)
2. Biological Specimen Bank(s)
3. Laboratories
4. Other

Meeting Support Costs (Excluding Travel)

1. Semi-annual Group Meetings
2. Scientific and Administrative Meetings
3. Other

Staff and Consultant Travel

Excludes only travel paid for as an incidental component of a subcontract, and any travel paid for with Development or Discretionary Funds.

1. Travel Related to Operational Functions
2. Travel Related to Statistical and Data Management Functions
3. Committee Leadership Travel
4. Protocol Chairs' Travel
5. Travel for Personnel at Member Participating Sites (usually per algorithm)
6. Audit Travel
7. Consultant Travel
8. Other

Per-case Reimbursement Costs - Central Operations

1. Initial Registration Capitation
 - a. For Non-U10 Member Participating Sites
 - b. Supplements for U10s Beyond Established Annual Obligation
2. Correlative Studies Capitation
3. Pathology and Laboratory Reimbursement and Shipping
4. Annual Follow-up Capitation

Non-U10 Member Participating Site Costs (exclusive of per-case reimbursement and equipment costs)

1. Performance Site-based IT Equipment (e.g., Remote Data Capture Needs, PCs, Terminals, Personal Digital Assistants)
2. Other Costs

Member Participating Site U10 Costs (exclusive of those in above categories)

Exclude protocol and committee chair effort (these are under Scientific Leadership above) and exclude all travel.

1. Principal Investigator effort
2. Administrative Personnel effort
3. Routine Office Costs, e.g.
 - Supplies
 - Phone/Fax; Postage/Shipping; Printing, etc.
 - PCs/Workstations and Software
 - Furniture
 - Office Equipment (non-IT)
4. Per-Case Costs
 - a. Estimated Costs of Enrollment, including:
 - Physician Time
 - CRA (or equivalent) Time (at ~40 Enrollments per CRA)
 - IRB and Regulatory Costs
 - Research Pharmacy Costs
 - Audit Preparation
 - b. Per-Case Fee for Management of Affiliates

GRAND TOTAL FOR COOPERATIVE GROUP:

Attachment #12: Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies

The following early stopping guidelines for slowly-accruing phase 3 studies conducted under the NCI Clinical Trials Cooperative Group Program are stated in terms of the percentage of projected accrual during given quarter(s). For example, Quarter 5-6 accrual signifies the number of patients enrolled on trial during Quarters 5 and 6 after activation, divided by the number of patients that were projected to be enrolled during that time period based on the accrual rate specified in the protocol design.

These guidelines apply only to phase 3 trials that have not had a formal interim efficacy analysis presented to the Data and Safety Monitoring Board (DSMB) before the end of the 6th quarter from study activation.

These guidelines apply to all randomized phase 3 trials that were activated after April 1, 2004.

Guidelines:

If Quarter 5-6 accrual is:

≤ 20% of projected, then stop the trial

<50% and >20% of projected, then the study team is given six (6) months to improve accrual.

If the average accrual rate in Quarter 8 is below 50% then the trial will have to be amended to reflect actual accrual. The implications of this new accrual rate on study relevance and feasibility should be discussed in the proposed amendment.

Implementation

As soon as the Quarter 5 and 6 accrual figures become available, the Group's Statistics and Data Management Center will provide to the Group Chair and the responsible NCI Program Director the average accrual for Quarters 5 and 6 (as well as the projected accrual from the protocol). The Group Chair will either close the trial or notify the investigators that they have another six (6) months in which to improve accrual according to the guidelines described above.

For trials that are closed or amended, the Group will notify the Group Data and Safety Monitoring Boards (DSMBs) of the closure or amendment at their next regularly scheduled meeting. Group Chairs may consult with their DSMB in the early closure decision, if so desired. In the unusual circumstance that the Group Chair believes that the guidelines are inappropriate for the given trial, he or she will initiate a discussion with the responsible NCI Program Director to reach a joint decision concerning what to do about the trial.

Attachment #13: NCI Clinical Trials: Prioritization/Scientific Quality Initiative

Implementation Plan

The following document is the NCI-approved February 7, 2006 version of the initial implementation plan for the prioritization/scientific quality initiative proposed in the report of the NCI Clinical Trials Working Group (CTWG) to and accepted by the National Cancer Advisory Board in June 2005. This implementation plan is related to phase 3 clinical trials in cancer treatment and describes the general composition and working guidelines for disease-specific steering committees. The first disease site selected to be part of this initiative is the Gastrointestinal Cancer ("GI Steering Committee").

PRIORITIZATION/SCIENTIFIC QUALITY INITIATIVES

New Initiative 2: Establish a network of Scientific Steering Committees to address design and prioritization of phase III trials that leverages current Intergroup, Cooperative Group, SPORE, and Cancer Center structures and involves the broad oncology community.

The CTWG recommended the following elements for the implementation plan. This initiative was deliberated and approved by the National Cancer Advisory Board.

