NATIONAL CANCER INSTITUTE

NATIONAL CLINICAL TRIALS NETWORK PROGRAM GUIDELINES

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

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Part 1: Overview of the NCTN Program

I. Introduction

A. Purpose and Content of Guidelines

These Guidelines for the National Cancer Institute (NCI) **N**ational **C**linical **T**rials **N**etwork (NCTN) have been developed by staff of the Division of Cancer Treatment and Diagnosis (DCTD), NCI, in consultation with staff of the Division of Cancer Prevention (DCP), 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 program executed by an integrated Network of Groups conducting multi-disciplinary, comprehensive, clinical treatment and advanced imaging trials across a broad range of diseases and diverse patient populations, especially definitive, late phase, multi-institutional clinical trials.

This Guidelines document is divided into four parts as described below:

- **Part 1 – Overview of the NCTN Program**
  This part describes the NCI National Clinical Trials Network (NCTN) Program and its policies and procedures, including the Terms and Conditions of Award.

- **Part 2 – Guidelines for Submission of New Applications & Description of Review Process**
  This part describes the application, budgetary issues, and peer review processes for new applications.

- **Part 3 – Guidelines for Submission of Continuing Applications**
  This part describes the application and budgetary issues for non-competing continuation applications.

- **Part 4 – Appendices**
  This part contains appendices relevant to the policies and procedures associated with the NCTN Program and with the application and review processes.

A variety of other rules and regulations affect the NCTN Program (e.g., NIH Grants Policy, policies of the Office of Human Research Protections, etc.). These Guidelines are intended to cover NCI/DCTD's special requirements for the NCTN Program and to supplement NIH and U.S. Department of Health and Human Services (DHHS) policies. These Guidelines, as well as the policies of all awardees under the NCTN Program, must adhere to NCI, NIH, and DHHS policies. Applicants should contact the responsible NCI Lead Program Director and the NCI/DCTD Senior Program Specialist for the NCTN Program if they believe these Guidelines conflict with other applicable federal policies in order to resolve any apparent discrepancies in the interpretation of these Guidelines.

B. Background, Overview, and Purpose of the NCTN Program

For more than 50 years, the NCI has supported a standing clinical trials infrastructure – the NCI National Clinical Trials Cooperative Group Program (also referred to as the "Group Program") – funded through the Division of Cancer Treatment and Diagnosis (DCTD) to conduct large-scale, clinical treatment trials across the nation. The Group Program has successfully completed many important trials that have led to new treatments for cancer patients. Its activities have involved more than 3,100 institutions and 14,000 investigators enrolling between 20,000 to 25,000 patients in clinical treatment and advanced imaging trials each year over the past decade. The Group Program has promoted the evaluation of multi-modality treatments and combinations of novel agents. In addition, studies supported by Group Program have emphasized clinical trials in members of special populations (e.g., children, young adults, and underserved populations) and clinical trials focused on rare tumor types. This

focus has allowed the Group Program to complement, rather than duplicate, research supported by the private sector.

Cancer medicine has evolved in recent years into a more molecularly-based discipline. Diagnosis is being improved through genetic sub-classification as well as functional imaging of tumors and new treatments are being developed aimed at specific cancer-related pathways. As part of its effort to take advantage of new discoveries in oncologic science, NCI asked the Institute of Medicine (IOM) in 2009 to review the NCI-sponsored Clinical Trials Cooperative Group Program. The IOM report (http://iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx) noted that, despite its impressive record of accomplishment, the current trials system has become less efficient, has difficulty prioritizing studies, and has been underfunded for the number of trials that it conducts. The IOM report recommended that the existing adult Clinical Trials Cooperative Groups be consolidated into a smaller number of Groups, each with greater capabilities and appropriate incentives to promote better overall system integration. Consolidation should promote efficiency by encouraging a structural makeover of clinical trial group operations centers and statistics and data management centers. It should also facilitate prioritization in clinical research by focusing trials even more than before on questions unlikely to be addressed by the private sector.

Based on the IOM review recommendations as well as additional input received by the NCI from stakeholders across the oncology community, the NCI has developed a comprehensive plan to transform the previous NCI-sponsored Clinical Trials Cooperative Group Program that funded several separate organizations conducting cancer treatment trials into a new consolidated and integrated Program referred to as the NCI National Clinical Trials Network (NCTN).

C. Overall Goal of the NCTN Program

The overall goal of the NCTN Program is to conduct definitive, randomized, late phase clinical treatment trials and advanced imaging trials across a broad range of diseases and diverse patient populations, as well as development efforts preliminary to those trials, as part of the NCI's overall clinical research program for adults and children with cancer.

In order to achieve the overall goal of the Program, essential features of the NCTN will include:

- A coordinated, collaborative, and inclusive process, i.e., involving broad representation from the oncology community including academic and community clinical investigators, translational science investigators, statisticians, and patient advocates for generating concepts, primarily for late phase, definitive, clinical trials to evaluate innovative cancer treatments in specific cancers and/or with a focus on specific modalities (e.g., imaging, radiation, surgery);

- Prioritization of trial concepts for development and conduct by national NCI-managed disease and modality-specific steering committees composed of leading cancer experts and advocates from the extramural community, including Network Group representatives, as well as NCI, consistent with national priorities for clinical cancer research;

- Efficient and timely activation, conduct, and completion of clinical trials meeting all regulatory requirements, through the effective integration of scientific expertise and clinical trials management capabilities; and

- Incorporation of innovative science into clinical trials through collaboration among institutions and investigators with expertise in various medical specialties/disciplines relevant to treatment of adult and childhood cancers (e.g., pharmacology, clinical oncology, imaging) as well as those with expertise to integrate translational science into design and conduct of NCTN trials.

D. Anticipated Organization of Key Components of the NCTN Program

In the NCTN Program, **a Network Group is defined as a clinical trials group with a dedicated Operations Center and an associated Statistics and Data Management Center responsible for the design and development of**

clinical trials as well as the conduct of trials via member institutions/sites that enroll patients. Member sites of Network Groups include institutions/sites that are funded either directly by the Network Group Operations Center for their participation in NCTN trials or through other funded key components of the NCTN (i.e., Lead Academic Participating Sites award) or through related NCI-sponsored programs that fund participation (i.e., Community Clinical Oncology Program, Minority-based Community Clinical Oncology Program). Network Groups are expected to collaborate with each other and with NCI to achieve the overall goal of the Program. Member institutions/sites of Network Groups will be able to enroll patients on all adult Phase 3 trials as well as select early phase trials, irrespective of the specific Network Group that is leading the trial. In addition, select trials for adolescent and young adults will be open to all member institutions/sites. Network Groups will also provide trial operations, data management, and statistical support for approved, multi-center Phase 2 and Phase 3 trials originating outside the Network.

Each Network Group will have an integrated organizational structure encompassing scientific leadership, statistics, clinical trial operations, data management, and administration. Network Groups will be funded through an Operations Center award (covering scientific leadership, trial operations, and general administration including oversight of member institutions/sites enrolling patients) and a separate Statistics and Data Management Center award (covering statistical design and data management). Organizations may also apply for a separate, integrated, translational science support center award with support from one or more Network Groups - i.e., Operations Center(s) and associated Statistics and Data Management Center(s) – to facilitate integration of translational science into the design of clinical trials conducted by the supporting Network Group(s).

In addition to the awards described above, the NCTN Program will involve several awards to Lead Academic Participating Sites or institutions to support scientific leaders at those sites who are affiliated with one or more Network Groups to provide leadership in the design and conduct of trials as well as to support patient enrollments at their sites to NCTN trials. The Program will also support an award for an organization to provide core services related to incorporating appropriate quality assurance and credentialing of radiotherapy and imaging techniques/approaches in clinical trials to all the Network Groups and an award to sponsor a corresponding Canadian clinical trials organization to partner with the Network Groups in the U.S. in the design and conduct of NCTN trials.

Each of these key components of the NCTN Program is described briefly below.

1. **Network Group Operations Centers**
   The Operations Center will provide scientific leadership for developing and implementing multi-disciplinary, multi-institutional trials in a range of diseases and special populations with specific scientific strategy and goals. The scientific goals may include strategic innovation in advanced technology for specific research areas (e.g., advanced imaging methods/agents, radiotherapy) and the testing of innovative concepts and tools in prospective, multi-institutional clinical trials. Operations Centers will be responsible for trial operations including timely protocol development and management, compliance with FDA and OHRP regulatory and patient protection requirements, audits, training, quality assurance, and site support. The Operations Center is expected to be closely integrated with the Statistics and Data Management Center in all aspects of trial operations through jointly developed policies and procedures for clinical trial development and conduct. The Operations Center will also be responsible for Network Group administration, including financial management, monitoring of member institution/site performance, coordination of biospecimen collection from patients on clinical trials, and adherence to all applicable NIH/NCI policies and regulations. Network Group Operations Centers will also provide trial operations for approved, multi-center phase 2 and phase 3 trials originating outside the Network Group.

2. **Network Group Statistics and Data Management Centers**
   These Centers will be responsible for providing the statistical expertise required to ensure effective scientific design and conduct of clinical trials as well as leadership in innovation in statistical methodology. The Centers will also be responsible for data management, data analysis, and statistical analysis for NCTN trials led by the Network Group (including approved, multi-center phase 2 and phase 3 trials that originate

from outside the Network Group) as well as for translational and other ancillary studies associated with the trials, working closely with trial operations staff from the associated Network Group Operations Center.

3. **Network Group Integrated Translational Science Centers**
   These awards will provide support for leadership and expertise to facilitate incorporating translational science into Network Group clinical trials.

4. **Network Lead Academic Participating Sites**
   These academic institutions/sites will provide scientific leadership in development and conduct of clinical trials in association with 1 or more adult Network Groups as well as substantial accrual to clinical trials conducted across the entire NCTN. The eligibility to apply for these awards is restricted to clinical academic centers. For the purposes of this award, clinical academic centers are distinguished from large medical centers whose primary mission is patient care, as in addition to patient care, clinical academic centers have comprehensive medical training programs and preclinical laboratories that perform basic science research.

5. **Network Radiotherapy and Imaging Core Services Centers**
   This institution/organization will provide scientific and technical expertise for incorporation of appropriate, integrated quality assurance and image data management for applicable clinical trials conducted by the NCTN that require specialized quality assurance or imaging data management and/or assessment. In addition, the centers will also provide similar services for other approved NCI-supported clinical trials programs that collaborate with the NCTN Program (e.g., NCI/DCTD early phase clinical trial programs).

6. **Canadian Collaborating Clinical Trials Network**
   This Canadian organization will be a non-profit clinical trials organization capable of being a full partner with the U.S. Network in the conduct of large-scale, multi-site clinical trials. Incorporation of a Canadian Clinical Trials Network as a collaborating partner brings an additional advantage as U.S. Network Groups are anticipated to have Canadian member sites. A Canadian network will be able to help reduce duplicative regulatory staff at each U.S. Network Operations Center.

7. **Interactions with Other NCI-supported Programs**
   In addition to the 6 key components of the NCTN that are described above and will be directly funded by the NCTN Program, other NCI grant and contract supported Programs and their awardees as well as NCI Advisory Committees will have important supporting roles in carrying out the research objectives of the NCTN Program. Thus the NCTN awardees will be expected to interact as appropriate with such entities/programs as the NCI Clinical Trials Tumor Banks, the Community Clinical Oncology Program (CCOP) and Minority-Based Community Clinical Oncology Program (MB-CCOP), the NCI Cancer Trials Support Unit, the pediatric and adult NCI Central Institutional Review Boards, and NCI Advisory and Scientific Committees including the NCI Scientific Steering Committees.

   7.1 NCI Clinical Trials Tumor 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 aimed at specific cancer-related pathways. 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. High-quality biological specimen banks containing uniformly collected specimens from such trials along with validated clinical and outcome data are essential for development and delivery of new diagnostic and predictive tools to guide the use of targeted therapies In particular, Network 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 of high-quality, well annotated human specimens from NCTN trials is funded and administered by DCTD through the NCTN Cooperative Agreement

awards. Review of research project requests for use of biospecimens banked from NCTN trials is also administered by DCTD through the NCTN Program. The infrastructure to support banking of the biospecimens collected from NCTN trials is funded and administered through a separate U24 Cooperative Agreement award.

For information on this U24 Cooperative Agreement award mechanism administered by the Cancer Diagnosis Program (CDP) in DCTD, see RFA-CA-09-504 entitled "Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials" at http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-504.html. These biological specimen banks function under the rules developed for this U24 Cooperative Agreement and 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 under the Human Specimen Banking U24 awards 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 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 as well as 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 Network Group may request funding under the NCTN Program to cover costs for staff/personnel at the Operations Center and Statistics and Data Management Center to coordinate activities with the associated tumor banks for its clinical trials.

7.2 NCI Community Clinical Oncology Programs (CCOPs) & Minority-Based CCOPs (MB-CCOPs)

The Community Clinical Oncology Program (CCOP) is a network funded by the NCI Division of Cancer Prevention to support testing and validation of medical interventions against cancer, and for delivering the benefits of scientific discovery to the public and community physicians. The network increases involvement of community oncologists and other health professionals in NCI-approved clinical trials as full research partners; improves the quality of cancer care in local communities by disseminating research findings; and boosts participation of minority and underserved populations in cancer clinical trials.

The CCOP Network was created in 1983 as a national mechanism for community-based physicians to partner with academic investigators. The primary goal was to accelerate implementation of NCI clinical trials for cancer prevention, control and treatment. The Minority-Based CCOP program started in 1990 as a companion mechanism to reach areas with large minority populations.

Both CCOP and MB-CCOP institutions participate in the NCTN Program's clinical treatment and advanced imaging trials through their membership in particular Network Groups.

More information on the CCOP Network is available at: http://dcp.cancer.gov/programs-resources/programs/ccop and on the MB-CCOP Network at: http://ncccp.cancer.gov/Related/MBCCOP.htm.

7.3 NCI Cancer Trials Support Unit (CTSU)

The Cancer Trials Support Unit (CTSU) is a service of the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP) developed to provide administrative support for the clinical trials conducted by the NCTN Program as well as other NCI-supported clinical trial programs.

Three key areas in which the CTSU supports the NCTN include the following:

(1) facilitating access to all phase 3 trials conducted by the NCTN as well as selected earlier phase trials (depending on the accrual needs of the trial and its suitability for broad enrollment) and selected trials for adolescent and young adults;

(2) providing 24/7 centralized, web-based, patient enrollment for all NCTN trials via the Open Patient Enrollment Network (OPEN) supported by Network Group membership rosters and institutional review board (IRB) approvals provided via the Regulatory Support Services (RSS); and

(3) providing support for the Common Data Management System (CDMS), including remote data entry, used for all NCTN trials, and helping to harmonize procedures and policies related to operational aspects of trial conduct across the NCTN Program.

More information regarding the CTSU, including other services and new initiatives, is available at: http://www.ctsu.org.

7.4 NCI Central Institutional Review Boards (CIRBs)

The NCI Central Institutional Review Board Initiative (CIRB) provides a centralized approach to human subject protection through a "facilitated review" process that streamlines local IRB review of adult and pediatric national multi-center cancer treatment trials. The Initiative consists of two central IRBs, one for adult trials and one for pediatric trials. The adult CIRB reviews all phase 3 adult NCTN studies and select phase 2 studies and the pediatric CIRB reviews all NCTN phase 2, phase 3 and pilot studies. Under the current CIRB model, the CIRB conducts full Board review of a new study, the local IRB chair or an IRB subcommittee at participating institutions reviews the CIRB materials for local context and if approved, the CIRB becomes the IRB of record for the life of that study.

The benefits to research participants include study review by individuals who represent a broad range of oncology expertise including patient advocates, oncology physicians, nurses and other health professionals as well as ethicists. The benefits to local IRBs include the ability to carry out local review without convening the entire Board. Continuing reviews, amendments and non-local adverse events (AEs) are handled by the CIRB as well. The benefits to investigators include time saved since they can download an already completed IRB application for each study as well as eliminating the need to submit amendments, continuing reviews and non-local AEs to their IRB. In addition, subjects are enrolled in trials faster since the full local IRB does not need to meet.

In 2012, the NCI is conducting a pilot program to change the model for the NCI CIRBs to that of a full IRB (i.e., single IRB of record) for participating institutions. It is anticipated that this will become the NCI CIRB operating model for the future. All Network Group member institutions/sites as well as Lead Academic Participating Sites, CCOPs, and MB-CCOPs will be expected to be members of and use the NCI CIRBs (adult and/or pediatric) for all trials under the purview of the NCI CIRBs. Additional information on the NCI CIRB is available at: www.ncicirb.org.

7.5 NCI Advisory & Scientific Committees

The NCI Advisory and Scientific Steering Committees associated with clinical trials and translational research activities funded by the NCI are described briefly below. Information on these Advisory Committees is available at: http://ccct.cancer.gov/committees/overview and information on the NCI Scientific Committees is available at: http://transformingtrials.cancer.gov/steering/overview. The NCI Coordinating Center for Clinical Trials (CCCT) is the administrative organization overseeing the activities of these Committees. General information on CCCT is available at: http://ccct.cancer.gov/about/overview.

7.5.1 NCI Clinical Trials and Translational Research Advisory Committee (CTAC)

The NCI Clinical Trials and Translational Research Advisory Committee (CTAC) is an external oversight committee, governed by the provisions of the Federal Advisory Committee Act, that advises the NCI Director on the NCI-supported national clinical and translational research enterprises, including both intramural and extramural research. Committee members include leading authorities in clinical trials and translational research. The CCCT Director serves as the Executive Secretary for CTAC and the CCCT staff facilitates operations. General information on CTAC is available at: http://deainfo.nci.nih.gov/advisory/ctac/ctac.htm.