1. Overall Approach

The implementation plan is designed to leverage existing Intergroup, Cooperative Group, Specialized Programs of Research Excellence (SPORE), and Cancer Center structures by creating Scientific Steering Committees for each major disease area as well as for pediatric oncology and symptom management/supportive care. All phase III concepts and protocols funded by the National Cancer Institute (NCI), regardless of mechanism (i.e., Cooperative Group, SPORE, Cancer Center, P01, etc.), will be prioritized through this process. The Scientific Steering Committees are designed to provide robust analysis of proposed concepts and facilitate the sharing of ideas among a broad range of clinical investigators, basic and translational scientists, NCI staff, community oncologists, and patient advocates in the development of those concepts.

2. Scientific Steering Committee Participants

- a. Size. Each Scientific Steering Committee will have approximately 10-25 participants depending on the complexity of the disease addressed and the number of Cooperative Groups or other multi-site networks with active programs for the disease.
- b. Composition. Each Scientific Steering Committee will be constituted such that the non-NCI participation is maintained as follows:
 - At least 50% clinical investigators from the Cooperative Groups or other NCI-funded multi-site networks.
 - 25% investigators from relevant SPOREs, P01s, and R01s, including basic or translational scientists.
 - Approximately 10% community oncologists.
 - Approximately 10% patient advocates.
 - At least one extramural biostatistician.
 - If relevant to the disease in question, experts in surgical oncology, radiation oncology, pediatric oncology, radiology, and transplantation will be added unless these specialties are already represented by investigators from the Cooperative Groups, SPOREs, P01s, etc.

- c. Participants. Each Scientific Steering Committee will have the following categories of participants.
- Cooperative Group/Multi-Site Network Investigators
 - i. Each Cooperative Group that has an active Disease Committee will be represented by the Disease Committee Chair. The Cooperative Group Chair and the Disease Committee Chair will select an alternate representative who will be invited to all face-to-face Committee meetings and will represent the Group in the absence of the Disease Committee Chair. The Cooperative Group representatives on the Scientific Steering Committee will determine if the alternates are invited as observers to phone or on-line meetings. If a given Disease Committee has two co-chairs, no alternate will be needed. The two co-chairs will determine on a meeting-by-meeting basis which co-chair will serve as the official representative and which will serve as the observer.
 - ii. For diseases with non-Cooperative Group, NCI-funded multi-site networks (e.g., neuro-oncology and bone marrow transplant), each network would also select a clinical investigator to serve on the Committee and an alternate.
 - iii. The Pediatric Oncology Committee will include participants selected by the Children's Oncology Group and the Pediatric Brain Tumor Consortium. Other pediatric oncology investigators will be invited to participate to achieve the >50% representation for clinical investigators.
 - iv. The Symptom Management Committee will include Community Clinical Oncology Program (CCOP) clinical investigators nominated by the CCOP PIs or the Cooperative Groups. At least 50% of the CCOP representatives should be CCOP PI nominees.
 - NCI Staff Liaisons
 - i. Chief, Clinical Investigations Branch (CIB)
 - ii. Head, Therapeutic Disease Area, CIB; for the Symptom Management Committee, this representative will be from the Division of Cancer Prevention (DCP).
 - iii. Biostatistician from the Biostatistics Research Branch appointed by the Director, Division of Cancer Treatment and Diagnosis (DCTD).
 - iv. Senior investigator from the relevant NCI intramural branch and/or laboratory appointed by the Deputy Director, Clinical Research, Center for Cancer Research.
 - SPORE, P01 and R01 investigators
 - i. The number of investigators representing each of the funding mechanisms will be decided by the clinical investigators on the Scientific Steering Committee in consultation with NCI staff. One factor will be the relative funding distribution for the relevant disease. There will be at least one representative from each funding mechanism. Representatives will include basic and translational scientists as well as clinical investigators conducting phase II trials.
 - ii. SPORE representatives will be selected by consensus of the relevant SPORE PIs. In cases where pre-existing Intergroup structures already include SPORE representatives, the Disease Committee Chair participants in consultation with NCI staff may decide to retain those individuals as the SPORE representatives.
 - iii. P01 and R01 representatives will be selected by the Disease Committee Chair participants in consultation with NCI staff based on nominations solicited from the Directors of NCI-designated Cancer Centers.
 - iv. Basic or translational scientists should represent at least 10% of the overall Scientific Steering Committee participation.
- d. Additional Participants. The following participants will be selected by the clinical investigators on the Scientific Steering Committee in consultation with NCI staff.
- Community Oncologists
 - i. One representative on each Scientific Steering Committee. One or more alternates will be named to ensure that at least one community oncologist is in attendance at each meeting.
 - ii. Physicians active in NCI-sponsored clinical trials in relevant disease (i.e., members of CCOPs or Cooperative Group affiliates).
 - iii. Selected based on recommendations from CCOPs, Cooperative Groups, and Cooperative Group affiliates.