The CTAC Strategic Planning Subcommittee for the NCTN evaluates the clinical trial portfolio across the entire NCTN and provides recommendations to CTAC regarding the evaluation/prioritization decisions of the NCI Scientific Steering Committees (e.g., NCI disease-specific Steering Committees, Clinical Imaging Steering Committee) and reviews the overall trial portfolio for gaps and balance among the different disease areas and modalities.

7.5.2 NCI Scientific Steering Committees (SSCs)

The NCI Scientific Steering Committees strive to enhance the NCI's entire clinical trials enterprise through implementation of prioritization and scientific quality initiatives under the purview of the NCI Clinical Trials and Translational Research Advisory Committee (CTAC)

As part of that process, NCI disease-specific Scientific Steering Committees (SSCs) evaluate/prioritize phase 3 and large, early-phase clinical trials conducted by the NCTN Program. A Clinical Imaging Steering Committee evaluates/prioritizes large primary advanced imaging studies. The NCI SSCs and Clinical Imaging Steering Committee are composed of leading cancer experts and advocates from outside the Institute, NCTN Network Group representatives, and NCI senior investigators who meet regularly to:

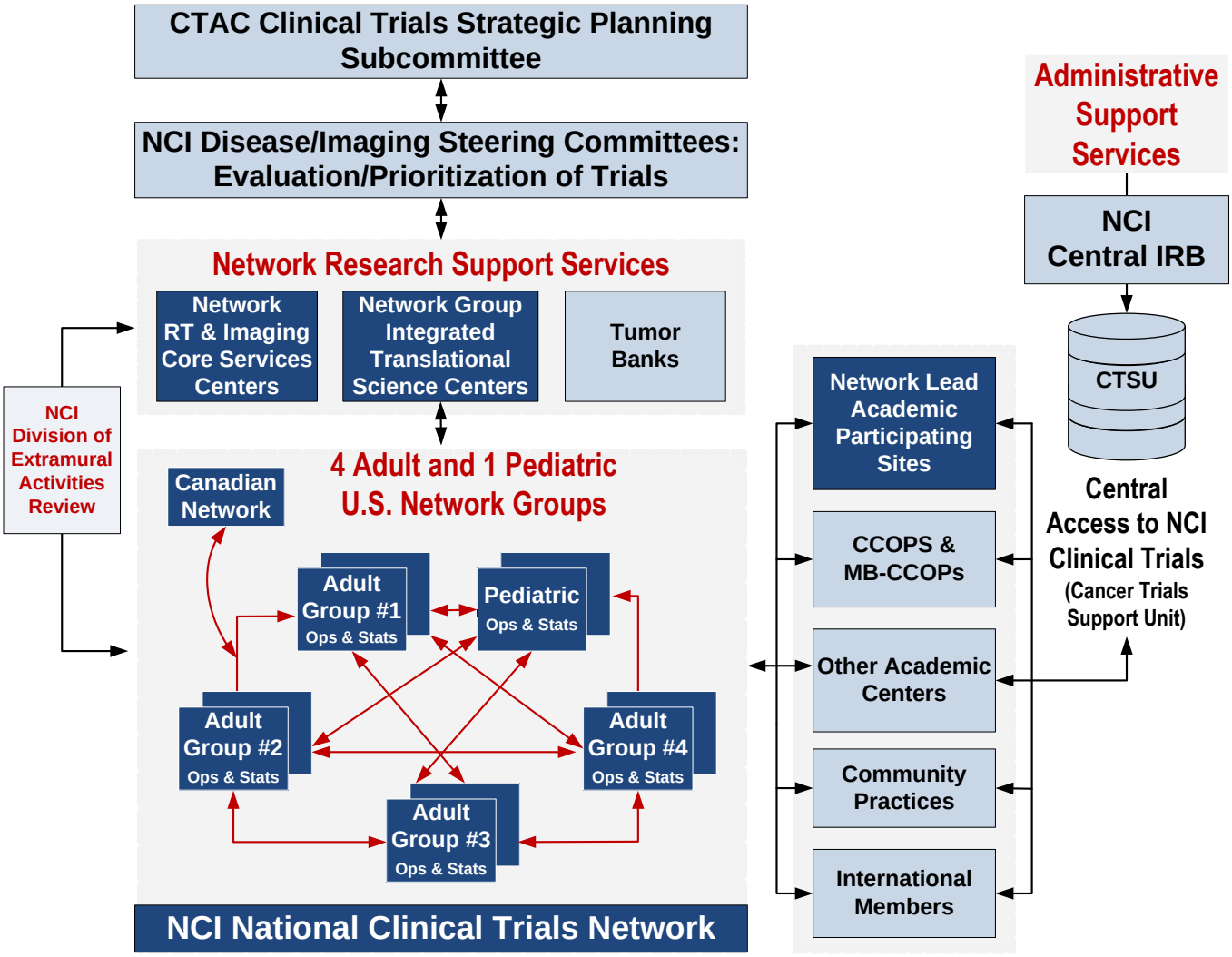
- increase the transparency and openness of the trial design and prioritization process;
- enhance patient advocate and community oncologist involvement in clinical trial design and prioritization; and
- convene Clinical Trials Meetings to identify critical questions, unmet needs, and prioritize key strategies.

These Committees may also establish one or more Task Forces and/or Working Groups that focus on specific sub-categories of disease or other scientific areas of interest. General information on the NCI Steering Committees is available at: http://transformingtrials.cancer.gov/steering/overview.

7.5.3 NCI Clinical and Translational Research Operations Committee (CTROC)

The Clinical and Translational Research Operations Committee (CTROC), an internal NCI advisory committee composed of representatives from NCI Divisions, Offices, and Centers involved in NCI-supported clinical trials and translational research, provides strategic oversight for NCI clinical trials and translational research programs and infrastructures, including informatics. The Committee reviews and prioritizes clinical trials and translational research programs proposed by Divisions, Centers, and Offices to coordinate efforts Institute-wide. CTROC also oversees and approves applications under the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) to support essential biomarker, imaging, and quality of life studies as well as Cost-Effectiveness Analysis (CEA) proposals which are associated with Network Group clinical trial concepts approved for conduct under the NCTN Program that are eligible for BIQSFP funding. Information on the BIQSFP is available at: http://biqsfp.cancer.gov/.

Organizational Structure for the NCI National Clinical Trials Network (NCTN) Program



Dark blue boxes in the illustration above identify the 6 key components of the NCI NCTN Program that are covered by these Guidelines:

1) ***Network Group Operations Centers - Adult and Pediatric***
2) ***Network Group Statistics and Data Management Centers (SDMCs) – Adult and Pediatric***
3) ***Network Group Integrated Translational Science Centers***
4) ***Network Lead Academic Participating Sites***
5) ***Network Radiotherapy and Imaging Core Services Centers***
6) ***Canadian Collaborating Clinical Trials Network***

II. Goals of NCTN Research

A. Clinical Treatment Trials & Advanced Imaging Trials

The clinical research focus of the NCTN Program is the conduct of treatment and advanced imaging clinical trials in oncology. The primary goal of NCTN research is to conduct definitive, randomized, late phase clinical treatment trials and advanced imaging trials (and some development efforts preliminary to those trials if needed), as part of the NCI's overall clinical research program for adults, young adults and adolescents, and children with cancer. The definitive evaluation of newly developed therapies, including multi-modality treatments, combinations of novel agents, and molecularly-based treatment and advanced imaging approaches, for cancer care will benefit patients and practitioners as well as the entire oncology research community. An equally important focus of the NCTN is an emphasis on trials in special populations (e.g., children, adolescents and young adults, and underserved populations) and rare tumors. This focus allows the NCTN Program to complement, rather than duplicate, research conducted by the private sector.

Each Network Group should attempt to accomplish the design of trial concepts and the initiation, conduct, and analysis of approved trials 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 the highest priority activities and trials. The responsibility for overall financial management also includes careful consideration of the financial impact of proposed trials, 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 onsite auditing. To the extent it is practical and consistent with the scientific aims, cost containment at all levels of study conduct should be a factor in protocol design.

Network Groups are encouraged to seek other sources of funding to accomplish their full research agenda. Indeed, the standing infrastructure supported by NCI resources for the Network Groups serves as a unique asset in competing for other NIH funding as well as private sources of funding to support specific aspects of a Network Group's overall research program.

B. Ancillary Studies

The database of patient information accumulated in the course of NCTN clinical trials, the systematic large-scale collection of biospecimens from those trials, and the opportunity to correlate specific features of those biospecimens with patient outcome, provide the Network Groups with unique opportunities to address scientific questions about molecular genetics, epidemiology, pathology, and other cancer-related topics. Such investigations can add considerable strength to a Network Group's total scientific program and are encouraged. While integral or integrated studies associated with a phase 3 or large, randomized phase 2 trial may be eligible for financial support through the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) at: http://biqsfp.cancer.gov/, 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 ancillary studies. Although the NCTN supports the collection of biospecimens in conjunction with clinical trials conducted by the NCTN, direct funding for correlative science studies outside of BIQSFP and/or specific NCI/DCTD approved administrative supplements for specific trials is not provided under or in association with the NCTN Program. Access to biospecimens collected in conjunction with an NCTN trial will be guided by the appropriate review process (see Part 1: Section IV.C.3. of these Guidelines) regardless of the funding source used for the collection or storage of the biospecimens. Funding for services of Reference Laboratories is not provided under the NCTN Program.

C. Cancer Control, Symptom Management, Prevention, and Quality of Life Studies

The Network Groups supported by the NCI/DCTD NCTN Program may also apply to be a Research Base under the Clinical Community Oncology Program (CCOP) to receive funding from the NCI Division of Cancer Prevention (DCP) for the design and conduct of cancer control, symptom management, prevention studies, and quality of life (QOL) studies, including QOL studies associated with NCTN trials. The peer review of a CCOP Research Base application from a Network Group is performed separately from the peer review of a Network Group

application for the NCTN Program. Although QOL studies may be conducted in conjunction with a clinical trial conducted by the NCTN Program, DCP reviews, approves, and funds such studies; they are not funded under the NCTN Program. Support for Network Group committee liaisons in these areas to coordinate with DCP and other organization supporting these types of studies can be funded under the NCTN Program to facilitate collaborations on NCTN trials.

D. Collaborations Among Network Group and with Other Organizations on Clinical Trials

Network Groups are encouraged to collaborate with each other and 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. Collaborations with other Network Groups and NCI-supported programs and investigators are a distinct component of the peer review assessment of the Network Group.

E. NCTN Clinical Trials Originating from Outside the Network Groups

As part of the Terms and Conditions of Award, Network Groups are required to provide trial operations, data management and statistical support for multi-center phase 2 and 3 trials originating outside the Network Groups provided that such trials are evaluated/prioritized by the NCI disease-specific Steering Committees and approved by NCI/DCTD for development utilizing the resources supplied by the NCTN Program. Network Radiotherapy and Imaging Core Services Centers are also required to provide core services support for such trials as well as collaborations with other sponsored NCI clinical trials programs (e.g., early phase clinical trials networks) approved by NCI/DCTD under the NCTN Program but which are not evaluated by the NCI disease-specific Steering Committees. This subset of trials that originates outside the Network Groups will require the same level of attention and commitment from a Network Group as does a study developed by a Network Group member. The Network Group is expected to integrate the investigator who conceived the trial proposal into the development and conduct of the trial.

F. Conduct of NCTN Clinical Research

Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and the 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. Network Groups as well as all other key components of the NCTN 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: http://www.fda.gov/oc/gcp/default.htm.

The integrity of clinical data is a function of the entire process of data collection and analysis. Network Groups as well as the other key components of the NCTN 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.

III. General Management & Network Operating and Funding Principles

A. General Management

Direct programmatic oversight of the NCTN Program is provided by the NCI Division of Cancer Treatment and Diagnosis (DCTD) and its programs. The Chief of the Clinical Investigations Branch within the Cancer Therapy and Evaluation Program (CTEP), DCTD, NCI is the Lead Program Director of the NCTN Program. The Lead Program Director works with the Co-Program Directors for the key components of the NCTN Program from the Biometric Research Branch, the Cancer Diagnosis Program, the Cancer Imaging Program, and the Radiation Research Program as well as other NCI Senior Scientific and Administrative staff from all the branches within CTEP, other DCTD and NCI programs and offices, and the NCI/DCTD Senior Program Specialist to oversee the NCTN Program.

NCI/DCTD staff involved with the NCTN Program also work closely with NCI staff from the Division of Cancer Prevention (DCP), especially DCP program staff for the Community Clinical Oncology Program (CCOP) and the Minority-Based CCOP (MB-CCOP) Program, to manage the NCTN Program as the CCOPs and MB-CCOPs participate directly in the clinical trials of the NCTN and the Network Groups of the NCTN also can serve as Research Bases for the CCOP program. General information on DCTD, DCP, and the programs involved in the direct programmatic oversight as well as the scientific and administrative activities of the NCTN Program is available from the NCI public website at the URLs listed below:

NCI Division of Cancer Treatment and Diagnosis (DCTD): http://dctd.cancer.gov/

NCI/DCTD Cancer Therapy Evaluation Program (CTEP): http://ctep.cancer.gov/

NCI/DCTD Biometric Research Program (BRB): http://brb.nci.nih.gov/

NCI/DCTD Cancer Diagnosis Program (CDP): http://dctd.cancer.gov/ProgramPages/cdp/default.htm

NCI/DCTD Cancer Imaging Program (CIP): http://imaging.cancer.gov/

NCI/DCTD Radiation Research Program (RRP): http://rrp.cancer.gov/

NCI Division of Cancer Prevention (DCP): http://prevention.cancer.gov/

NCI/DCP Community Clinical Oncology Program (CCOP) and Minority-Based CCOP (MB-CCOP): http://prevention.cancer.gov/programs-resources/programs/ccop

External strategic oversight of the NCTN Program is provided by the NCI Clinical Trials and Translational Research Advisory Committee (CTAC), especially the Strategic Planning Subcommittee of CTAC. Internal strategic oversight of the NCTN Program is provided by the NCI Clinical and Translational Research Operations Committee (CTROC). These programs are described in Part 1 – Section I.D.7.5 of these Guidelines.

B. NCTN Leadership Management Committee

The NCTN Leadership Management Committee is composed of key members of NCI/DCTD and NCI/DCP involved in the direct programmatic oversight of the NCTN Program and the Senior Leaders of the Network Group Operations Centers, the Network Group Statistics and Data Management Centers, the Network Radiotherapy and Imaging Core Services Centers, and the Canadian Collaborating Clinical Trials Network involved in the direct management of clinical trials and support services. This management committee makes key recommendations regarding the policies, procedures, and conduct of the NCTN Program to the NCI as described in Part 1 – Section IV.D.4. of these Guidelines). The goal is for the NCI/DCTD and extramural NCTN senior leadership to work collaboratively in managing the Program.

C. Network Operating Principles

As described in the background section of these Guidelines, the purpose of the new NCTN Program is to provide standing support for a consolidated and integrated national Network that conducts treatment trials and advanced imaging trials in oncology for both adult and pediatric patients on an ongoing basis. In this Network, Groups will collaborate with each other and with NCI to achieve the research objectives of the Network based on operating principles that stress harmonization of procedures used by the individual Network Groups and their member institutions/sites, required use of standard tools and services for clinical trial conduct (e.g., centralized patient enrollment and regulatory support, common data management system, core services support for radiotherapy and imaging in clinical trials) to ensure that NCTN trials are developed and conducted as efficiently as possible and with collaboration and coordination among the Network Groups and other NCI-supported program and investigators.

1. Access to NCTN Trials & Crediting for Patients Accrual to Trials

Network Groups member institutions/sites will be able to enroll patients on all adult phase 3 trials (and selected phase 2 trials) conducted by the Network, irrespective of the specific Network Group which is leading the trial and providing data management and statistical analysis for it. Lead Academic Participating Sites (as well as any affiliates included in their award) and CCOPs/MB-CCOPs will be able to credit any Network Group to which they belong for any treatment or advanced imaging trial for adult cancer patients. Other member institutions/sites of the adult Network Groups are also allowed to credit any Network Group of which they are a member for patient accrual except that non-Canadian international sites must credit the Network Group that is leading the NCTN trial if they are a member of that Group to ensure consistency of regulatory oversight outside North America. Canadian sites that belong to more than 1 Network Group may also need to credit the Network Group that holds a Clinical Trial Application (CTA) for the trial in Canada per the Health Canada regulations.

It is also anticipated that affiliates of main members for a particular Network Group will follow the crediting decision of the main member for a particular trial; however, that is at the discretion of the Network Groups through their membership rules. Institutions/sites that are members of the pediatric Network Group must credit the pediatric Network Group when it is leading a trial.

Earlier adult phase trials will also be open Network-wide, depending on the accrual needs of the trial and its suitability for broad enrollment. In addition, it is anticipated that selected trials for adolescent and young adults will be open Network-wide.

Note: International sites (i.e., non-U.S. sites) that are full members of any of the Network Group Operations Center or the Canadian Collaborating Clinical Trials Network may not be able to participate in all NCTN trials because of special regulatory issues specific to the country of the international member. The Network Group Operations Centers must specify any potential restrictions related to enrollment from international members prior to trial activation. For trials being conducted under an NCI/DCTD IND, this information must be reviewed and approved by NCI prior to trial activation.