- Patient Advocates
 - i. Two representatives on each Scientific Steering Committee. The Committee will ensure that at least one patient advocate is in attendance at each meeting.
 - ii. Selected from the Consumer Advocates in Research and Related Activities (CARRA) registry or based on recommendations from Disease Committees and patient advocacy organizations.
 - Extramural biostatistician selected based on nominations from Cooperative Groups. An alternate will be appointed to serve in the absence of the primary participant and will be invited to other meetings as described above for Disease Committee Chair alternates.
 - Representatives of the following specialties will be invited to participate if relevant and not included in the participants representing the Cooperative Groups, SPOREs, etc. Candidate representatives will be nominated by the Cooperative Groups.
 - i. Radiation oncologist
 - ii. Surgical oncologist
 - iii. Pediatric oncologist (to address needs of adolescents and young adults)
 - iv. Radiologist/imaging expert
 - v. Transplant expert
 - When requested by the Scientific Steering Committee, NCI may provide input concerning the scientific or consumer expertise on the Scientific Steering Committees.
- e. Subject Matter Experts.
- As needed for consideration of individual concepts, subject matter experts will be included to provide specific expertise. Scientific Steering Committee participants, staff from CIB or the Coordinating Center for Clinical Trials (CCCT), or the Cooperative Group or PI submitting the concept may request inclusion of specific subject matter experts.
 - Subject matter experts might include the following:
 - i. NCI staff from the Investigational Drug Branch (IDB), the Cancer Diagnosis Program, the Radiation Oncology Sciences Program, the Cancer Imaging Program, the Center for Cancer Research, the Organ Systems Branch, etc.
 - ii. Correlative science, quality of life, symptom management or healthcare economics experts.
 - iii. Representatives from industry, CMS, FDA, the IDSC or other experts in early therapeutics development.
- f. Invited Observers. The leadership of all NCI Divisions, Centers, Offices and Programs involved with clinical trials (i.e., CTEP, IDB, DTP, CDP, CIP, BRB, DCP, DCCPS, CCR, OTCR, NCICB, OC, OESI, etc.) and the Cooperative Group Chairs will be invited to attend Scientific Steering Committee meetings and will receive copies of agendas and minutes.

3. Scientific Steering Committee Responsibilities

a. State of the Science Meetings

- The Scientific Steering Committees will organize periodic, 1-3 day State-of-the-Science Meetings to identify critical questions and unmet needs, to prioritize key strategies and future concepts to test, and to facilitate innovation. Meetings will be informal and certain information will be kept confidential, upon request, to encourage discussion of newly-breaking results and ideas, and facilitate brainstorming. Status and results of selected phase II trials would be a special feature at each meeting.
- Frequency and length of meeting will vary with disease site and specific agenda items. A Scientific Steering Committee participant or other recognized expert will be chosen by the Committee to chair each meeting. The CIB Therapeutic Disease Head will assist the Chair in conduct and organization of the meeting, including agenda development and speaker selection.
- Attendees will include a broad range of clinical, basic, and translational investigators from Cooperative Groups, CCOPs, SPOREs, Cancer Centers, NCI, FDA and industry whose work is relevant to the

specific disease, as well as community oncologists and other oncology health care providers, patient advocates, and senior strategic thinkers from throughout oncology.

- Agenda will be set by the Scientific Steering Committee, but all attendees will be invited and encouraged to present new concepts and data not on the formal agenda.
- Based on input from the State-of-the-Science Meeting, the Scientific Steering Committee will develop 1-3 key strategic priorities for future phase III trials, including both near term (6-12 months) and long term (18-36 months) initiatives, and disseminate these priorities to the relevant oncology communities.

b. Phase III Concept Development, Evaluation, and Prioritization

- The Scientific Steering Committees will develop phase III concepts from an elemental stage, as well as evaluate and refine ideas for phase III trials developed by Cooperative Group Disease Committees or investigators from Cancer Centers, SPOREs, P01s, etc. Based on these deliberations, the Committee will work to achieve consensus on which concepts should be submitted to NCI for approval.
- Concepts proposed by the Scientific Steering Committees will be submitted to NCI through the lead Cooperative Group for that concept. If the concept originated outside the Cooperative Group structure, the originating investigator will serve as the Principal Investigator (PI), and the Scientific Steering Committee will select a Cooperative Group partner that will appoint a co-PI for the concept.
- Given the active participation of NCI staff in Committee deliberations, it is expected that the majority of concepts will be reviewed and approved by the appropriate NCI program staff using an expedited process.
- If Committee deliberations indicate significant scientific or clinical differences of opinion concerning the concept, NCI staff could conduct a formal scientific quality review including extramural experts.
- A concept could not be rejected by NCI program staff without a formal scientific quality review.
- Therapeutic trial concepts recommended by CIB for activation will, as necessary, be reviewed by the Associate Director, Cancer Therapy Evaluation Program (CTEP), and the Director, DCTD, from a broad programmatic and budget perspective, including prioritization across diseases. The Director, DCP, will perform this same review for symptom management trials. Certain recommended concepts may not be approved for activation based on this review.
- Once the concept is approved by NCI, a protocol will be prepared by the lead Cooperative Group jointly with NCI using a rapid protocol assembly process. The Scientific Steering Committee will be given the opportunity to comment on the protocol before NCI provides its approval.

c. Monitoring of Phase III Trial Conduct

The Scientific Steering Committees will monitor implementation of national phase III trials through the Cooperative Group and Cancer Trials Support Unit (CTSU) structures and periodically evaluate trial status in terms of accrual, unforeseen implementation issues, etc.

- d. If pre-existing Intergroup practices include discussion or prioritization of Cooperative Group or other phase II trials, those practices will be continued by the Scientific Steering Committee.

4. Scientific Steering Committee Structure

a. Leadership.

- Scientific Steering Committees will be chaired preferably by a former Cooperative Group Disease Committee Chair or other well-recognized expert in the disease. The Chair will be selected by the non-NCI participants in the Steering Committee based on nominations from Cooperative Groups and Steering Committee participants.
- Large Committees might decide to select a Chair and Chair-Elect with the Chair-Elect succeeding to the Chair position and a new Chair-Elect selected.
- Nominations for Chair or Chair-Elect will be solicited from the Cooperative Groups and Steering Committee participants. If more than two individuals are nominated, the Steering Committee will implement a run-off style voting process.
- The Director, DCTD, will meet with the Chair (or Chair-Elect) candidates prior to election to ensure that they understand the scope of responsibilities and are able to commit the necessary time.

b. Task Forces.

- In large diverse diseases such as gastrointestinal (GI) cancer, the Steering Committee might decide to form individual Task Forces for specific disease subcategories.
- Task Forces would propose topics for State-of-the-Science-Meetings and develop, evaluate, and prioritize phase III concepts.
- Concepts recommended by the Task Forces would then be evaluated by the full Committee prior to submission to NCI.
- Task Forces might also be formed to conduct the following
 - i. Organization of State-of-the-Science Meetings.
 - ii. Development of specific phase III concepts.
 - iii. Evaluation of phase III concepts submitted by Cooperative Groups or individual investigators from SPOREs, Cancer Centers, P01s, etc.
 - iv. Monitoring of ongoing phase III trials.
 - v. Organization of annual community oncologist and patient advocate Focus Groups (see New Initiative 3).Task Force work would be subject to review by the full Steering Committee.
- Task Forces may include Steering Committee participants plus other subject matter experts, as needed, and would be selected by procedures established by each Steering Committee.
- Each Task Force would be chaired by a non-NCI Steering Committee participant or an alternate selected by the non-NCI Steering Committee participants. At its option, the Steering Committee may also appoint a Vice-Chair who is not a Steering Committee participant or alternate.

c. Community Oncologist and Patient Advocate Focus Groups.
(see New Initiative 3)

5. Operating Policies and Procedures

Each Scientific Steering Committee will develop operating policies and procedures in consultation with CCCT and CTEP/CIB or DCP staff. CCCT and CTEP/CIB or DCP staff will develop a draft set of operating policies and procedures for their respective Scientific Steering Committees to use as a starting point to help assure effectiveness and consistency across diseases. The policies and procedures would address the following:

- a. Required elements for phase III concept proposals based on the submission form that CTEP currently uses for this purpose.
- b. Process for the development of concepts by the Scientific Steering Committee or its Task Forces.
- c. Criteria and process for evaluation and prioritization of concepts, including novelty, lack of duplication, strength of proposed clinical outcomes, trial design attractive to patients and treating physicians, strength of correlative science, cost/benefit, relevance to disease specific strategic priorities, etc.
- d. Schedule for concept submission, turn-around time for a decision or request for additional information in response to a concept submission, etc.
- e. Decision-making process for determining which concepts to submit to NCI.
- f. Process for tracking and monitoring ongoing phase III trials.
- g. Procedures for selection of participants and Chair as well as policies on length of service.
- h. Process for establishing participants and leadership of Task Forces.
- i. Mechanisms for assisting the Chair in management and administration of the Committee, such as appointment of a Coordination or Executive Team.

6. Scientific Steering Committee Roles and Responsibilities.

a. Chair.

- Conduct meetings and establish agendas.
- Review submitted ideas, concepts, and issues and discuss them with the CIB Therapeutic Disease Head prior to inclusion in meeting agenda.

- Form Task Forces based on operating procedure developed by the Steering Committee.
 - Ensure that concepts are developed, evaluated, and prioritized in a timely and scientifically rigorous manner.
 - Guide the development of strategic priorities based on the State-of-the-Science meetings.
 - Ensure that recommended trials reflect the strategic priorities.
- b. CIB Therapeutic Disease Head.
- Assist Chair in conduct of meetings and development of meeting agenda.
 - Review submitted ideas, concepts, and issues and discuss them with the Chair prior to inclusion in meeting agenda.
 - Prepare written comments on each concept developed or considered by the Committee to ensure the Committee is aware of NCI's position.
 - Assist in preparation of a written summary of deliberations concerning each concept and the decisions taken for review by the Chair and Committee.
 - Prepare a description of key strategic priorities resulting from the State-of-the-Science meetings for review by the Chair and Committee.
 - Serve as the NCI representative on all Task Forces.
 - Serve as liaison for CTEP and DCTD concerning Committee deliberations.
- c. CCCT Project Manager¹ (Designated Federal Official).
- Organize and staff Steering Committee and Task Force meetings.
 - Coordinate preparation and distribution of agendas, minutes, and other meeting materials.
 - Develop operating policies and procedures for review by Chair and Committee participants.
 - Coordinate Committee, Task Force, and Chair selection processes.
 - Develop and implement procedures and tools to facilitate concept submission, evaluation, and feedback. Assist CIB Therapeutic Disease Head in reviewing concepts, ideas, and other agenda items and drafting summaries of Scientific Steering Committee and State-of-the-Science meetings.