2. Submission of Data and Biospecimens for NCTN Trials

All data, as well as any biospecimens collected, for an NCTN trial must be sent by the institutions/sites participating in the trial to the Network Group that is leading the trial, unless an exception is approved by the NCI to accommodate the needs of a specific trial.

3. Use of the NCI Central Institutional Review Board

All U.S. institutions/sites participating in NCTN trials as members of 1 or more Network Groups (including Network Lead Academic Participating Sites, CCOPs, and MB-CCOPs) are required to use the pediatric and/or adult NCI Central Institutional Review Board for any NCTN trial under an NCI CIRB's purview. See http://www.ncicirb.org for information on the requirements for a signatory institution under the NCI CIRBs. This requirement may be waived by the Lead NCTN Program Director through an exemption review process if the institution/site can adequately show that NCTN studies can be reviewed in a timely manner by its local IRB (or other Central IRB) that is equivalent to the review timelines for the NCI CIRB (i.e., about 35 to

48 days for initial review) or if the institution/site can demonstrate other exceptional circumstances that preclude it from using the NCI CIRB. This requirement does not apply to international (non-U.S.) institutions/sites participating in NCTN trials (including member institutions/sites of the Canadian Collaborating Clinical Trials Network), given different regulatory requirements/procedures covering human subjects protection in other countries.

4. Trial Proposals Originating From Outside the Network Groups

Network Groups will provide trial operations, data management and statistical support for trials originating from within the Network but **also** for approved, multi-center phase 2 and 3 trials originating outside the Network that are prioritized for development by the disease-specific Scientific Steering Committee and approved for development by NCI/DCTD as part of the NCTN Program. Network Radiotherapy and Imaging Core Services Centers will also provide core services support for such trials as well as for other approved collaborations with NCI-supported trials (e.g., NCI-sponsored early phase clinical trials) under the NCTN Program. In special circumstances, administrative supplements may be provided to Network Groups to help support trial conduct and integral/integrated translational science based on a direct solicitation for a trial from NCI/DCTD, particularly for clinical trials in rare cancers. As the primary vehicle for definitive, large-scale, controlled clinical treatment and advanced imaging trials sponsored by the NCI, the Network Groups should strive to provide a transparent, user-friendly operation for all NCI-sponsored investigators who have trial concepts approved by the NCI Scientific Steering Committees.

D. Network Funding Principles

In keeping with the need for collaboration across the NCTN, funding for data collection and management and for biospecimen collection is provided in a consistent manner for institutions/sites that enroll patients on NCTN trials. The funding to cover the costs for these activities is provided on a "per enrolled patient" basis ("per case management funding") based on a total cost figure. The funding is provided directly by the NCI/DCTD to Network Lead Academic Participating Sites, by NCI/DCP to CCOPs and MB-CCOPs, and through Network Group Operations Centers for their member institutions/sites which are not Lead Academic Participating Sites, CCOPs, or MB-CCOPS.

Any separate, non-NCI/DCTD funding (i.e., funding not provided under the Cooperative Agreements of the NCTN Program) dispensed by a Network Group to cover costs associated with patient enrollment on NCTN trials that it leads must be provided to all qualified institutions/sites that participate in its NCTN trials regardless of which Network Group the enrolling institution belongs to and/or credits with the patient accrual. This principle is considered an essential feature of the NCTN Program and the Terms and Conditions of Award as it is fundamental to ensure fairness for work performed across the Network.

The principles covering "per case management funding" are outlined below, including providing "high-performance per case management funding" to cover the additional data collection, management, and follow-up costs/workloads at institutions (with acceptable audit standings) that enroll a large number of patients. Eligibility for such "high-performance" funding is based on specific thresholds set by NCI/DCTD (with specific thresholds for Lead Academic Participating Sites, CCOPs and MB-CCOPs, pediatric institutions/sites, and other member institutions/sites of the Network Groups).

1. Grant Funding for Key Components of the NCTN Program

The allowable costs under the Cooperative Agreements for each of the key components of the NCTN Program are described under the budget section of the application process for new applications in Part 2 of these Guidelines. In general, the funds can support costs associated with personnel (e.g., operational staff, scientific and administrative committees leaders, principal investigators for specific trials), travel, appropriate equipment, and other operational costs related to the conduct of clinical trials; however, costs for patient recruitment, patient care, laboratory tests, and reference laboratory research are not allowed under the grant funding for the NCTN Program, unless approved by the Lead NCTN Program Director and Associate Director, CTEP for exceptional circumstances related to a specific trial. Funding for research laboratory tests **must** be supported from other resources, including BIQSFP funds, commercial and

charitable funds, and/or specific administrative supplements to the Cooperative Agreements under the NCTN Program in special situations.

2. Funding for Data Collection/Management & Biospecimen Collection on "Per Case" Basis

NCI funding for institutions participating in all NCTN trials to cover the costs related to data collection/management and biospecimen collection (also called "per case management funding") associated with enrolled patients is provided in 2 ways:

1) grant funding from NCI to Lead Academic Participating Sites, CCOPs, and MB-CCOPs or

(2) grant funding from NCI to Network Groups which then contract with member institutions/sites via purchase service or subcontract agreements on a "per-case" basis.

Any threshold level of accrual used to determine budgets/funding is based on accrual to all NCTN trials regardless of which Network Group Operations Center is credited with the accrual by the enrolling site. These threshold levels are also based on the number of patients who are enrolled on intervention treatment or advanced imaging arms of clinical trials only (i.e., threshold levels are not based on number of patients who undergo screening when it is part of the clinical trial or for whom biospecimens are collected). Also, advanced imaging interventions are weighted at 50% of a treatment intervention given the more limited intervention and follow-up required in those studies.

2.1 Network Lead Academic Participating Sites Funding

NCI/DCTD funding given to adult Network Lead Academic Participating Sites is based on a "level-of-effort" as outlined in their budget application. This "level-of-effort" budget covers data collection/management and biospecimen collection for a certain number of adult cancer patients enrolled on an annual basis (accrual threshold) as well as other infrastructure support to the sites. This "level-of-effort" is based on a "per-case" algorithm utilizing the amounts estimated for "High-Performance Per Case Management" funding as well as other funding categories as specified in Part 4: Appendices – Section IV of these Guidelines for the portfolio of trials that the site anticipates it will support. In addition, the Lead Academic Participating Sites may receive administrative supplements to cover costs associated with the enrollment of additional patients above the threshold for this type of award.

2.2 CCOPs and MB-CCOPs Funding

Funding to CCOPs and MB-CCOPs for enrollment of patients to NCTN trials is provided by the Division of Cancer Prevention based on a similar system as the one used for the Network Academic Participating Sites but with different thresholds for patient accrual used to estimate the level of funding provided via their grant awards.

2.3 Pediatric Network Group Member Institutions/Sites Funding

NCI/DCTD funding given to the pediatric Network Group Operations Center for its member institutions/sites, which are not CCOPs or MB-CCOPs, is provided to these sites through purchase service agreements or subcontracts using a special algorithm for either "Intervention Per Case Management" or "High-Performance Per Case Management" funding to a site as well as other funding "Per Case" categories as specified in Part 4: Appendices – Section IV. The "High-Performance Per Case Management" funding is based on a different threshold for patient accrual than that used for adult patient accrual given the smaller pediatric patient population and more limited sources of private funding available for pediatric trials. In addition, pediatric sites may also receive additional infrastructure support based on the overall level of patient accrual at their site since they are not eligible for the adult Network Academic Participating Sites awards which provide this type of support to high-performance sites engaged in NCTN trials that enroll adult cancer patients on NCTN trials.

2.4 Adult Network Group Member Institutions/Sites Funding

NCI/DCTD funding given to an adult Network Group Operations Center for its member institutions/sites which are not Lead Academic Participating Sites, CCOPs, or MB-CCOPs is provided to these sites through purchase service agreements or subcontracts using an algorithm for "Basic Intervention Per Case Management" funding as well as other funding "Per Case" categories as specified in Part 4: Appendices – Section IV for patient enrollment to the entire portfolio of NCTN trials that these member institutions/sites credit to the adult Network Group Operations Center. These members will also be eligible for special program/initiative for "High-Performance" sites administrated via the CTSU as described below.

2.5 Categories of "Per Case Management" Funding

The various categories of NCI/DCTD supported "per case management" funding are described below.

- **Screening Per Case Management Funding:** Funding to cover data management costs for patients enrolled on a trial that require specific screening with informed consent as part of the trial (e.g., investigational molecular test of their tumor) and who do not subsequently undergo the study treatment/intervention and/or randomization because of the screening results.

- **Basic Intervention Per Case Management Funding:** Funding to cover data management costs for enrolled patients who undergo the study treatment/intervention and/or randomization. Basic intervention funding is divided into therapeutic (treatment intervention or pilot studies) or advanced imaging interventions. This base amount is set at the same level for all treatment trials; however, the base amount for advanced imaging trials may be different. This funding category also includes funding for average follow-up per case data management for an NCTN trial (i.e., separate payments for follow-up are not provided). Please note that the basic intervention per case cost includes any screening performed on study (i.e., per case funding is provided for an enrolled patient for either screening or intervention but not both). Likewise, intervention per case management funding is provided at either the basic level or the high-performance level, but not both – see the information on high-performance intervention per case management funding below.

- **Advanced Imaging Trial Per Case Management Funding:** Funding to cover data management and imaging costs for complex imaging used in advanced imaging trials (above the base intervention per case amount described above) would be provided to all NCTN participating sites by the Network Group Operations Center with a specialty focus in this area that leads these trials (including providing the funding to other Network Group Operations Centers for their members which participate in the trials) as these studies are expected to be limited in number relative to the number of treatment trials.

- **Biospecimen Collection Per Case Management Funding:** Funding to cover biospecimen collection and any associated management costs for patients enrolled on study who undergo the study treatment/intervention and/or randomization for trials with required or optional biospecimen collections – this category of funding would not be expected to be given in association with screening per case funding except in unusual circumstances.

- **Special Per Case Management Funding:** Funding to cover additional data collection/management costs for patients enrolled on study who undergo the study treatment/intervention and/or randomization, usually for very complex trials and/or trials in rare disease areas or rare disease subsets as well as any special ancillary study funding. This category of funding is approved by NCI/DCTD on a trial by trial basis only.

- **High-Performance Intervention Per Case Management Funding for Lead Academic Participating Sites, CCOPs/MB-CCOPs and Member Institutions/Sites of the Pediatric Network Group:** Funding

to cover additional data management costs/workload and follow-up at institutions (with acceptable audit standings) that enroll a large number of patients (based on specific threshold levels set by NCI/DCTD for pediatric patient enrollment and for adult patient enrollment on NCTN trials (with adult thresholds designated by NCI/DCTD for CCOP and MB-CCOP vs. Lead Academic Participating Sites vs. other Network Group member institutions/sites separately). It is anticipated that this funding will be provided to Lead Academic Participating Sites for accrual at the main academic center if the threshold accrual level for Lead Academic Participating Site awardees is sustained, and it covers all follow-up data management costs for these patients. "High-Performance" per case funding for affiliates that are included in a Lead Academic Participating Site grant award (i.e., if complete management services for the affiliates is provided by the Lead Academic Participating Sites) may be possible, pending funds availability based on whether the affiliates meet special threshold accrual levels for this category of sites set by NCI/DCTD each year as described below.

Different accrual targets will be applied to different categories of sites funded via separate grant programs as follows: (1) Lead Academic Participating Sites (excluding affiliates); and (2) CCOPs and MB-CCOPs; and (3) pediatric sites that are institutional members of the pediatric Network Group Operations Center. The priority for funding of high-performance sites is to cover these 3 categories of sites first providing they meet their threshold levels for accrual. These sites are a priority because they undergo peer-review as high-performing institutional sites from academic and community sites based on accrual potential and scientific leadership.

- **High-Performance Intervention Per Case Management Funding for Other Member Institutions/Sites for the Adult Network Groups:** A special Network initiative will be available on an annual basis to select other categories of "high-performance" sites participating in the NCTN Program, provided funding is available. Selection of these sites is based on a specific accrual threshold level to all trials across the Network set by NCI/DCTD each year. If funding constraints exits at the particular threshold selected in any year, the priority order for funding will be: (1) other U.S. sites not covered by the 3 categories described above (including affiliates of Lead Academic Participating Sites); (2) Canadian sites; and (3) other international sites.

  Based on their selection as "high-performance" sites, these sites will receive additional infrastructure support during the subsequent year (e.g., support for time and effort for Clinical Research Associates and other health care professions involved in the conduct of NCTN trials, as well as training for support personnel, and travel and equipment needs related to clinical trial conduct) in order to leverage their support for the entire NCTN Program to help ensure the trials are completed more quickly. "Eligibility" for this program will be based on threshold accrual rates for single institutions (not networks of institutions/sites). If an affiliate that is part of a Lead Academic Participating Sites award is eligible for this funding, the funding will be provided via the Lead Academic Participating Site award. Funding for other eligible sites, which do not have NCI grant funding for infrastructure support for activities across the Network, will be made via contract using the NCI Cancer Trials Support Unit (CTSU) under NCI/DCTD's direction.

- **Quality of Life Per Case Management Funding:** Funding to develop and to cover data collection/management costs associated with patient enrollment in quality of life sub-studies incorporated into NCTN treatment or advanced imaging clinical trials is **not** provided by NCI/DCTD except in special circumstances as described below.

  "Quality of Life Per Case Management" funding is provided by the NCI Division of Cancer Prevention (DCP) through its CCOP/MB-CCOP grants and to other member institutions/sites of the Network Groups (including the Network Lead Academic Participating Sites) through DCP grants to the Network Groups as CCOP Research Bases. DCP also provides funding to develop these types of studies through CCOP Research Bases grants to Network Groups.

If a Network Group in the NCTN Program (including the Canadian Collaborating Clinical Trials Network) does not have a CCOP Research Base grant from DCP, "Quality of Life Per Case Management" funding for DCP-approved quality of life studies incorporated into NCTN trials led by other Network Groups can be provided by the NCI/DCTD grant to the Network Group Operations Center and/or the Canadian Collaboration Clinical Trials Network for participation in these studies by the member institutions/sites of the Network Group which is not a CCOP Research Base.

Note: This exception is provided in order to ensure that DCP-approved quality of life studies incorporated into NCTN trials are available to all members of the Network participating in the NCTN trial. However, NCI/DCTD funding cannot be used, under any circumstances, by a Network Group that does not have a CCOP Research Base grant to develop quality of life studies or provide "quality of life per case management" for NCTN trials that it leads as the NCI/NIH peer-review for such research activities is part of the CCOP Research Base grants (i.e., it is not part of the NCI/NIH peer review of the NCTN Program grants). If a Network Group that does not have a CCOP Research Base wishes to include such a "quality of life" sub-study in an NCTN treatment trial that it is leading, the Network Group may wish to collaborate with another Network Group which does have a CCOP Research Base grant to conduct the quality of life sub-study as part of a collaboration.

- **Non-NCI/DCTD Funding for Patient Enrollment:** Other funding may be given for data collection/management and biospecimen collection for patients enrolled on NCTN trials which is not provided by NCI/DCTD under the Cooperative Agreements for the NCTN Program. This funding is usually provided by other NCI programs (e.g., "per case" funding for QOL data collection through grants funded by the Division of Cancer Prevention) or by industry collaborators. These funds are permitted as long as they cover costs not already paid for under the NCTN Program's Cooperative Agreements. All data and biospecimens collected via these funding mechanisms are still subject to the complete Terms and Conditions of Awards under the Cooperative Agreements of the NCTN Program.

2.6 Notification of "Per Case Management" Funding for Trials

Prior to activation of a trial by a Network Group Operations Center, the specific mix of per case funding provided by NCI/DCTD for data collection/management and/or biospecimen collection must be specified and approved by the Lead NCTN Program Director for all categories (Screening, Base Intervention, Special, Advanced Imaging, and Biospecimen Collection) except for "High-Performance" per case funding which is based on threshold accrual levels and not by trial. Additional funding provided by other NCI/NIH programs as well as by industry, charitable organizations, and other sources must also be specified. This type of funding also requires review and approval by NCI/DCTD in order to verify that the funding does not duplicate NCI/NIH funding. **It is a fundamental requirement of the NCTN Program that the "per case management" funding, whether provided by NCI/DCTD, other NCI programs, or other entities (e.g., industry collaborators), for a specific trial MUST be provided to ALL qualified institutions/sites participating in that trial.**

It is understood that qualified institutions/sites would need to meet general program requirements (e.g., be a member in good standing in the NCTN Program, meet protocol-specific requirements related to safe delivery of the protocol intervention) to be able to enroll patients and receive funding. Funding cannot be restricted based on membership in a particular Network Group. To ensure transparency and fairness across the Network, all payments associated with an NCTN trial will be required to be listed for each NCTN trial according to the categories described above on the member side of the Cancer Trials Support Unit (CTSU) website.

3. Program Income for Key Components of the NCTN Program

Under the Cooperative Agreement grants awarded for all key components of the NCTN Program, awardees are allowed to accept funds from non-governmental sources to support NCTN research that is not supported in part or in full by the NCI (e.g., additional per case management funding supplementing the

NCI/DCTD basic intervention per case funding, support for correlative science studies associated with trials conducted under the NCTN Program). These funds are considered "Program Income" and must be reported under the Terms and Conditions of Award for the key components of the NCTN Program as outlined in Part 1 - Section IV.A.2. of these Guidelines unless they are exempted under the NIH grant policy for program income available at:
http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income. These funds are considered a valuable resource to help further the clinical research of the entire Program. Nevertheless, the Cooperative Agreements for the NCTN Program always define the operational principles under which the awardees must function to ensure the independence of the research conducted regardless of whether program income is or is not available for specific clinical trials conducted by the NCTN.