7. Conflict of Interest/Confidentiality

Policies and procedures will be established for managing conflicts of interest and maintaining confidentiality of non-public information with regard to Scientific Steering Committee discussions. These policies and procedures will apply to all Scientific Steering Committee participants, as well as all participants in Task Forces.

- a. Scientific Conflict of Interest. Potential scientific conflicts of interest will be managed as follows:
- The Scientific Steering Committee participants include many individuals other than investigators from potential phase III sites, including SPORE, P01, and R01 investigators as well as community oncologists, patient advocates, and NCI staff.
 - All Cooperative Group investigators specializing in a given disease or subspecialty would have an opportunity to participate fully in any phase III trial activated, and NCI policies will be modified to reward such collaborative participation.
 - Steering Committee discussions will be held under confidentiality, with open disclosure of relevant conflicts of interest and attribution of comments.
 - Conflict of interest procedures will be drafted such that any Steering Committee or Task Force participant, who has a significant conflict of interest with regard to a specific phase III concept or other issue, will be expected to disclose that conflict and recuse themselves from the discussion. If any participant believes that another participant has a potential conflict that has not been disclosed, the concern should be brought to the attention of the Chair. The Chair will decide whether recusal is appropriate or will ask the Steering Committee participants to make that decision.
 - The Chair will work with CIB and CCCT staff to establish written policies and procedures for managing scientific conflict of interest.
 - The policies and procedures should be in place by March, 2006.

¹ All activities conducted in coordination with Chair and CIB Therapeutic Disease Head.

b. Financial Conflict of Interest

- The Chair will work with the NCI staff liaisons, CCCT staff, and NIH legal counsel to develop a guidance document based on the current NIH and FDA policies for managing financial conflicts of interest.
- A draft guidance document should be completed by March, 2006.

c. Confidentiality

- All participants in Steering Committee or Task Force discussions will sign written confidentiality agreements covering all non-public information of which they become aware during such discussions.
- The Chair will work with the NCI staff liaisons, CCCT staff, and NIH legal counsel to develop either a comprehensive agreement covering all Steering Committees associated confidential information or a confidentiality provision to be included in the conflict of interest documents signed by each participant covering specific concepts.
- The draft confidentiality agreement or provision should be available for review by the participants' parent institutions by March, 2006.

8. Arbitration

Any disagreement that arises on scientific matters between individual investigators and the Scientific Steering Committee, or the Scientific Steering Committee and the NCI, may be brought to arbitration. The arbitration panel will be composed of three members – one selected by each party to the disagreement and the third member selected by mutual agreement between the two parties. If the disagreement is between the Scientific Steering Committee and the NCI, the NCI participants in the Committee will not be involved in selecting the panel member representing the Committee.

9. Scientific Steering Committee Organization and Operation

a. Meeting Schedule.

- The meeting location will be determined by the Scientific Steering Committee in consultation with the CIB Therapeutic Disease Head, Designated Federal Official (DFO), and CCCT staff.
- Each Scientific Steering Committee will meet face-to-face at least three times annually. Meetings will be coordinated, whenever possible, with existing scientific meetings or the periodic State-of-the-Science meetings. Additional meetings will be held by teleconference or web meeting format.
- Task Forces will meet as needed to address specific concepts, protocols or other topics either face-to-face or by teleconference/web meeting format.

b. Time Commitment.

- Scientific Steering Committee and Task Force participants are expected to commit approximately 10-15 days per year.
- The Scientific Steering Committee Chair is expected to commit approximately 20 days per year.

c. Staff Support.

Meeting organization and materials, preparation of summary minutes of Scientific Steering Committee and Task Force meetings, etc. will be provided through the CCCT.

Timeline: Implementation of the Scientific Steering Committees will be staggered with the process being implemented for two disease areas in each of the first two years (FY06 and FY07). Since this represents a significant restructuring of the process for designing phase III trials, a formal evaluation will be conducted at the end of FY07. If the initial implementation is judged successful, the process will be extended to all disease areas by September 2010.

New Initiative 3: Enhance patient advocate and community oncologist involvement in clinical trial design and prioritization through representation on Steering Committees and creation of patient advocate and community oncologist focus groups.

1. Representation on Scientific Steering Committees (see New Initiative 2)

- a. Each Scientific Steering Committee will have one community oncologist and two patient advocate participants and will ensure that at least one representative of each group is in attendance at each meeting.
- b. Community oncologist representatives will be physicians actively participating in NCI funded clinical trials such as members of CCOPs and Cooperative Group affiliates. They will be selected based on recommendations from CCOPs or Cooperative Groups and their affiliates.
- c. Patient advocate representatives will be selected from the Consumer Advocates in Research and Related Activities (CARRA) registry or based on recommendations from the Disease Committees of Cooperative Groups and patient advocacy organizations. All patient advocate representatives should be trained and knowledgeable prior to participation. Prospective candidates will be invited to a Steering Committee meeting to meet other participants and participate in the discussions prior to final appointment.
- d. If recommended by at least two Steering Committee participants, the Steering Committee will ask Focus Group participants (see below) to provide broader community oncologist and/or patient input to design of a specific trial. This consultation will utilize and build on the relationships and knowledge gained from the annual Focus Group meetings and could be easily arranged by teleconference or web meeting format. The goal is to provide the necessary feedback over a 1-2 week time period so as to not delay decision making on a trial.

2. Focus Groups

- a. Each Scientific Steering Committee will convene annual patient and community oncologist Focus Groups to solicit general input and promote efficient trial accrual.
- b. The patient Focus Groups will be conducted in collaboration with advocacy organizations, ideally taking advantage of existing meetings that bring knowledgeable constituents together.
- c. The community oncologist Focus Groups will be conducted in association with meetings of American Society of Clinical Oncology (ASCO), Association of Community Cancer Centers (ACCC), or the CCOPs.
- d. Focus Group agendas would include three topics.
 - Broad, open-ended discussion of current issues facing patients and community physicians, respectively, when making treatment decisions.
 - Important treatment questions that could or should be answered by trials.
 - Presentation and discussion of clinical trial designs currently under consideration and future trial designs proposed to answer new questions.
- e. The community oncologist and patient advocate Scientific Steering Committee participants will chair the respective Focus Groups and organize them in cooperation with a Task Force named for that purpose with staff support from the CCCT.

3. Community Oncologist/Patient Advocate Steering Committees

- a. Community Oncologist and Patient Advocate Steering Committees will be established to provide input regarding the involvement of community oncologists and patient advocates in the NCI clinical trials enterprise.

- b. Each Steering Committee will meet annually to discuss issues concerning clinical trials across disease states, share best practices, and identify areas for improvement.
- c. Steering Committee participants will include the community oncologist and patient advocate representatives on the various Scientific Steering Committees as well as, if needed, additional participants representing CCOPs and patient advocacy organizations. The CIB Therapeutic Disease Head will serve as the NCI representative on the Community Oncologist Steering Committee.
- d. Participants in the Community Oncologist and Patient Advocate Steering Committees who are not participants in the Scientific Steering Committees will be selected by the community oncologists and patient advocates, respectively, who are Scientific Steering Committee participants.
- e. The Steering Committees will each select a Chair by a process and for a period determined by the Steering Committee.
- f. The Steering Committee meetings will be organized and staffed by the CCCT.

Timeline: Focus Groups will be convened during the first year that a Scientific Steering Committee is in operation for the relevant disease. Community oncologist and patient advocate Steering Committees will be established during FY07.

Attachment #14: List of Abbreviations

ABBREVIATION	FULL TERM	ABBREVIATION	FULL TERM
AD	Associate Director, CTEP, DCTD	LOI	Letter of Intent
AdEERS	Adverse Event Expedited Reporting System	NCAB	National Cancer Advisory Board
ARA	Awaiting Receipt of Application	NCI	National Cancer Institute
BRB	Biometric Research Branch (in DCTD)	NIH	National Institutes of Health
CBO	Common Budget Outline	OD	Office of the Director at the NCI
CCOP	Community Clinical Oncology Program (in DCP)	OGA	Office of Grants Administration
CDE	Common Data Elements	OHRP	Office for Human Research Protections
CDP	Cancer Diagnosis Program (in DCTD)	ORI	Office of Research Integrity
CDUS	Clinical Data Update System	PHS	Public Health Service
CFR	Code of Federal Regulations	PI	Principal Investigator
CIB	Clinical Investigations Branch (in CTEP)	PIO	Protocol and Information Office (in CTEP)
CIP	Cancer Imaging Program (in DCTD)	PMB	Pharmaceutical Management Branch (in CTEP)
CIRB	Central Institutional Review Board at NCI	PRC	Protocol Review Committee (in CTEP)
CRA	Clinical Research Associate	RAB	Regulatory Affairs Branch (in CTEP)
CRADA	Cooperative Research and Development Agreement	RPC	Radiological Physics Center
CSA	Clinical Supply Agreement	RRP	Radiation Research Program (in DCTD)
CSR	Center for Scientific Research (at NIH)	RSS	Regulatory Support System (in CTSU)
CTA	Clinical Trial Agreement	SDMC	Statistics and Data Management Center
CTCAE	Common Toxicity Criteria for Adverse Events	SOP	Standard Operating Procedure
CTEP	Cancer Therapy Evaluation Program (in DCTD)	SPORE	Specialized Programs of Research Excellence (in OD)
CTMB	Clinical Trials Monitoring Branch (in CTEP)	SRA	Scientific Review Administrator
CTSU	Cancer Trials Support Unit	QARC	Quality Assurance Review Center
CTWG	Clinical Trials Working Group	URL	Uniform Resource Locator (internet address of resource)
DAR	Drug Accountability Record		
DCP	Division of Cancer Prevention		
DCTD	Division of Cancer Treatment and Diagnosis		
DEA	Division of Extramural Activities		
DHHS	Department of Health and Human Services		
DMC	Data Monitoring Committee		
DRB	Diagnostics Evaluation Branch (in CDP)		
DSMB	Data and Safety Monitoring Board		
FDA	Food and Drug Administration		
FWA	Federalwide Assurance (for OHRP)		
GCP	Good Clinical Practice		
HIPAA	Health Insurance Portability and Accountability Act		
IDB	Investigational Drug Branch (in CTEP)		
IND	Investigational New Drug Application		
IRB	Institutional Review Board		
IRG	Initial Review Group		