IV. Terms & Conditions of Award for Cooperative Agreements for NCTN Program Key Components

A. General Terms and Conditions of Award for All Key Components of the NCTN Program

The administrative and funding instrument used for all the key components of the NCI National Clinical Trials Network (NCTN) Program is a Cooperative Agreement (U10 or U24 as outlined in the table in **Part 2 – Section 1.A. of these Guidelines)**.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

1. General Programmatic Responsibilities

The awardees' programmatic responsibilities for the conduct of the research supported under the Cooperative Agreement for each of the key components of the NCTN Program are described in the documents listed below and any subsequent modifications to these documents:

- **NCI National Clinical Trials Network (NCTN) Program Guidelines (i.e., "these Guidelines")**
  http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

- **NCI/CTEP Investigators Handbook (Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis, NCI)**
  http://ctep.cancer.gov/handbook/index.html

- **Guidelines for Monitoring of Clinical Trials for Cooperative (i.e., Network) Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU)**
  http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm

Specific portions of these documents, as enumerated in the Funding Opportunity Announcement for each of the key components of the NCTN Program (as well as in specific sections of the NCI NCTN Program Guidelines), are incorporated by reference as program-specific Terms and Conditions of Award.

2. Program Director(s)/Principal Investigator(s) Primary Responsibility & Program Income Reporting

The PD(s)/PI(s) will have the primary responsibility for:

- Development of an overall research strategy for the development of clinical trials for the NCTN Program as well as all key components related to the conduct of approved clinical trials.

- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, NIH, and NCI policies and within the limits of any accepted binding NCI/NIH collaborative agreements with biotechnology and pharmaceutical partners and as governed by NCI-approved Data Sharing Plans and NCI-approved review for use of biospecimens collected in association with NCTN trials.

- Awardees are allowed to accept funds from non-governmental sources to support NCTN research that is not supported in part or in full by the NCI. These funds are considered **"Program Income"** (e.g., additional per case data management funding supplementing the NCI/DCTD base per case funding, support for correlative science studies associated with trials conducted under the NCTN Program) and must be reported under the Terms and Conditions of Award for the NCTN Program unless they are associated with an exempted category under the NIH grant policy for program income, available at: http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income.

  All key components of the NCTN Program must report these funds to the NCI on an annual basis (in the non-competitive Type 5 application – the annual progress report) and must indicate the clinical trial that the funds are being used to support (or other functional component if the funds are not provided to support specific trials). The Terms and Conditions of Award for all the Cooperative Agreements under the NCTN Program define the operational principles under which the awardees must function to ensure the independence of the research conducted regardless of whether program income is or is not available for any of the awards.

- Programmatic responsibilities for the individual key components of the NCTN Program are described in detail under "Specific Cooperative Agreement Terms & Conditions of Award for the Key Components of the NCTN Program" in Part 1 – Section IV.B. of these Guidelines.

3. NIH Staff Programmatic Responsibility

NIH staff has substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below.

An NCI Program staff member(s) acting as a Project Scientist(s) will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. Additional NCI staff members may be designated to have substantial involvement (e.g., in the role of Project Coordinators). The NCI Project Scientist(s)/Coordinator(s) will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications. If such participation is deemed essential, these individuals will seek NCI waiver according to the NCI procedures for management of conflict of interest.

Additionally, an NCI program director acting as Program Official will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. Some Program Officials may also have substantial programmatic involvement (as Project Scientists/Coordinators). In that case, the individual involved will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications or will seek NCI waiver as stated above.

The main NCI responsibilities are related to research efforts of the Network and include but are not limited to the following activities:

- responsibilities as a drug sponsor for investigational agent or device development for NCI-sponsored or co-sponsored IND and/or IDE clinical trials;
- serving as scientific liaisons to awardees of key components of the NCTN Program and participation in scientific meetings of the key components;
- informing Network investigators of scientific opportunities resulting from NCI-supported clinical research programs;
- oversight of data and safety monitoring plans and boards for NCTN clinical trials;
- oversight of data management and monitoring programs for NCTN trials as well as onsite auditing programs and quality assurance programs for the NCTN Program, including oversight of core services for radiotherapy and imaging supporting NCTN trials;

- facilitating coordination of the clinical trial activities and collaborations between the Network and other NCI-sponsored programs and investigators;
- facilitating the evaluation of clinical trial concepts and protocol development as well as review of correlative science study requests for use of biospecimens collected in association with NCTN trials;
- ensuring compliance with FDA requirements for investigational agents and ensuring compliance with OHRP and other federal requirements and regulations for research involving human research subjects;
- advising awardees concerning mechanisms established by the awardees for quality control of therapeutic and diagnostic modalities; and
- monitoring the progress and performance of the key components of the NCTN Program.

Programmatic responsibilities for NIH Staff (i.e., NCI/DCTD staff) are completely described under "NCI/DCTD Responsibilities" in Part 1 – Section IV.C. of these Guidelines.

The NCI will have access to all data (including imaging data) collected and/or generated under this Cooperative Agreement and may periodically review the data. The NCI may also review all records related to awardees' performance under the award for appropriate collection, review, and distribution of biospecimens collected in association with NCTN trials.

In case of insufficient patient accrual per the protocol specified timelines and/or NCI/DCTD slowly accruing guidelines for trials, inability to meet the scientific aims of the Cooperative Agreement, or noncompliance with the Terms and Conditions of Award, the NCI reserves the right to reduce award budget, withhold support, suspend or terminate the award.

4. Joint Responsibility

Areas of Joint Responsibility include:

- General aspects of collaboration on study development and conduct especially with respect to compliance with federal regulations for clinical trial research (and with respect to ensuring that when new avenues of cancer therapy involving investigational drugs are pursued, trials are designed, when appropriate, such that the clinical information obtained would be acceptable to the FDA for inclusion in a potential licensing application), conduct of Data and Safety Monitoring Boards for Phase 3 trials and randomized Phase 2 trials, development of collaborative trials and international trials, collective management of the NCTN including participating, if appropriate, in the NCTN Leadership Management Committee that makes recommendations to NCI for modifications to the Program as well as to standard NCTN common tools and services.

- Review of recommendations from the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) on strategic directions for the NCTN Program.

- Joint programmatic responsibilities for the awardees of the key components of the NCTN and the NIH staff Programmatic responsibilities for NIH Staff (i.e., NCI/DCTD staff) are described in detail under "Collaborative Responsibilities (Awardees of NCTN Key Components and NCI/DCTD)" in Part 1 – Section IV.D. of these Guidelines.

5. Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution, except for areas of dispute that are already addressed by the appeal process within the Terms and Conditions of Award for decisions regarding approval of study proposals and the types of studies supported by the NCTN Program as described in Part 1 – Section IV.E. of these Guidelines.

For other scientific and programmatic matters that are not covered by the appeals process, a Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the Network Group representatives on the NCTN Leadership Management Committee chosen by them without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee.

The appeals process and this special dispute resolution procedure do not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

B. Specific Terms and Conditions of Award for the Key Components of the NCTN Program

1. Specific Awardee Rights & Responsibilities - Network Group Operations Centers

Throughout these Terms and Conditions of Award, "Network Group Operations Center" refers to the organizational structure which is composed of the key personnel (including the scientific and administrative leaders of the Center and its scientific research and administrative committees) and the member institutions/sites (including the institution/site physicians and clinical research associates), responsible for implementing clinical trials and collaborating on research goals of the NCTN Program through the Network Group Operations Center. In addition, throughout these Terms and Conditions of Award, "Network Group Operations Center," refers to all of its member institutions/sites no matter how the membership is defined by a particular Network Group Operations Center.

1.1 Clinical Trial Development Program

1.1.1 Overall Research Strategy

It is the responsibility of the Network Group Operations Center to develop and articulate an overall research strategy for the Network Group which reflects an integrated scientific approach both within and across specified disease areas, addresses important unmet clinical needs and national research goals, includes disease areas appropriate and beneficial to the NCTN, and within the confines of ethical constraints applicable to early and late phase clinical trials for oncology patients, includes novel or improved ways and/or methods to enhance the Network Group's research strategy and the goals of the entire NCTN.

1.1.2 Scientific Research and Administrative Committees

The Network Group Operations Center is responsible for establishing scientific research committees and administrative committees and developing a process for the selection of leadership for these committees. The Network Group Operations Center should ensure that committees involve appropriate representation from the various stakeholders involved in cancer clinical trial research including a range of scientific and clinical experts and patient advocates. The Network Group Operations Center is responsible for establishing clear operating principles and procedures for committees and facilitating their operations by arranging meetings and establishing and maintaining electronic communication tools.

Scientific research committees are defined as committees that function primarily to develop and oversee the conduct of clinical trials and studies within a defined research strategy (e.g., disease committee such as a breast committee that conducts trials in breast cancer, other scientific committees such as an experimental therapeutics committee or a correlative science committee). Administrative Committees are defined as committees that provide essential core service functions to help effect other aspects of the Network Group's research strategy (e.g., Patient Advocacy, Clinical Research Associates, Auditing, Pathology, Surgery).

Correlative science studies, especially integral and integrated studies, are increasingly central to the interpretation of clinical trials data, particularly for studies of molecularly targeted agents. Scientific research committees play a key role in the development and conduct of correlative science studies associated with Network Group protocols. Funding for integrated and integral correlative science studies is not provided by the NCTN award (except in exceptional circumstances via an administrative supplement by NCI/DCTD for a specific trial) but may be applied for via BIQSFP funding for phase 3 and randomized phase 2 trials. Other sources of funding may be sought for correlative science studies that are not eligible for BIQSFP funding (e.g., other NCI and NIH grant funding, industry funding).

<u>Organizational Structure:</u> The Network Group Operations Center is responsible for the Constitution and By-laws for the Network Group. The Constitution and By-laws should define

the organizational structure, composition, and specific responsibilities of each Network Group committee (scientific and administrative) as well as study teams and membership for institutions/sites.

Scientific Research Committees: The primary responsibilities of the scientific research committees is to develop the specific trial proposals (Letters of Intent (LOI) and Concepts) for approval by the NCTN Program, oversee protocol development and trial conduct for approved studies, and to help effect the Network Group's overall research strategy. Disease committees (e.g., breast, gastrointestinal, thoracic) are responsible for adhering to procedures for study/protocol development, including adhering to time-lines for Concept and LOI development and subsequent protocol development for approved Concepts and LOIs as set out by the Network Group Operations Center for compliance with NCI/DTCD Operational Efficiency Working Group timelines. Other committees (e.g. correlative science, experimental therapeutics, experimental imaging sciences) are responsible for providing input to or developing ancillary studies for disease committee trials that enhance the quality of the Network Group's overall research strategy.

Study Monitoring by Scientific Committees & Study Teams: The primary responsibility for study monitoring resides with the Study Chair, Study Statistician and other members of the study team that helps develop and oversees conduct of a specific study. The scientific research committee (e.g., disease committee) is responsible for assuring that the study team is satisfactorily meeting its responsibilities for study monitoring.

Administrative Committees: Administrative committees provide essential core service functions to support the Network Group's research program. For example, a patient advocacy committee may provide guidance to a disease committee 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 Network Group's research agenda (e.g., Audit Committee).

1.1.3 Young Investigator Mentoring/Training:

The Network Group Operations Center is responsible for having a mentorship program to involve young investigators in Network Group clinical trial research and to help train them eventually to take on leadership responsibilities for clinical trials and/or committees.

1.1.4 Communications Support

The Network Group Operations Center is responsible organizing and disseminating information about the Network Group's scientific activities and major changes in administrative policies and procedures to its members through annual or biannual Network Group meetings that review the Group's progress, establish priorities, and plan future activities. Additional meetings among Network Group members and meetings with NCI staff may be held as needed. Relevant Network Group 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 Network Group members and NCI staff.

The Network Group Operations Center is responsible for establishing routine electronic communication between itself, the associated Network Group Statistics and Data Management Center, Cancer Trials Support Unit (CTSU), and member sites participating in its trials to facilitate protocol development, trial conduct, and study monitoring. Relevant communication methods include website postings, e-mail, teleconferences, and video-conferences.

1.1.5 Publications

The Network Group Operations Center is responsible for ensuring timely preparation and submission of all Network Group publications for peer review. **Network Groups must adhere strictly to the publication policy described in these Terms and Conditions of Award.**

Acknowledgement of NCI Support and Scope of Publication Policy: Publication or oral presentation of work done via the Network Group's Cooperative Agreements requires appropriate acknowledgment of NCI support. The definition of publications for this Cooperative Agreement includes Network Group abstracts, press releases, print-media articles/manuscripts, electronic media articles/presentations, letters, etc., related to findings and results from NCI-sponsored studies. All Network Group publications must reference the NCI protocol title in the manuscript or abstract title whenever relevant to the publication.

Publication Timelines: Timely publication of major Network Group findings is central to the mission of the Group and is a primary means by which the Network 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.

It is expected that preliminary results of major phase 3 trials will be presented at a scientific meeting within 6 to 8 months of completion of the study analysis (if not sooner based on the relevance of the results). It is a requirement under the Terms of Awards that a full manuscript on the study results be prepared and submitted for publication in the peer-reviewed literature (not as an abstract) within 1 year of the availability of the primary study results based on the completion date of the study recorded in the U.S. National Library of Medicine database, clinicaltrials.gov. Exceptions to this policy must be approved in writing by the Lead NCTN Program Director (e.g., an exception may be made for results that are being analyzed for a marketing/licensing application to the FDA by a company partner). **Also, these timelines may be modified in the future by NCI institute-wide requirements that are in development.**

It is also a requirement of these Terms of Award that the results of all NCTN studies be submitted as required by the Food and Drug Administration Amendments Act (FDAAA) Section 801 to comply with the rules defined for inclusion of clinical trial information in clinicaltrials.gov.

The Network Group Operations Center should have mechanisms for monitoring the performance of the Center, its associated Statistics and Data Management Center, and scientific committees in meeting these time-lines and should have corrective action plans in place for when these time-lines are not met.

Pre-Publication Review:

- 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.

- For publications associated with NCI-sponsored Network Group studies that do not involve agent(s) supplied under CTEP Collaborative Agreements (except as noted below for press releases), the Lead NCTN Program Director must receive a copy of the manuscript or abstract 30 days in advance of publication and a copy of abstracts should be provided 3 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. Review timing for publications other than abstracts or manuscripts should be discussed with appropriate NCI/DCTD staff.

- All press releases issued by the NCI and/or the Network Group on primary study findings and results require review by NCI, NIH, and DHHS. Pre-review timing for press releases on study finding and results must be discussed with and approved by the Lead NCTN Program Director. Network Groups are encouraged to send drafts of press releases on other topics to NCI for pre-review and/or pre-release notice.

- In addition to the requirements listed above, Network Groups should consider carefully whether any findings from clinical trials that are pending reporting/publication may have major impact for public health in the particular disease area. If there is the potential for major impact for public health, the Network Group must inform the Lead NCTN Program Director and work closely with NCI to ensure that the information is released to the public in as timely a manner as possible and in a manner to ensure appropriate communication about the results, including how they may affect other ongoing trials and the treatment of patients on those trials.

Post-Publication Reporting & Submission to NIH Manuscript System:

- Network Groups must report publication references in their competitive Type 1 and non-competing Type 5 applications for major clinical trial results and important associated studies to demonstrate the scientific accomplishments of their research strategy. Only references for the manuscripts for key findings should be reported. Copies of manuscripts cannot be submitted as part of the research plan or as appendix material.

- The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central *upon acceptance for publication*. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication. More information about this policy or the submission process is available on the NIH Public Access Policy website at: http://publicaccess.nih.gov/.

1.1.6 Data Rights

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 and biotechnology companies will have access to all data generated under CTEP Collaborative Agreements; however, the companies may contract directly with the Network Groups for access to non-Clinical Data Update System (non-CDUS) data and reports.

1.2 Member Site Accrual Program

Network Group Operations Centers are responsible for providing significant accrual to the NCTN through its institutional and other participating site members and affiliates, CCOP and MB-CCOP members, and Lead Academic Participating Site members and affiliates that credit the Network Group with accrual to NCTN trials.

Membership Roster: The Network Group Operations Center is responsible for having a comprehensive and consolidated membership roster of all its sites and associated investigators and research staff and for maintaining the roster for both auditing and financial management purposes with "real-time" status of all members within the Regulatory Support System (RSS) of the NCI Cancer Trials Support Unit (CTSU). All member institutions/sites must have appropriate and accurate NCI institutional codes approved by NCI. Institutions/sites are assigned to one of the following mutually exclusive categories across the entire Network for the NCTN Program for purposes of NCI/DCTD funding and crediting of accrual: (1) Lead Academic Participating Site (academic center and its essential components); (2) Affiliates included in a Lead Academic Site award (because they are completely managed by the Lead Academic Participating Site); (3) CCOP; (4) MB-CCOP; (5) Pediatric site; and (6) other Network Group member institutions/sites. For example, a site that is a CCOP has that designation across the NCTN Program regardless of the number of Network Groups to which it belongs.