Attachment #15: Website References

Website References in order of their appearance in the text of these Guidelines

[Website Reference 1] - <http://www.nci.nih.gov/aboutnci/organization/>
Website to Guide Readers to Information on Other NCI Divisions/Branches

[Website Reference 2] - <http://www.fda.gov/oc/gcp/default.htm>
Good Clinical Practice in FDA-Regulated Clinical Trials

[Website Reference 3] - <http://www.ctsu.org>
Cancer Trials Support Unit (CTSU) Website

[Website Reference 4] - <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-017.html>
Cancer Diagnosis Program's Request for an Application (RFA) on Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials

[Website Reference 5] - <http://www.cancerdiagnosis.nci.nih.gov/>
Cancer Diagnosis Program's Website

[Website Reference 6] - <http://ctep.cancer.gov/investigatorResources/ctcgp%5Fguidelines/>
NCI Clinical Trials Cooperative Group Program Guidelines

[Website Reference 7] - http://ctep.cancer.gov/investigatorResources/default.htm#investigators_handbook
Investigator's Handbook

[Website Reference 8] - http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm
NCI-CTMB Guidelines for On-site Monitoring of Clinical Trials and CCOP Research Bases and the Cancer Trials Support Unit (CTSU)

[Website Reference 9] - http://ctep.cancer.gov/protocolDevelopment/default.htm#lois_concepts
Letter of Intent (LOI) Template Under Protocol Development

[Website Reference 10] - http://ctep.cancer.gov/protocolDevelopment/default.htm#lois_concepts
Concept Template Under Protocol Development

[Website Reference 11] - http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations
Intellectual Property Option Under Guidelines for Collaborations with Industry

[Website Reference 12] - <https://webapps.ctep.nci.nih.gov/ctmbais/ctmbaislogin.startup>
CTMB Auditing Information System (CTMB-AIS)

[Website Reference 13] - <http://www.ncicirb.org>
NCI Central IRB Website

[Website Reference 14(a)] - <http://www.hhs.gov/ohrp/>
Office for Human Research Protections Website

[Website Reference 14(b)] - <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>
Specific Information on the OHRP Website Related to Federal Regulations (45CFR46) on Human Subjects Protection

[Website Reference 15] - http://grants.nih.gov/grants/funding/women_min/women_min.htm
NIH Policies on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects – Policy Implementation

[Website Reference 16(a)] - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>
NIH Guide Notice on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (Amendment October 2001).

[Website Reference 16(b)] - http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm
NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001 (COMPLETE COPY OF UPDATED GUIDELINES)

[Website Reference 17] - <http://grants.nih.gov/grants/funding/children/children.htm>
NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects – Policy Implementation

[Website Reference 18] - http://ctep.cancer.gov/protocolDevelopment/default.htm#cde_data_pol_cdus
NCI Cooperative Group Data Monitoring Committee Policy (for Phase 3 Trials) Under Protocol Development

[Website Reference 19] - <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>
NIH Policy for Data and Safety Monitoring

[Website Reference 20] - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
Further NIH Guidance on Data and Safety Monitoring for Phase 1 and Phase 2 trials

[Website Reference 21] - <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines>
Essential Elements of Data and Safety Monitoring Plans for Clinical Trials Funded by the NCI

[Website Reference 22] - http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm
Adverse Event Expedited Reporting System (AdEERS)

[Website Reference 23] - <http://www.cancerdiagnosis.nci.nih.gov/assessment/progress/markerdev.htm>
Diagnostics Evaluation Branch (DRB) of the Cancer Diagnosis Program (CDP) Program for the Assessment of Clinical Cancer Tests (PACCT) – Clinical Tumor Marker Study Guidelines

[Website Reference 24] - http://ctep.cancer.gov/protocolDevelopment/default.htm#cde_data_pol_cdus
Information on Common Data Elements (CDE) Approved for Use in CTEP-sponsored Clinical Trials

[Website Reference 25] - <http://ctep.cancer.gov/protocolDevelopment/default.htm#monitoring>
Information on Study Monitoring of Cooperative Group Trials

[Website Reference 26] - http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers
NCI's Common Terminology Criteria for Adverse Events (CTCAE)

[Website Reference 27(a)] - <http://grants.nih.gov/grants/funding/phs398/phs398.html>
PHS 398 Grant Application

[Website Reference 27(b)] - <http://grants.nih.gov/grants/funding/424/index.htm>
SF424 (R&R) Application and Electronic Submission Information

[Website Reference 28] - <http://grants.nih.gov/grants/guide/notice-files/NOT-CA-02-002.html>
Information on Applications Directed to the NCI

[Website Reference 29] - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-012.html>
Information on Mail Addressed to the NIH

[Website Reference 30] - http://grants.nih.gov/grants/policy/nihgps_2001/
NIH Grants Policy Statement

[Website Reference 31] - <http://www.nih.gov/grants/guide/notice-files/not98-024.html>
NIH Policy & Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (3/6/98)

[Website Reference 32] - <http://deainfo.nci.nih.gov/advisory/irg.htm>
Initial Review Group (IRG) Website and Roster of Members of Subcommittee H - Clinical Groups

[Website Reference 33] - <http://grants.nih.gov/grants/funding/2590/2590.htm>
PHS 2590 Non-Competing Grant Progress Report

[Website Reference 34] - http://grants.nih.gov/grants/policy/data_sharing
NIH Data Sharing Policy

[Website Reference 35] - http://ctep.cancer.gov/protocolDevelopment/default.htm#cde_data_pol_cdus
NCI Clinical Trials Cooperative Group Program Data Sharing Policy Under Protocol Development

[[Website Reference 36](http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies)] - http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies
NCI Clinical Trials Cooperative Group Program Guidelines for the Development, Conduct and Analysis of Clinical Trials with International Collaborating Institutions Under Investigator Resources

[[Website Reference 37](http://rpc.mdanderson.org/rpc/)] - <http://rpc.mdanderson.org/rpc/>
Radiological Physics Center (RPC) Website

[[Website Reference 38](http://www.qarc.org/)] - <http://www.qarc.org/>
Quality Assurance Review Center (QARC) Website

[[Website Reference 39](http://integratedtrials.nci.nih.gov/ict/)] - <http://integratedtrials.nci.nih.gov/ict/>
Information on the Clinical Trials Working Group (CTWG) initiative and its final report to the National Cancer Advisory Board in June 2005, entitled “Restructuring the National Cancer Clinical Trials Enterprise”

[[Website Reference 40](http://deainfo.nci.nih.gov/grantspolicies/index.htm)] - <http://deainfo.nci.nih.gov/grantspolicies/index.htm>
NCI Clinical Trials Policy

[[Website Reference 41](http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies)] - http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies
CTEP Conflict of Interest Policy for Cooperative Group Phase 3 Clinical Trials Under Investigator Resources

[[Website Reference 42](http://ctep.cancer.gov/protocolDevelopment/default.htm#protocol_development)] - http://ctep.cancer.gov/protocolDevelopment/default.htm#protocol_development
Cooperative Group Common Budget Outline in MS Excel File Format Under Protocol Development Helps

[[Website Reference 43](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-053.html)] - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-053.html>
Guidance Document on Inclusion of Manuscripts/Publications in Appendix Material with NIH/NCI Grant Applications

[[Website Reference 44](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html)] - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>
Required Education on the Protection of Human Subject Participants

[[Website Reference 45](http://www.nihms.nih.gov/)] - <http://www.nihms.nih.gov/>
NIH Manuscript Submission System

[[Website Reference 46](http://publicaccess.nih.gov/)] - <http://publicaccess.nih.gov/>
NIH Public Access Policy

[[Website Reference 47](http://publicaccess.nih.gov/FAQ.htm)] - <http://publicaccess.nih.gov/FAQ.htm>
NIH Public Access Policy – FAQ

Other Federal Citations for NIH Grants/Cooperative Agreements Involved in Human Subjects Research & Their Corresponding Website References

Access to Research of Data through the Freedom of Information Act

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are: (1) first produced in a project that is supported in whole or in part with Federal funds; and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this funding opportunity in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget section of the application. In addition, applicants should think about how to structure informed consent statement and other human subjects procedures given the potential for wider use of data collected under this award.

Sharing of Model Organisms

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Standards for Privacy of Individually Identifiable Health Information

This Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

Healthy People 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. The funding opportunity announcement (FOA) for this cooperative agreement is related to one or more of the priority areas. Potential applicants can obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

Authority and Regulations

This program is described in the Catalogue of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency Review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service (PHS) Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All

awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American People.

Loan Repayment Program

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The Loan Repayment Program (LRP) is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40-hour week) for 2 years to the research. For further information, please see <http://www.lrp.nih.gov/>.