Collection and Transmission of Data and Biospecimens: All data, as well as any biospecimens collected, for an NCTN trial must be sent by the institutions/sites participating in the trial to the Network Group that is leading the trial, unless an exception is approved by the NCI/DCTD to accommodate the needs of a specific trial. The Network Group Operations Center is responsible for overseeing the timely collection and transmission of data and biospecimens from all its member institution/sites to NCTN trials for patient accruals that are credited to the Network Group. Collection and banking of tissues and other biological specimens is an increasingly important aspect of Network Group clinical research. For NCTN trials that it leads, the Network 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. The Network Group Operations Center is also responsible for ensuring that all its members submit required biospecimens for NCTN trials when the Network Group Operations Center is credited with the accrual even if the Network Group is not leading the trial.

Trial Access and Crediting of Patient Enrollment: Network Groups member institutions/sites must be able to enroll patients on all adult phase 3 trials (and selected phase 2 trials) conducted by the Network, irrespective of the specific Network Group which is leading the trial and providing data management and statistical analysis for it. Member institutions/sites of the adult Network Groups are allowed to credit any Network Group to which they belong for patient accrual except that non-Canadian international sites must credit the Network Group that is leading the NCTN if they are a member of that Group to ensure consistency of regulatory oversight outside North America. Canadian sites that belong to more than 1 Network Group may also have to credit the Network Group that holds a Clinical Trial Application (CTA) for the trial in Canada if a CTA is required per Health Canada regulations. **Note:** International sites (i.e., non-U.S. sites) that are full members of any of the Network Group Operations Center or the Canadian Collaborating Clinical Trials Network may not be able to participate in all NCTN trials because of special regulatory issues specific to the country of the international member. The Network Group Operations Centers must specify any potential restrictions related to enrollment from international members prior to trial activation.

It is also anticipated that affiliates of main members for a particular Network Group will follow the crediting decision of the main member for a particular trial; however, that is at the discretion of the Network Groups through their membership rules. Institutions/sites that are members of the pediatric Network Group must credit the pediatric Network Group when it is leading a trial.

Use of the NCI Central Institutional Review Board: All U.S. institutions/sites participating in NCTN trials as members of 1 or more Network Groups (including Network Lead Academic Participating Sites, CCOPs, and MB-CCOPs) are required to use the pediatric and/or adult NCI Central Institutional Review Board for any NCTN trial under an NCI CIRB's purview. This requirement may be waived by the Lead NCTN Program Director through an exemption review process if the institution/site can adequately show that NCTN studies can be reviewed in a timely manner by its local IRB (or other Central IRB) that

is equivalent to the review timelines for the NCI CIRB (i.e., about 35 to 48 days for initial review) or if the institution/site can demonstrate other exceptional circumstances that preclude it from using the NCI CIRB. This requirement does not apply to international (non-U.S.) institutions/sites participating in NCTN trials (including member institutions/sites of the Canadian Collaborating Clinical Trials Network), given different regulatory requirements/procedures covering human subjects protection in other countries.

Exemption requests with supporting documentation of the timely IRB review from member institution/sites of the Network Group must be submitted to the Lead NCTN Program Director by the supporting Network Group. If an exemption is granted, the Network Group Operations Center is responsible for including reports of IRB timelines for their sites that have received an approved exemption in its annual progress report as well as any other pertinent information. The Lead NCTN Program Director may withdraw the exemption and require that the institution/site use the NCI CIRB for applicable NCTN studies if justification for the exemption is not warranted on a continuing basis.

1.3 Operational Management

1.3.1 Governance, Organizational Structure, Policies & Procedures, and Membership

The Group's Operations Center is responsible for coordinating study proposals, 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 Network Group Operations Center, including issuing subcontracts or purchased services agreements related to per case funding as well as overall management of the funds associated with the Cooperative Agreement. The Network Group Operations Center is also responsible for specifying the mix of funding available for the trial that it leads prior to trial activation as well as for providing information in a timely manner on appropriate modifications in funding on the trial during the course of accrual. The Network Group is also responsible for providing this information if it is the primary lead in the U.S. for an international trial (excepting trials led by the Canadian Collaborating Clinical Trials Network). Specific responsibilities of the Operations Center include the following:

Governance: The Network Group Operations Center is under the leadership of a "designated" Network Group Chair elected by the Network Group membership, who coordinate(s) all the scientific and administrative decisions related to Network Group-funded activities and the Network Group's institutional members with the assistance of the staff of the associated Network Group's Statistics and Data Management Center. The Multiple Principal Investigator (PI) option is encouraged for the Network Group Operations Center award given the team science approach of the research effort. Information on the Multiple PI Option is available at http://grants.nih.gov/grants/multi_pi/index.htm. If this option is used, the Network Group Operations Center should designate a "Contact PI" among the multiple PIs. The designated Network Group Chair (or Contact Principal Investigator under the Multiple PI option) is also responsible for all grant-related activities and for communication about these activities with the appropriate NCI/DCTD staff.

Organizational Structure, By-laws, and Standard Operating Procedures: The Network Group Operations Center is responsible for development and maintenance of an organizational structure for the Network Group, including a Constitution and By-laws for the Group. The organizational structure of the Network Group Operations Center should be established with clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of the Network Group Director of Operations (who must also be listed as key personnel in the Network Group Operations Center application and award). The

Operations Center is also responsible for the preparation and maintenance of Standard Operating Procedures (SOPs) that cover all aspects of the Network Group's activities.

The organizational structure should encompass the Scientific Research and Administrative Committees that the Network Group will need to support its research objectives as well any Executive Committee that the Network Group elects to establish. There should be clearly defined term limits and succession/transition plans for the senior leadership of the Network Group and for the leadership of its committees. Terms for the key scientific leadership positions of a Network Group (e.g., designated Network Group Chair, disease committee Chairs, etc.) should be limited to encourage participation by new investigators and to ensure a diversity of views over time. The process for filling elected positions for scientific leadership positions should be well described in the By-laws of the Network Group along with details of any exceptions to term limits.

Institutional Membership: As described under the Member Site Accrual Program section above, the Network Group Operations Center is responsible for establishing, maintaining, and monitoring all its members (i.e., Lead Academic Participating Site members and affiliates, CCOPs, MB-CCOP, pediatric sites, and other member institutions/sites) that participate in NCTN trials and credit the Network Group with patient accrual. The Network Group Operations Center must have a single consolidated roster of all these member categories for the Group that is incorporated into the CTSU Regulatory Support Services (RSS) and the Oncology Patient Enrollment Network (OPEN) systems to ensure that patients can be enrolled with appropriate crediting and accounting. As noted above under the Member Site Accrual Program section, institutions/sites are assigned to one of the following mutually exclusive categories across the entire Network for the NCTN Program for purposes of NCI/DCTD funding and crediting of accrual: (1) Lead Academic Participating Site (academic center and its essential components); (2) Affiliates included in a Lead Academic Site award (because they are completely managed by the Lead Academic Participating Site); (3) CCOP; (4) MB-CCOP; (5) Pediatric site; and (6) other Network Group member institutions/sites. For example, a site that is a CCOP has that designation across the NCTN Program regardless of the number of Network Groups to which it belongs.

1.3.2 Development of Study Proposals & Protocols for Clinical Trials

The Network Group Chair shall designate other Network Group investigators to serve as Study Chairs for each proposed study/protocol. The Network Group Operations Center is responsible for establishing policies and procedures for development and submission of Network Group study proposals and protocols to the NCI/DCTD/CTEP Protocol and Information Office (PIO) in a timely fashion for review and approval by NCI. The Operations Center is also responsible for assembling appropriate study teams for both protocol development and overseeing conduct of approved trials. The Network Group Operations Center has these responsibilities for conduct of approved trials regardless of whether the trial proposal originates from an investigator within or outside the Network Group. As the primary vehicle for definitive, large-scale, controlled clinical treatment and advanced imaging trials sponsored by the NCI, the Network Groups should strive to provide a transparent, user-friendly operation for all NCI-sponsored investigators who have trial concepts approved by the NCI Scientific Steering Committees or NCI/DCTD's Protocol Review Committee for conduct under the NCTN Program.

Study proposals and protocols (as well as correlative science studies requesting use of biospecimens collected during the conduct of NCTN trials) should be developed, submitted, and implemented in accordance with instructions set forth in the DCTD Investigator Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI) available at:
http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm, including the use of all required standard forms. Study proposal and protocols should also be developed per the

timelines required under the Operational Efficiency Working Group recommendations as referenced in the Investigator Handbook and available at: http://ctep.cancer.gov/SpotlightOn/OEWG.htm. Network Group SOPs should include time-lines for the development of LOIs and Concepts from initial submission of the study idea to NCI through study activation. The SOPs should also include mechanisms for monitoring the performance of the Network Group Operations Center and Network 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 Network Group's performance in meeting time-lines for study/protocol development should be provided in its Annual Progress Report.

In general, study proposals for treatment or advanced imaging clinical trials are evaluated as either Letters of Intent (LOI) or Concepts depending on the whether the proposal is reviewed/evaluated by the NCI/DCTD Cancer Therapy Evaluation Program (CTEP) Protocol Review Committee (PRC) or by an NCI Scientific Steering Committee (i.e., disease-specific or clinical imaging Steering Committees) and protocols are reviewed as briefly described in Part 1 – Section IV.D.3 of these Guidelines. The Operations Center is responsible for communicating the results of the NCI/DCTD review/evaluation process, including NCI Scientific Steering Committee decisions, to relevant Network Group committees and Network Group members.

In addition, correlative science studies embedded in NCTN clinical trials as well as requests for use of biospecimens collected in conjunction with an NCTN trial that were "banked" must undergo review and approval as outlined in Part 1. Section IV.D.3 of these Guidelines. This review policy applies even if the collection or storage of specimens was funded from sources outside the NCTN Program as the NCTN clinical trials was supported by the NCI/DCTD under these Terms and Conditions of Award which requires review under a process approved by NCI/DCTD unless a specific exemption to the review policy is granted by NCI/DCTD.

1.3.3 Conduct of Clinical Trials

Specific regulations regarding conduct of NCTN trials include the following:

- NCI/DCTD Approval Prior to Trial Activation and Approval of Protocol Amendments: Since public funds are used to support Network Group studies sponsored under the NCTN Program Cooperative Agreement, no Network Group study using funds supplied under the Cooperative Agreement can be opened without prior approval from the NCI/DCTD as communicated in approval letters sent to the Network Group Chair directly from the CTEP Protocol and Information Office (PIO). The Network Group also is not allowed to expend any NCI funds under this Cooperative Agreement to support any study disapproved by the NCI/DCTD. In addition, all protocol amendments must be submitted to CTEP's PIO and be approved by NCI/DCTD prior to implementation. Depending on the nature of the amendment, the trial may or may not be put on hold to further accrual and/or treatment until the amendment is approved.

  The required evaluation and review process for NCTN trials is explained in Part 1: Section IV.D.3. of these Guidelines with additional information in the DCTD Investigator Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI) available at: http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm.

- INDs for Studies: In addition, Network Group phase 3 trials (including phase 2/3 studies) using funds supplied under this Cooperative Agreement cannot be conducted under a company IND; all phase 3 IND trials supported, in whole or in part, under this Cooperative Agreement must be conducted under a Network Group IND or a DCTD IND (e.g., CTEP or CIP IND). This also applies to phase 3 trials requiring an IDE. Phase 1 and phase 2 trials may be

conducted under Network Group or company INDs or IDEs with appropriate monitoring per the Network Group data and safety monitoring plan or Data and Safety Monitoring Board (Data Monitoring Committee) policy for randomized phase 2 trials.

- Agents from NCI/DCTD Collaborators: All NCTN studies using NCI/DCTD-sponsored investigational agents or agents supplied by CTEP, CIP, or other DCTD programs under Collaborative Agreements (such as Cooperative Research and Development Agreements [CRADAs], Clinical Trial Agreements [CTAs], and Clinical Supply Agreements [CSAs]) must be conducted in accordance with the terms of the NCI/CTEP Intellectual Property Option to Collaborators, found on the CTEP website at: http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm, 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. When NCI/DCTD and the Network Group contract with the same company (or companies) for support for the same trial (i.e., trials conducted under a NCI/DCTD Collaborative Agreement, the Group contracts may require review by the appropriate DCTD program at the discretion of NCI (see Part 4 – Appendices - Section I.F. in these Guidelines).

- NCTN Required Tools and Services: Network Groups are **required** to use standard NCTN tools and services for all NCTN trials including, but not limited to: (a) the Common Data Management System for study design/build and data collection with case report reports (CRFs) designed by the SDMC that are compliant with the NCTN Program approved sections of the data dictionary for common data elements in the NCI Cancer Data Standards Registry and Repository (caDSR) (see https://cabig.nci.nih.gov/community/concepts/caDSR/); (b) NCTN information system for tracking biospecimen collection from NCTN trials (in development); (c) NCTN Oncology Patient Enrollment Network (OPEN) and Regulatory Support Services (RSS) via the Cancer Trials Support Unit (CTSU) for central registration and randomization of patients onto NCTN trials; (d) the NCI Common Terminology Criteria for Adverse Events (CTCAE); (e) the Comprehensive Adverse Event and Potential Risks (CAEPR) for agents, if available; (f) the NCTN specification for appropriate designation of per case management funding for trials prior to study activation; and (g) review of all pediatric phase 2 and phase 3 trials and all adult phase 3 trials and selected phase 2 trials by the appropriate NCI Central Institutional Review Boards.

- Adverse Event Reporting and Patient Safety: The Network Group Operations Center must establish a system for assuring expedited reporting of all serious 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 v4.0 (CTCAE) or most recent version, which is NCI and DCTD's standard language for reporting adverse events in oncology clinical trials.

- For agents under DCTD-sponsored INDs, this involves reporting to the appropriate DCTD program via the Adverse Event Expedited Reporting System (AdEERS), or its successor application, according to the guidelines specified in each protocol. **Network Groups must also use AdEERS, or its successor application, for expedited reporting of serious adverse events for all NCTN trials** (even those not under a DCTD IND or not under any IND/IDE) since AdEERS provides reporting pathways for studies that do not include DCTD IND agents, as well as pathways for studies that do not include any agents (e.g. surgical only study, radiation only study). Serious adverse event reporting for all NCTN trials should follow the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

All Network Group studies funded under this Cooperative Agreement, in whole or in part, must use also use CTEP CAEPRs for agents used in NCTN trials even if the agent is used in a trial that is not under a CTEP IND or CIP IND.

In addition, for any study using agents under a CTEP or other DCTD-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 (IDB) and Clinical Investigations Branch (CIB) at CTEP, or the Clinical Trials Branch at CIP if a CIP IND imaging agent is involved before any action is taken. For NCTN studies that are not being conducted under a DCTD 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 Clinical Investigations Branch at CTEP (or Clinical Trials Branch at CIP if an IND imaging agent is involved) before any action is taken.

In general, for studies with these types of immediate safety issues that are under monitoring by a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) as defined in Part 1: Section IV.B.1.5.6, immediate notification should be made to the DSMB/DMC Chair and the Lead NCTN Program Director. For therapeutic studies that are not under DSMB/DMC monitoring, immediate notification should be made to the disease liaison physician in the Clinical Investigations Branch at CTEP (along with the agent liaison physician in the Investigational Drug Branch at CTEP for studies being conducted under CTEP IND) with a copy to the Lead NCTN Program Director. For imaging studies that are not under DSMB/DMC monitoring and/or those being conducted in under CIP IND, immediate notification should be made to the physician imaging agent liaison in the Clinical Trials Branch at CIP with a copy to the Lead NCTN Program Director.

- CTRP/clinicaltrials.gov Registration and Outcomes Reporting: All NCTN trials must also be registered and appropriate information updated in the NCI Clinical Trials Reporting Program (CTRP) as described at: http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main as well as registered in the U.S. National Library of Medicine clinical trials database (i.e., at www.clinicaltrials.gov). Changes in the trial design and accrual as well as results reporting from NCTN trials are also required to be reported in clinicaltrials.gov as required under the Food and Drug Administration Amendments Act (FDAAA), Section 801. The Network Group Operations Center should work with its associated Network Group Statistics and Data Management Center to coordinate activities to ensure information on Group NCTN trials is appropriately updated in these systems.

- CDUS/CDS Reporting: In addition, data must be submitted on all NCTN trials, as appropriate, to the NCI/DCTD Clinical Data Update System (CDUS/CDS) at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm. The Network Group Operations Center should work with its associated Network Group Statistics and Data Management Center to coordinate activities to ensure information on Network Group NCTN trials is appropriately updated in all these systems.

- DSMB/DMC Recommendations for NCTN Trials: The Network Group Operations Center in conjunction with the associated Network Group Statistics and Data Management Center (SDMC) is required to send a listing (or an email with internet access link to a listing) of all Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) recommendations accepted by the Network Group Chair(s) to the Lead NCTN Program Director after every scheduled DSMB/DMC meeting. DSMB/DMC recommendations accepted by the Network Group Chair(s) after ad hoc DSMB/DMC meetings/calls must also be communicated to the Lead NCTN Program Director.

- Early Trial Closure: The Network Group Operations Center must establish policies and procedures for early closure of studies in conjunction with the associated SDMC. The Operations Center should explicitly describes 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/DCTD have approved early stopping guidelines for slowly-accruing phase 3 studies for the NCTN Program, including phase 2/3 trials (see Part 4 – Appendices – Section I.F). If accrual is behind expectations for a specific trial, the Network Group should involve the appropriate NCI/DCTD 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 policy for study closure. 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) for any NCTN trial, regardless of whether it is under CTEP IND or not.

  For any Network Group phase 1 or phase 2 trial for which CTEP is the IND sponsor of one or more study agents or is providing agent(s), the Network Group must notify and receive approval from the appropriate CTEP staff (i.e., Investigational Drug Branch physician agent liaison and Clinical Investigations Branch physician disease liaison) 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 (i.e., the Clinical Investigations Branch physician disease liaison and the Lead NCTN Program Director) prior to closure of the study 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 NCTN or CTEP-sponsored trials as well as in the study which is being closed.

  For all Network Group phase 3 studies, the Network Group's DSMB should have reviewed the study and recommended study closure and the Network Group Chair should have concurred with this decision, with the exception of phase 3 studies being closed per the NCTN 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 Network Group Chair, **the Network Group must inform and discuss closure of the study with the Lead NCTN Program Director or his/her designee before closure of the study and before disclosure to Network Group members, the PI(s) and 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, this notification also helps 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 coordinate public dissemination of the information and address public inquiries about the trial. For additional information related to Network Group DSMBs, see Part 4 – Appendices – Section VIII.

1.3.4 Quality Assurance and Onsite Auditing

The Network Group is responsible for establishing mechanisms to assure the accuracy and reliability of the Network 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 (i.e., this is a shared responsibility). In addition, the Clinical Trials Monitoring Branch (CTMB) of CTEP provides direct oversight of each Group's monitoring program, which includes onsite auditing as one component as described in the CTMB Guidelines at:
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm

Quality Assurance of Group Clinical Trials: Quality assurance is a complex undertaking spanning the entire range of studies conducted by the Group including: screening, biomarker, omics, diagnostic, interventional, therapeutic and imaging modalities. Key items that should be addressed in a Group's quality control procedures include the following:

- *Study Monitoring:* The Network Group Operations Center is responsible for overall organization and oversight of study teams that monitor data from specific clinical trials and with appropriate coordination with the associated Network Group Statistics and Data Management Center.

- *Member Performance Evaluations:* The Network Group Operations Center is responsible for oversight of all its members (i.e., institutional member and affiliates, Lead Academic Participating Sites and affiliates, CCOPs, and MB-CCOPs) including placing members on probation for inadequate performance and for removing them from the Network Group if performance is not adequate during the probationary period or at any time during which the participating site does not meet established Network Group standards. Performance factors to be considered include the following:
  - Accrual of adequate number of eligible patients onto NCTN trials;
  - Timely and accurate submission of required data;
  - Conscientious observance of protocol requirements;
  - Compliance with regulatory requirements for the protection of human subjects and Good Clinical Practice;
  - Participation in study development, leadership, and publication;
  - Participation in Network Group leadership and/or other Group activities; and
  - Summary reports of the results of performance evaluations should be submitted with the annual progress reports.

- *Training Program:* The Network Group should have training activities that address data collection, data management, and overall data quality, including but not limited to the following areas:
  - Training of new Clinical Research Associates (CRAs) in the Group's data submission policies and ongoing training of all CRAs concerning changes to Group procedures and instructions for data submission in new protocols;
  - Instruction of Study Chairs on their responsibilities for study monitoring;
  - Instruction of Principal Investigators and other investigators at member participating Sites on their responsibilities for complying with Group SOPs, including conflict of interest and all other federal regulations at their institution/site and any additional site(s) for which the member site has oversight responsibility; and
  - 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.

- *Central Review and Correlative Science/Translational Research Committees*: Committees should be established for conducting central review of the following major elements that affect the outcome of specific clinical or provide integral/integrated translational science associated with specific trials, including the following:
  - *Integral or Integrated Correlative Science and/or Translational Research Committees:* integral and/or integrated correlative science or translational science studies included in Network Group trials that address specific and important scientific hypotheses (or are integral to the primary study design) should be appropriately designed. Funding for these studies is not provided directly by the NCTN award but may be applied for via BIQSFP funding or through other sources, including administrative supplements from NCI/DCTD in certain cases for specific trials.
  - *Pathology*: Pathology review may be either by a committee within the Network Group or by an external reference panel. Prospective central verification of pathologic diagnosis may be required for specific trials in which it is integral or essential to the study design (i.e., cases in which known variability in the accuracy of histologic (or other) diagnosis is a potentially serious problem and in which pathology data is integral to appropriate study design and analysis). Funding for this central review, whether retrospective or prospective, is not provided by the NCTN award; however, it can be provided via BIQSFP funding or through other sources.
  - *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 and should be provided via coordination with the Network Radiotherapy and Imaging Core Services Centers.
  - *Imaging support including diagnostic imaging:* When relevant, central review (either prospective or retrospective) of imaging in NCTN trials may be required for evaluating response, establishing a diagnosis, and/or screening of patients and should be provided via coordination with the Network Radiotherapy and Imaging Core Services Centers.
  - *Systemic Therapies (Chemotherapy, Immune Therapy or other Biologic Therapies):* Central review may be performed by the Network Group study team for the trial to determine protocol compliance with dose administration and dosage modification.
  - *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) by the Network Group study team for the trial.

Onsite Auditing: Both the Network Group's Operations Center and its associated Statistics and Data Management Center have responsibilities with respect to onsite auditing, and the Network Group's SOPs should clearly delineate how these responsibilities are apportioned between the two Centers. In particular, Network Group's Operations Center and its associated Statistics and Data Management Center should ensure that policies and procedures are in place to ensure that auditors participating in the onsite auditing program maintain confidentiality of all patient materials.

The Network Information on the requirements for onsite auditing is provided by Guidelines from the Clinical Trials Monitoring Branch (CTMB) of NCI/DCTD/CTEP available at:
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm
In order for the NCI to review the Network Group's compliance with this requirement, each Network Group should provide annually an accounting of audit activities for all its members (see the Suggested Format for Reporting Onsite Auditing Activities in Part 4 – Appendices – Section II.A.9).

CTMB also provides direct oversight of each Network Group's auditing program. The purpose of an audit is to document the accuracy of data submitted to the Network 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 Network 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 Network Group Operations Center is responsible for oversight of all its members enrolling patients on NCTN studies that any member credits to the Network Group regardless of whether the Network Group is leading the trial or not. This includes ultimate oversight responsibility for CCOP and MB-CCOP members as well as Lead Academic Participating Sites and their affiliates when accrual for an enrollment in an NCTN trial is credited to the Network Group. The Network Operations Center should be aware of all affiliate sites participating in its trials under the aegis of an institutional member, CCOP, MB-CCOP, or Lead Academic Participating Site via its consolidated roster. Any members of a Network Group found not to be in compliance with the NCI Guidelines for Onsite Monitoring by the CTMB may be suspended from participating in any NCTN trials until a corrective action plan is submitted by the institution/site to the Network Group and is reviewed and approved by the Network Group and CTMB/CTEP.

Additional information on quality assurance required of Network Groups with respect to trial data (including Operations Center responsibilities) and, in particular, **procedures a Network 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. Please see Part 1 - Section IV.D.4 of these Guidelines on Quality Assurance regarding reporting of audit issues and potential cases of scientific misconduct**.

1.3.5 Financial Management

The Network Group Operations Center is responsible for the financial management of the Center, including appropriate funding for all Center activities and provision of appropriate NCI/DCTD approved total cost for various categories of “per case management” funding to member institutions/sites through purchase service agreements or subcontracts as well as funding for other important scientific and administrative services needed for Center functions such as support for Study Chairs and Scientific Research Committee Chairs.

In addition, the Network Group Operations Center should have policies and procedures in place with their member institutions/sites and related affiliates to ensure that “per case management” funding provided to these members by the Network Group is dispersed to the site in the total cost amount required by NCI/DCTD for the particular category of “per case management” funding (see Part 4 – Appendices – Section IV.A. for information on the anticipated total cost figures for the various categories of “per case management” funding anticipated for the initial project period under the NCTN Program.

The Network Group Operations Office should also ensure that the funding is allocated at the site so that investigators and clinical research staff from different departments and disciplines at the institution that participate in NCTN trials are appropriately represented in the disbursement of funding. For example, the Principal Investigator(s) at an institution/member site, with which a Network Group has a subcontract or purchase service agreement (PSA) for work related to enrollment of patients and conduct of trials in the NCTN Program, may be a member of the Medical Oncology department at the institution, yet work under the subcontract or PSA is performed across multiple departments at the institution (e.g., surgery, pathology, radiation oncology). The Network Group should strive to ensure that all member institutions/sites distribute funding to all departments involved in support of NCTN clinical trials in a manner that reflects the work performed by the various members of the clinical research team.

Any separate, non-NCI/DCTD funding (i.e., funding not provided under the Cooperative Agreements of the NCTN Program) dispensed by a Network Group to cover costs associated with patient enrollment on NCTN trials that it leads must be provided to all qualified institutions/sites that participate in its NCTN trials regardless of which Network Group the enrolling institution belongs to and/or credits with the patient accrual. This principle is considered an essential feature of the NCTN Program and the Terms and Conditions of Award as it is fundamental to ensure fairness for work performed across the Network.

1.4 Program for Collaborations and Participation in Collective Management

The Network Group Operations Center is responsible for developing collaborations with other Network Groups as well as other NCI-sponsored programs and investigators (e.g., SPOREs, Cancer Centers, R01/P01 investigators) to augment and enhance the clinical research strategy and research productivity of its portfolio of clinical trials conducted in the NCTN. In addition, the Network Group Operations Center is also responsible for participating in the collective management of the Network including participation in appropriate NCTN Program activities and initiatives (e.g., NCI Scientific Steering Committees, NCI CIRB, etc.) and through the NCTN Leadership Management Committee by making recommendations to NCI for modifications to the Program as well as to standard NCTN common tools and services.

Each Network Group Operations Center is required to have policies to encourage other Network Groups to name co-principal investigators for studies that the Center leads (in disease areas that other Network Groups have scientific research goals and/or scientific research committees) in order to augment accrual via collaboration on its NCTN trials.

1.5 Compliance with Federal Regulations for Clinical Research & Resource Sharing Plans

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

1.5.1 Office for Human Research Protection (OHRP) Assurances

The Network Group Operations Center must assure that each member (this includes all affiliates or participating sites enrolling patients under any of the membership categories for the Network Group) has a current, approved Federalwide Assurance (FWA), on file with OHRP. Information on assurances is available on the OHRP website at: http://www.hhs.gov/ohrp/. In addition, federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with 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.

1.5.2 IRB Review of NCTN Trials by Member Institutions/Sites

The Network Group Operations Center must assure that each protocol for an NCTN trial that one of its member institutions/sites credits to the Network Group is reviewed and approved by the appropriate Institutional Review Board (IRB) of the Network Group member prior to patient entry via the Regulatory Support Services (RSS) of the CTSU, and assure that each protocol is reviewed annually by the IRB so long as the protocol is active (it is anticipated that the adult or pediatric NCI CIRB will be the IRB of record in most cases). The Network Group must ensure that each member site of the Group forwards its regulatory documents to RSS, otherwise the site will not be allowed to enroll patients on NCTN trials.

1.5.3 Assurance of Appropriate Informed Consent by Member Institutions/Sites

The Network Group Operations Center must have procedures in place to ensure that each member institution/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. The template for the NCI informed consent document must be

used for all NCTN trials, with appropriate modifications as approved by NCI/DCTD for specific trials during the protocol development and review process. Information on the NCI informed consent templates is available at: http://cancer.gov/clinicaltrials/patientsafety/simplification-of-informed-consent-docs/page3.

1.5.4 IRB Review of the Network Group Operations Center

Institutional Review Board (IRB) review of the Network Group Operations Center grant is required. The IRB should determine and document that the Network Group Operations Center has sufficient mechanisms in place to ensure that (1) oversight of data management and analysis by the associated Network Group Statistics and Data Management Center 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 member institution/site participating in a trial; (3) each member institution/site holds or is covered under an applicable OHRP-approved Federalwide Assurance (FWA); (4) each protocol is reviewed and approved by the IRB covering the member institution/site prior to the enrollment of subjects; (5) any substantive modification by the institutional member/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: http://www.hhs.gov/ohrp/.

1.5.5 Inclusion of Women, Minorities, and Children 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 at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. 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 Network 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. 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.

Note: A Network Group Operations Center should report this data for all patients enrolled on studies it leads regardless of whether it is credited with the patient enrollment or not and this data should be reported in the Network Group Operations Center annual progress reports. Final analyses of sex/gender and ethnic/racial differences must be reported in the required Final Progress Report or any future competitive renewal applications.

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 as described at: http://grants.nih.gov/grants/funding/children/children.htm. For cancer clinical research, Network 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 Network Group devoted to pediatric cancer research, 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.

1.5.6 Data and Safety Monitoring Policy and Plans

The Network 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. Data and Safety Monitoring Boards (DSMBs) or Data Monitoring Committees (DMCs) must be established that comply with the "NCI NCTN Program Data Monitoring Committee Policy" as provided in Part 4 – Appendices – Section VIII. For the purposes of these Guidelines, the terms DSMB and DMC are used interchangeably to refer to committees established under with this policy. The DSMB/DMC must be used to monitor all phase 3 trials and randomized phase 2 trials led by the Network Group. The Network Group's DSMB/DMC policy and membership roster, as well as any changes/modifications to the policy or membership roster, must be submitted to and approved by the Lead NCTN Program Director.

Monitoring Plans for Trials Not Under DSMB/DMC: Data and Safety Monitoring plans developed for other Network 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: http://grants.nih.gov/grants/guide/notice-files/not98-084.html, with additional description at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html. Further information concerning essential elements of Data and Safety Monitoring Plans for clinical trials funded by the NCI is available at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines.

1.5.7 Resource Sharing Plans

Data Sharing Policy: The Network Group Operations Center 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: http://grants.nih.gov/grants/policy/data_sharing. The Network Group Operations Center's policy for data sharing must be submitted to and approved by the Lead NCTN Program Director. A template to help Network Group Operations Centers develop their own Data Sharing Policies is provided in Part 4 – Section VII of these Guidelines. 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/DCTD 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 NCI/DCTD (i.e., the Lead NCTN Program Director in conjunction with the NCI/DCTD Regulatory Affairs Branch). Release of data may also be subject to the terms of any contracts the Network Group Operations Center has with other entities which cover any of the requested data.

Biospecimen Sharing Policy: The Network Group Operations Center is required to follow the NCI/DCTD policy regarding review of requests for use of banked biospecimens collected in association with NCTN trials that it leads by CTEP's Protocol Review Committee or an NCI/DCTD-approved NCTN Correlative Science Committee as described in Part 1 – Section IV.C.3. Network Group Operations Centers are also required to have a plan/policy in place to describe how information on its inventory of biospecimens will be made available to the public that is submitted to and approved by the Lead NCTN Program Director, Associate Director Cancer Diagnosis Program, and Program Director of the Tumor Banking Program for the Network Groups. This inventory should be consistent with standards established by the Network Tumor Banking Committee for the NCTN Program.

Network Group Operations Centers should also have plans in place regarding the following types of resources, as appropriate for the clinical research it conducts: Sharing Model Organisms and Genome Wide Association Studies (GWAS).

1.5.8 Education on the Protection of Human Subjects

NIH policy requires education on the protection of human subject 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

1.5.9 Other Federal Regulations

Information on other federal regulations (and their associated citations/URLs) that may be applicable to the Network Group Operations Center's research is provided in Part 4: Appendices – Section IV.B.

1.6 Conflict of Interest Policy

The Network Group Operations Center receiving NIH funding from a grant or cooperative agreement must establish a Conflict of Interest Policy that is in compliance with all of the DHSS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: http://grants.nih.gov/grants/policy/coi. This policy should ensure that there is no reasonable expectation that any investigator or staff member of the Network Group Operations Center or at any of its member institutions/sites involved in the design, conduct, or reporting of research will be biased by any conflict of interest (using the definition of investigator provided in the NIH grants policy). This policy should also be in compliance with NCI/DCTD/CTEP's Conflict of Interest Policy for NCTN Phase 3 Clinical Trials found on the CTEP website at: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies.

1.7 Special Requests for Use of the NCTN Program Infrastructure Services

The infrastructure of the NCTN Program, including NCI/DCTD supported contract services, can only be used for NCTN trials approved by NCI/DCTD under this Cooperative Agreement. In special circumstances, a Network Group Operations Center may request limited use of certain services (e.g., regulatory support services (RSS), the Oncology Patient Enrollment Network (OPEN) for a related research effort or study such as a banking protocol not associated with a specific NCTN clinical trial that is supported by charitable funds or a related oncology research study funded by another NIH-funded program). These requests must be reviewed and approved by NCI/DCTD via an official written approval by the Lead NCTN Program Director and the Associate Director, CTEP. It is anticipated that only requests that are compatible with and are anticipated to benefit the overall research goals of the NCTN Program would be approved, subject to the availability of NCTN Program resources/funding, since the use of the requested services are funded under the NCTN Program.

2. Specific Awardee Rights & Responsibilities - Network Group Statistics and Data Management Centers

Throughout these Terms and Conditions of Award, "Network Group Statistics and Data Management Center" or "SDMC" refers to the organizational structure which is composed of the key personnel (including the scientific and administrative leaders of the Center) responsible for implementing statistical design and analysis as well as data management for clinical trials and collaborating on research goals of the NCTN Program through the Center.

2.1 Statistical Analysis Program & Collaborative Research and Collective Management

2.1.1 Statistical Leadership

The Network Group's Statistics and Data Management Center (SDMC) is responsible for the statistical leadership of the Network Group research agenda and all aspects of data management. The SDMC is responsible for helping the Network Group Operations Center develop the statistical research design and analysis plan for Network Group studies as well as for providing statistical analysis, appropriate interim monitoring plans, interpretations, and conclusions in regard to study data.

The SDMC conducts final study analyses at the protocol-prescribed time and participates on publication writing teams for the primary study analysis as well as secondary study analyses. Cross-protocol analyses may be performed by the SDMC, as necessary, to support the research agenda of the Network Group, Network Group collaborations as well as when requested by NCI/DCTD for the NCTN Program.

2.1.2 Governance, Organizational Structure, and Policies and Procedures

Governance: The Network Group's Statistics and Data Management Center (SDMC) is under the leadership of the "designated" Network Group Statistician, who coordinates the statistical and data management policies and procedures related to Network Group-funded activities with the assistance of the staffs of the associated Network Group's Operations Center. The Multiple Principal Investigator (PI) option is encouraged for the Network Group SDMC award given the team science approach of the research effort. Information on the Multiple PI Option is available at http://grants.nih.gov/grants/multi_pi/index.htm. If this option is used, the Network Group SDMC should designate a "Contact PI" among the multiple PIs. The Network Group Statistician (or Contact Principal Investigator under the Multiple PI option) or designee is also responsible for all grant-related activities and for communication about these activities with the appropriate NCI/DCTD staff.

Organizational Structure: The SDMC is responsible for development and maintenance of an organizational structure for the SDMC with clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of the Network Group Director of Operations (who must also be listed as key personnel in the Network Group SDMC application and award). . The SDMC must also agree to abide by the Constitution and By-Laws of its associated Network Group Operations Center.

Standard Operating Procedures: The SDMC must have Standard Operating Procedures (SOPs) covering all aspects of data management, study monitoring, and data analysis for Network Group trials. The SOPs should include plans for training Network Group investigators and Clinical Research Associates (CRAs) at member participating sites and Study Chairs and Study Teams about their responsibilities for data management and study monitoring.

2.1.3 Facilities and Equipment

The SDMC must have the appropriate facilities and equipment, especially with respect to information technology, to provide for complete data management for all aspects of the Network Group's clinical trials.

2.1.4 Collaborative Research and Collective Management

The SDMC is responsible for supporting the statistical analyses for collaborations with other Network Groups as well as other NCI-sponsored programs and investigators (e.g., SPOREs, Cancer Centers, R01/P01 investigators) to augment and enhance the clinical research strategy and research productivity of its portfolio of clinical trials conducted in the NCTN. The SDMC should also be able to provide statistical and data management support for trials that originate from outside the Network Group that are prioritized by the NCI Scientific Steering Committees and approved by NCI as well as for other collaborations with NCI-sponsored early phase clinical trials networks under the NCTN Program.

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

In addition, the SDMC is also responsible for participating in the collective management of the Network including participation in appropriate NCTN Program activities and initiatives (e.g., NCI Scientific Steering Committees, NCI CIRB, etc.) and through the NCTN Leadership Management Committee by making recommendations to NCI for modifications to the Program as well as to standard NCTN common tools and services.

2.2 Data Management

2.2.1 Data Management Policies and Use of Standard NCI Tools

The SDMC should establish data management policies and procedures for ensuring data accuracy, timeliness, completeness, and consistency for Network Group NCTN trials. The general categories that should be addressed by the SDMC data management policies are listed below.

- The SDMC should provide a data management system for central storage, security, processing and retrieval of study results that incorporates security features consistent with DHHS guidelines.

- The SDMC should have procedures for backing up the Network Group's clinical and administrative data, including intermittent duplication of the database with storage at a remote facility.

- The SDMC should protecting patient confidentiality at all steps in the submission and analysis of clinical trials data and ensure the technical integrity and security of patient in compliance with federal regulations, including the Health Insurance Portability and Accountability Act (HIPPA).

- The SDMC must ensure, in coordination with the Network Group Operations Center, that data management operating policies and practices are in compliance with the Network Group's official policy on sharing research data (e.g., Data Sharing Policy) as approved by NCI/DCTD.

- The SDMC is **required** to use standard NCTN tools and services for the design and conduct of NCTN trials including, but not limited to: (a) the Common Data Management System for study design/build and data collection with case report reports (CRFs) designed by the SDMC that are compliant with the NCTN Program approved sections of the data dictionary for common data elements in the NCI Cancer Data Standards Registry and Repository

(caDSR) (see https://cabig.nci.nih.gov/community/concepts/caDSR/); (b) NCTN information system for tracking biospecimen collection from NCTN trials (in development); (c) NCTN Oncology Patient Enrollment Network (OPEN) and Regulatory Support Services (RSS) via the Cancer Trials Support Unit (CTSU) for central registration and randomization of patients onto NCTN trials; (d) the NCI Common Terminology Criteria for Adverse Events (CTCAE); and (e) the Comprehensive Adverse Event and Potential Risks (CAEPR) for agents, if available.

During the approval process for study protocols and amendments, NCI/DCTD ensures that these standard NCTN tools and services are used. In addition, Network Group trial protocols will be periodically audited by NCI/DCTD to ensure that the tools related to common data elements in compliance with the NCTN Program approved sections of the data dictionary for common data elements in caDSR are used in the data collection instruments for the NCTN trials. If issues with compliance are identified, the NCI/DCTD will work with the Network Group to develop a corrective action plan.

2.2.2 Data Reporting Requirements

The SDMC must have policies and procedures in place to ensure that data reporting requirements are fulfilled in a timely manner including the major data reporting requirements outlined below.

Adverse Events: The SDMC should assist its associated Network Group Operations Center in meeting its responsibility for adverse event reporting. This includes using the most recently approved version of the Common Terminology Criteria for Adverse Events Version (CTCAE), which is the NCI's standard language for reporting adverse events in clinical trials, and is provided on the NCI/DCTD/CTEP website at: http://ctep.cancer.gov/reporting/ctc.html. Expedited reporting of all serious adverse events should be performed via CTEP's Adverse Event Expedited Reporting System or AdEERS (or its successor system), as described at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm according to the guidelines specified in each protocol.

Clinical Data Update System (CDUS/CDS): The SDMC, working with the associated Network Group Operations Center, is responsible for coordinating the timely reporting of data from Network Group clinical trials to CTEP using the Clinical Data Update System (CDUS) or its successor application as described at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm. 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 required to 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; however, complete reporting of CDUS data on adverse events may be required for phase 3 trials by CTEP under certain circumstances.

Clinical Trials Reporting Program (CTRP) & Clinicaltrials.gov Reporting System: The SDMC, working with the associated Network Group Operations Center, is responsible for coordinating the registration of and reporting on Network Group studies to the NCI Clinical Trials Reporting Program (CTRP) as described at: http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main as well as the U.S. National Library of Medicine clinical trials database (i.e., at www.clinicaltrials.gov). Changes in the trial design and accrual as well as results reporting from NCTN trials are also required to be reported in clinicaltrials.gov as required under the Food and Drug Administration Amendments Act (FDAAA), Section 801.

Report of Studies: The SDMC, working with the Network Group Operations Center, is responsible for providing a semi-annual Report of Studies on all Network Group trials. 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 Network Group Operations Center, for ensuring that copies of the Report are available to Group members and to the Lead NCTN Program Director. The Report of Studies may be provided to the Lead NCTN Program Director via electronic access to the member side of the Network Group website. If a Network Group determines that a Report of Studies is not needed biannually, the Network Group must seek approval from the Lead NCTN Program Director, providing the rationale for this request in writing.

NCI Access to Network Group Website and Data Files Requested by NCI: The SDMC in conjunction with the Network Group Operations Center is responsible for ensuring that the Lead NCTN Program Director at NCI/DCTD has access to the Network Group website, including the member side of the website.

Upon request by the NCI, the SDMC is also responsible for providing true copies of data files and supporting documentation for specific NCI-supported trials in a timely manner.

Data for Member Performance Evaluations, Audits, & Data Monitoring Safety Boards (DSMBs): The SDMC is responsible for providing accurate and timely reporting of data on accrual, data timeliness, and accuracy, protocol compliance, long term patient follow-up, and audit results related to the conduct of Network Group trials by member sites for Performance Evaluations of the sites. The SDMC will also provide all data required for member site auditing as well as data evaluation of trials for the Network Group's Data and Safety and Monitoring Board.

2.2.3 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 Network Group responsibility that primarily involves the SDMC. The elements described below are considered essential for study monitoring.

- 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.

- Ongoing assessment of patient eligibility, patient evaluability, and appropriate randomization

- Adequate measures to ensure timely submission of study data as well as adequate measures to ensure timely medical review and assessment of individual patients' data with rapid reporting of treatment-related morbidity information and measures to ensure communication of this information to all appropriate parties

- Interim evaluation of outcome measures and patient safety analyses

Study monitoring reports describing patient accrual and demographics, data timeliness, toxicity, and other items should be prepared as appropriate for Study Chairs, for Data and Safety Monitoring Boards (DSMBs), and for inclusion in the semi-annual Report of Studies.

2.2.4 Quality Assurance and Onsite Auditing

- The responsibilities of the SDMC for quality assurance including providing support for Member Site Performance Evaluations as described under the Data Reporting Requirements in Part 1.

Section IV.2.2.2 of these Guidelines. The SDMC responsibilities for onsite auditing include data reporting as describe in Part 1. Section IV.B.2.2.2 as well as other support necessary for the Network Group's onsite auditing program to maintain compliance with the NCI-CTMB Guidelines for Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) at: http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm.

2.3 Compliance with Federal Regulations for Clinical Research & Resource Sharing Plans

The Network Group Statistics and Data Management Center is responsible for assuring that it is in compliance with all applicable federal regulations related to human subjects protection including the confidentiality of patient data (e.g., the Health Insurance Portability and Accountability Act - HIPAA) and ensuring the technical integrity and security of its data management systems. Policies and guidelines to be addressed include the following:

2.3.1 IRB Review of Network Group SDMC

Institutional Review Board (IRB) review of the Network Group SDMC grant is required. The IRB should determine and document that the Network Group SDMC has sufficient mechanisms in place to ensure that data management and analysis and that Data and Safety Monitoring systems are adequate, especially with respect to protecting the confidentiality of patient data, given the nature of the research involved. Information on this requirement for IRB review can be obtained on the OHRP website at: http://www.hhs.gov/ohrp/.

2.3.2 Inclusion of Women, Minorities, and Children 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 at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. 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 Network 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial groups must be included in clinical trial protocols and the Network Group SDMC should ensure that it has appropriate procedures in place to address this requirement. 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 any future competitive renewal applications.

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 as described at: http://grants.nih.gov/grants/funding/children/children.htm. For cancer clinical research, Network Group SDMCs supporting 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 Network Group devoted to pediatric cancer research, 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.

2.3.3 Resource Sharing Plans

Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and GWAS Sharing Plan) are required for all key components of the NCTN Program. However, since it is expected that the Network Group SDMC will follow the Resource Sharing Plans of the associated Network Group Operations Center, the SDMC is required to follow these Resource Sharing Plans for all NCTN trials its supports. The Network Group Operations Center data sharing plan should comply with the NCTN Program Data Sharing Plan template as described in Part 4 - Appendices - Section VII for Network Group Operations Centers in these Guidelines.

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 NCI/DCTD/CTEP (i.e., the Lead NCTN Program Director in conjunction with the NCI/DCTD/CTEP Regulatory Affairs Branch). Release of data may also be subject to the terms of any contracts the Network Group Operations Center has with other entities which cover any of the requested data.

Biospecimen Sharing Policy: The Network Group Operations Center is required to follow the NCI/DCTD policy regarding review of requests for use of banked biospecimens collected in association with NCTN trials that it leads by CTEP's Protocol Review Committee or an NCI/DCTD-approved NCTN Correlative Science Committee as described in Part 1 – Section IV.C.3. Network Group Operations Centers are also required to have a plan/policy in place to describe how information on its inventory of biospecimens will be made available to the public that is submitted to and approved by the Lead NCTN Program Director, Associate Director Cancer Diagnosis Program, and Program Director of the Tumor Banking Program for the Network Groups. This inventory should be consistent with standards established by the Network Tumor Banking Committee for the NCTN Program. The SDMC is required to follow and support these policies for the trials led by its associated Network Group Operations Center.

Network Group Operations Centers should also have plans in place regarding the following types of resources, as appropriate for the clinical research it conducts: Sharing Model Organisms and Genome Wide Association Studies (GWAS). The Network Group SDMC is required to follow and support these policies for the trials led by its associated Network Group Operations Center.

2.3.4 Education on the Protection of Human Subjects

NIH policy requires education on the protection of human subject 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

2.3.5 Other Federal Regulations

The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central *upon acceptance for publication*. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication. More information about this policy or the submission process is available on the NIH Public Access Policy website at: http://publicaccess.nih.gov/.

Information on other federal regulations (and their associated citations/URLs) that may be applicable to the SDMC's activities is provided in Part 4: Appendices – Section IV.B.

2.4 Conflict of Interest Policy

The Network Group Statistics and Data Management Center (SDMC) receiving NIH funding from a grant or cooperative agreement must be in compliance with all of the DHSS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: http://grants.nih.gov/grants/policy/coi. This policy should ensure that there is no reasonable expectation that any investigator or staff member of the Network Group Statistics and Data Management Center involved in the design, conduct, or reporting of research will be biased by any conflict of interest (using the definition of investigator provided in the NIH grants policy). The SDMC policy should also be in compliance that of its affiliated Network Group Operations Center and with the general policies of the NCI and the NIH and with the NCI/DCTD/CTEP's Conflict of Interest Policy for NCTN Phase 3 Clinical Trials found on the CTEP website at: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies.

3. Specific Awardee Rights & Responsibilities - Network Group Integrated Translational Science Centers

Throughout these Terms and Conditions of Award, "Network Group Integrated Translational Science Center" refers to the organizational structure which is composed of the key personnel (including the scientific and administrative leaders of the Center) responsible for implementing translational science studies to be incorporated into NCTN trials as well as appropriate pilot studies to enable collection of preliminary data for further research.

3.1 Integrated Translational Science Program

3.1.1 Scientific Team Expertise/Leadership

The Network Group Integrated Translational Science Center Trials Principal Investigator(s) should provide the needed scientific expertise for development and design of research strategies for incorporating translational science studies into associated NCTN trials of the supporting Network Groups (i.e., Network Group Operations Center and the associated Network Group SDMCs). The Principal Investigator(s) and their associated staff should also be able to provide appropriate expertise to help Network Groups in hypothesis formulation and trial design during the early stages of development for trial proposals.

3.1.2 Governance, Organizational Structure, & Facilities and Equipment

Governance & Organization Structure: The Network Group Integrated Translational Science Center awardees are under the leadership of one or more Principal Investigators, who coordinate scientific activities conducted under this award in support of the translational science to be incorporated in associated Network Group(s)' clinical trials. The Multiple Principal Investigator (PI) option is encouraged for these awards given the team science approach of the research effort. Information on the Multiple PI Option is available at http://grants.nih.gov/grants/multi_pi/index.htm. If this option is used, a "Contact PI" should be designated from among the multiple PIs. The Principal Investigator (or Contact Principal Investigator under the Multiple PI option) or designee is also responsible for all grant-related activities related to this award and for communication about these activities with the appropriate NCI/DCTD staff.

Network Group Integrated Translational Science Center awardees are responsible for development and maintenance of a governance and organizational structure to incorporate appropriate integral and/or integrated translational science studies into clinical trials led by their associated Network Group(s). The organizational structure for the Integrated Translational Science Support for Network Trials award should include clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of any multiple PIs.

The governance and organizational structure for the award, including the senior leadership team, should also include representatives from the associated Network Groups that support the award.

Facilities and Equipment: The institutional facilities of the Network Group Integrated Translational Science Center Principal Investigator(s) should provide (in their physical plant and equipment) access to the necessary components for integrating translational science into the associated Network Group trials with respect to basic laboratory and investigator support.

3.1.3 Quality Assurance and Onsite Auditing

The Network Group Integrated Translational Science Center Principal Investigator(s) should have policies and procedures in place to assure quality assurance and control of any assays or other tests provided as part of pilot studies to obtain preliminary data. The Principal Investigator(s)

should also have policies and procedures in place for potential onsite auditing of assay/test performance by NCI/DCTD, if requested.

3.2 Pilot Studies and Collaborative Projects

The Principal Investigator(s) should be responsible for the design and analysis of pilot studies to collect preliminary data, if needed, to effectively incorporate specific translational science studies into late phase, definitive, NCTN trials. In addition, the Principal Investigator(s) are responsible for any collaborative projects with other NCTN Program components as well as other NCI-sponsored programs (e.g., SPOREs, NCI Cancer Centers) designed to facilitate hand-offs of translational science discoveries and/or early phase clinical trial results into later phase, NCTN trials.

Principal Investigator(s) are also responsible for ensuring that any pilot data or results from collaborative projects are published in a timely manner as per the publication policy outlined for the Network Group Operations Center in Part 1: Section IV.B.1.1.5 (Publications).

3.3 Compliance with Federal Regulations for Clinical Research

The Network Group Integrated Translational Science Center awardee(s) should have policies and procedures for ensuring that any work performed is in compliance with federal regulations regarding the protection of human subjects in clinical trials. In particular, policies and procedures related to confidentiality, integrity, and security of patient data should be in compliance with the Health Insurance Portability and Accountability Act (HIPAA). There should also be adequate safe-guards to ensure the technical integrity of assay/test performance in support of clinical trial research. Policies and guidelines to be addressed include the following:

3.3.1 IRB Review of the Network Group Integrated Translational Science Center

Institutional Review Board (IRB) review of the Network Group Integrated Translational Science Center grant is required. The IRB should determine and document that the Group Integrated Translational Science Center has sufficient mechanisms in place to ensure appropriate data management and analysis of translational science data and pilot studies as well as mechanisms to ensure protection of the confidentiality of patient data, given the nature of the research involved. Information on this requirement for IRB review can be obtained on the OHRP website at: http://www.hhs.gov/ohrp/.

3.3.2 Inclusion of Women, Minorities, and Children 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 at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. 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 Network 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial groups must be included in clinical trial protocols and the Network Group SDMC should ensure that it has appropriate procedures in place to address this requirement. 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 any future competitive renewal applications. The Network Group Integrated Translational Science Center should ensure that, when appropriate, translational science studies that it supports are incorporated into these reporting requirements

by its supporting Network Group Operations Center(s) and associated Network Group Statistics and Data Management Center(s) and have a policy in place to address this requirement.

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 as described at: http://grants.nih.gov/grants/funding/children/children.htm. For cancer clinical research, Network Group Integrated Translational Science Centers supporting 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 Network Group devoted to pediatric cancer research, 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.

3.3.3 Resource Sharing Plans

Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and GWAS Sharing Plan) are required for all key components of the NCTN Program. However, since it is expected that the Network Group Integrated Translational Science Center will follow the Resource Sharing Plans of the associated Network Group Operations Center(s) and the SDMC(s) supporting the Center, it is required to follow these policies for translational science studies (including pilot studies) its supports, if applicable. The Network Group Operations Center data sharing plans should comply with the NCTN Program Data Sharing Plan template as described in Part 4 - Appendices - Section VII for Network Group Operations Centers in these Guidelines.

Biospecimen Sharing Policy: The Network Group Operations Center is required to follow the NCI/DCTD policy regarding review of requests for use of banked biospecimens collected in association with NCTN trials that it leads CTEP's Protocol Review Committee or an NCI/DCTD-approved NCTN Correlative Science Committee. Network Group Operations Centers are also required to have a plan/policy in place to describe how information on its inventory of biospecimens will be made available to the public that is submitted to and approved by the Lead NCTN Program Director. The Network Group Integrated Translational Science Center is required to follow and support these policies for any pilot studies involving biospecimens that it conducts.

Network Group Operations Centers should also have plans in place regarding the following types of resources, as appropriate for the clinical research it conducts: Sharing Model Organisms and Genome Wide Association Studies (GWAS). The Network Group Integrated Translational Science Center is required to follow and support these policies pilot studies performed for/with a supporting Network Group.

3.3.4 Education on the Protection of Human Subjects

NIH policy requires education on the protection of human subject 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

3.3.5 Other Federal Regulations

The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central *upon acceptance for publication*. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication. More

information about this policy or the submission process is available on the NIH Public Access Policy website at: http://publicaccess.nih.gov/.

Information on other federal regulations (and their associated citations/URLs) that may be applicable to the Network Group Integrated Translational Science Center's activities is provided in Part 4: Appendices – Section IV.B.

3.4 Conflict of Interest Policy

The Integrated Translational Science Center awardee(s) receiving NIH funding from a grant or cooperative agreement must be in compliance with all of the DHSS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: http://grants.nih.gov/grants/policy/coi. The policy of the awardee(s) should ensure that there is no reasonable expectation any investigator or staff member at the Integrated Translational Science Center involved in the design, conduct, or reporting of research conducted in association with a Network Group Operations Center and its associated Network Group SDMC will be biased by any conflict of interest (using the definition of investigator provided in the NIH grants policy). The policy should also be in compliance with the NCI/DCTD/CTEP's Conflict of Interest Policy for NCTN Phase 3 Clinical Trials found on the CTEP website at: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies.

4. Specific Awardee Rights & Responsibilities – Network Lead Academic Participating Sites

Throughout these Terms and Conditions of Award, "Network Lead Academic Participating Site" refers to the organizational structure which is composed of the key personnel (including the scientific and administrative leaders at the Site) responsible for implementing NCTN clinical trials and collaborating on research goals of the NCTN Program with the Network Group Operations Centers and associated Network Group Statistics and Data Management Centers. In addition, throughout these Terms and Conditions of Award, "Network Lead Academic Participating Site," refers to the main academic institution/site as well as any affiliate site(s) included in the award if the Network Lead Academic Participating Site provides complete management services for the affiliate site(s) related to enrolling patients on NCTN clinical trials.

Definition of a Network Lead Academic Participating Site: An academic institution/organization for the purposes of this award is defined as a hospital and/or clinic program providing direct medical care to patients that is considered one integral organizational entity under a single financial management system and governance structure. Academic centers for the purposes of this award are distinguished from large medical centers whose primary mission is patient care. In addition to patient care, academic centers have comprehensive medical training programs and have preclinical laboratories that perform basic research.

Hospitals, clinics, military or VA hospitals or treatment facilities, and health care organizations that may provide services in collaboration with the applicant institution in a network, but which are not an integral component of the organization under a single financial management system and governance structure that comprises the applicant institution (i.e., Network Lead Academic Participating Site consisting of an academic center and its essential components), may not be considered part of that institution for the purposes of this award with respect to budgeting/funding with "high-performance intervention per case management" funding as described in Part 2 - Section II.E.1 in the of these Guidelines. These other organizations may be considered "affiliates" of the Network Lead Academic Participating Site and be included in the award under that designation (i.e., "affiliate"), if the Network Lead Academic Participating Site will provide complete management services for the affiliate site related to enrollment of patients on NCTN trials.

An academic institution/organization for the purposes of this award cannot be a Community Clinical Oncology Program Group (CCOPs) or Minority-based Clinical Oncology Program Group (MB-CCOPs) funded by the NCI Division of Cancer Prevention (DCP).

Annual Accrual Threshold to Maintain "High-Performance Intervention Per Case Management" Funding: It is anticipated that a Network Lead Academic Participating Site will maintain patient enrollment to therapeutic and/or advanced imaging interventions (not pilot studies) for all NCTN trials at a threshold rate of at least 55 to 70 patients per year or more; however, each Lead Academic Participating Site awardee will have a specific annual accrual threshold that is used to calculate its budget base. Since advanced imaging trials generally do not have as intensive an intervention or as long a follow-up period as therapeutic trials, this annual threshold rate for the Lead Academic Participating Site is calculated based on the number of patients enrolled on therapeutic intervention arms (i.e., patients undergoing screening only are not included) plus ½ the number of patients enrolled on advanced imaging trials. For example, if a Network Lead Academic Participating Site's budget is based on an annual accrual threshold of 80 patients across the Network and the academic site enrolls 70 patients to therapeutic intervention arms of clinical trials and 20 patients to advanced imaging trials in the first year of its award, it would have had 80 patient accruals that year and thus would have met its annual accrual threshold (70 therapeutic accruals + 20÷2 advanced imaging accruals = 70+10 = 80 patient accruals). If a Network Lead Academic Sites does not maintain this annual rate during the first 3 years of the award, funding for years 4 and 5 of the award may be adjusted with a decrease in the amount of "high-performance intervention per case management" funding or replacement of this funding with the lower "basic intervention per case management" funding for therapeutic trials. **Note:** Accruals from affiliates included in the Network Lead Academic Participating Sites award do not count toward the annual threshold accrual goal for the academic center.

4.1 Clinical Trial Program

4.1.1 Scientific Leadership & Contribution to NCTN Activities

Investigators at Lead Academic Participating Sites can demonstrate scientific leadership for NCTN trials as well as support of and participation in other NCTN activities in a variety of way through their membership in the Network Groups, including but not limited to the following:

- Offering eligible patients participation in NCTN studies and entering sufficient patients to meet accrual targets;
- Participating in research design and protocol development for NCTN studies, including collaborations between Network Groups and other NCI-supported programs and investigators, particularly at their institution;
- Providing primary or co-authorship on Network Group publications;
- Participating in the Scientific and Administrative Committees of the Network Groups;
- Participating in major meetings of the Network Groups and in other meetings deemed necessary for performance of the activities of Network Groups;
- Participating in NCTN activities and initiatives such as the NCI Scientific Steering Committees and associated Task Forces and Working Groups and their activities such as NCI Clinical Trials Planning Meetings; and
- Participating as members on the NCI Central IRBs.

4.1.2 Young Investigator and Leadership Mentoring/Training

The Lead Academic Participating Site should provide a mentorship program or activities to involve young investigators at their institution in clinical trial research and to help train them eventually take on senior leadership responsibilities for components of clinical trial research at the institution.

4.1.3 Operational Management (Governance/Organization, Institutional Support, Affiliates)

Governance & Organizational Structure: The Network Lead Academic Participating Site is under the leadership of the Site Principal Investigator(s), who coordinate(s) all the scientific and administrative policies at the institution related to NCTN activities as well as coordination with the Network Groups of which the Network Lead Academic Participating Site is a member. The Multiple Principal Investigator (PI) option is encouraged for these awards given the team science approach of the research effort. Information on the Multiple PI Option is available at http://grants.nih.gov/grants/multi_pi/index.htm. If this option is used, the Lead Academic Participating Site should designate a "Contact PI" among the multiple PIs. The Principal Investigator (or Contact Principal Investigator under the Multiple PI option) or designee is also responsible for all grant-related activities related to this award and for communication about these activities with the appropriate NCI/DCTD staff.

The Lead Academic Participating Site is responsible for development and maintenance of a governance and organizational structure to coordinate NCTN activities at the institution. The organizational structure of the Lead Academic Participating Site should be established with clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of any multiple PIs.

It is anticipated that the Principal Investigator(s) will be well integrated into the scientific and administrative senior leadership in clinical research at the Cancer Center or other academic institution, thereby fostering collaboration between the Network and other clinical and translational research investigators at the institution. In addition, the Principal Investigator(s) should be well integrated into the scientific and clinical activities of each of Network Group to which the institution belongs.

The Lead Academic Participating Site governance should clearly describe how activities related to the NCTN across various disciplines and departments at the institution will be coordinated and, in particular, describe how per case management funding associated with patient enrollment will be distributed to the various disciplines and clinical departments involved in NCTN trials at the institution. This is considered critical to achieve the aims of the NCTN which supports clinical trials across a broad range of diseases and involves multiple disciplines.

Institutional Support (Facilities, Equipment, and Programs): The Lead Academic Participating Site's facilities, equipment, and programs should include comprehensive medical training programs and preclinical laboratories that perform basic research to help foster collaborations with the clinical investigators at the site who participate in the NCTN that will enhance NCTN research.

Affiliates: If the Lead Academic Participating Site has affiliates, the affiliate network must be clearly described (including reference to the distinct NCI institutional codes for the affiliates that are used for patient enrollment). The Lead Academic Participating Site must provide all data management activities for the affiliate if it is included in the award (i.e., the Lead Academic Participating Site is responsible for complete monitoring and management of the enrollment of patients at affiliate sites to NCTN trials).

4.1.4 NCI Central Institutional Review Board Membership

All U.S. institutions/sites participating in NCTN trials as members of 1 or more Network Groups (including Network Lead Academic Participating Sites, CCOPs, and MB-CCOPs) are required to use the pediatric and/or adult NCI Central Institutional Review Board for any NCTN trial under an NCI CIRB's purview. See http://www.ncicirb.org for information on the requirements for a signatory institution under the adult NCI CIRB. This requirement may be waived by the Lead NCTN Program Director through an exemption review process if the institution/site can adequately show that NCTN studies can be reviewed in a timely manner by its local IRB (or other Central IRB) that is equivalent to the review timelines for the NCI CIRB (i.e., about 35 to 48 days for initial review) or if the institution/site can demonstrate other exceptional circumstances that preclude it from using the NCI CIRB.

Exemption requests with supporting documentation of the timely IRB review must be submitted to the Lead NCTN Program Director by the PI(s)/PD(s) of the Network Lead Academic Participating Site. If an exemption is granted, the Network Lead Academic Participating Site is responsible for including reports of IRB timelines in its annual progress report as well as any other pertinent information. The Lead NCTN Program Director may withdraw the exemption and require that the Network Lead Academic Participating Site use the NCI CIRB for applicable NCTN studies if justification for the exemption is not warranted on a continuing basis.

4.1.5 Clinical Trials Operations – Conduct of Clinical Trials & Data Management

The Lead Academic Participating Sites should have a clearly articulated process for prioritizing which NCTN trials to activate at their institutions. Investigators at Lead Academic Participating Sites form the cornerstone of the research programs for the Network Groups of the NCTN and must perform at a high level through submission of accurate and timely clinical data as well as ancillary materials necessary to support the NCTN (e.g., tumor specimens, imaging studies, pathology slides). The Principal Investigator(s) at each Lead Academic Participating Site is responsible for the performance of the academic center and its essential components as well as of any affiliates for which it provides complete management services and for assuring adherence to NCTN, Network Group, NCI, OHRP, and FDA policies and procedures.

It is the responsibility of the Principal Investigator(s) at the site to ensure that the procedures for data submission for each NCTN protocol are understood by all investigators at the academic center and its essential components as well as at any affiliates, and that protocol-specified data

are submitted accurately and in a timely manner to the appropriate Network Group Statistics and Data Management Centers.

4.1.6 Quality Assurance and Onsite Auditing

Responsibilities for quality assurance of the data (and biospecimens) submitted for NCTN trials as well as auditing include, but are not limited to, the following:

- *Pathology:* Submission of appropriate materials to allow verification of pathologic diagnosis, when relevant.
- *Biospecimens (including integral assays, -omics, Pharmcokinetics, Pharmacodynamics): Submission of appropriate biospecimens to allow for review/analysis of protocol-specified tests and parameters.*
- *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.
- *Chemotherapy & Other Systemic Therapies:* Submission of appropriate data to allow determination of protocol compliance with chemotherapy or other systemic therapy dose administration and dosage modification.
- *Surgery:* Submission of appropriate information to allow review of protocol-specified surgical procedures.
- *Diagnostic Imaging:* Submission of appropriate imaging data [images and associated meta-data (clinical or technical) as appropriate] to allow central review of staging, reported responses, and adequacy of imaging when required by a particular protocol or for an audit.
- *Onsite Auditing:* Cooperation with Network Groups' data monitoring and onsite auditing programs with appropriate compliance with the onsite auditing program requirements. See Quality Assurance in Part 1.IV.D.4 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.

4.2 Site Accrual Program

Network Lead Academic Participating Sites are responsible for accrual to all trials conducted across the NCTN from the main academic center and its essential components, and that of any affiliates included in their award, and for achieving threshold accruals at the main academic center and its essential components. Investigators at the Network Lead Academic Participating Sites should be involved in the acquisition of protocol-specified tumor specimens and other biospecimens in addition to all relevant protocol required clinical data. Network Lead Academic Participating Site investigators should ensure that biospecimens and/or other data required for ancillary studies are submitted to the appropriate laboratories/tumor banks and Network Group SDMCs.

Network Lead Academic Participating Sites are responsible for assuring that institutional investigators enrolling patients on NCTN trials are NCI registered investigators (i.e., have Form FDA 1572 on file with the NCI). Network Lead Academic Participating Sites also must ensure that the main institution, as well as any affiliates, are in compliance with NCI/DCTD/CTEP requirements for storage and accounting for investigational agents, including complying with NCI/DHHS Drug Accountability Records (DAR) procedures as described in the DCTD Investigators' Handbook at: http://ctep.cancer.gov/handbook/index.html and are in compliance with FDA requirements for investigational agents.

4.3 Compliance with Federal Regulations for Clinical Research

Lead Academic Participating Sites awardee(s) should have policies and procedures for ensuring compliance by the main academic center and its essential components (and any affiliates completely managed by the main academic institution/site) with the policies and procedures for meeting federal regulations for the protection of human subjects. These include the following:

- Assuring that all sites have current, approved Federalwide Assurances (FWAs) on file with OHRP;

- Assuring that each protocol is reviewed by the site IRBs prior to patient entry (or by the NCI Central IRB) and that each protocol is reviewed annually by the appropriate IRB as long as the protocol is active;
- Assuring that each patient (or legal representative) gives written informed consent prior to entry on study;
- Assuring that all regulatory documents verifying the FWA 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 NCI Cancer Trials Support Unit (CTSU) for all NCTN trials.
- Assuring that all investigators comply with procedures for assuring timely reporting of adverse events, including all expedited reporting of all serious adverse events, per the protocol documents of the NCTN trials in which the sites participate.

4.3.1 IRB Review of the Network Lead Academic Participating Site

Institutional Review Board (IRB) review of the Network Lead Academic Participating Site grant is required. The IRB should determine and document that the Network Lead Academic Participating Site has sufficient mechanisms in place to ensure appropriate data collection and data management of patients enrolled at the site (and affiliates, if applicable) as well as mechanisms to ensure protection of the confidentiality of patient data, given the nature of the research involved. Information on this requirement for IRB review can be obtained on the OHRP website at: http://www.hhs.gov/ohrp/.

4.3.2 Inclusion of Women, Minorities, and Children 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 at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. 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 Network 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial groups must be included in clinical trial protocols and the Network Group SDMC should ensure that it has appropriate procedures in place to address this requirement. 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 any future competitive renewal applications. Network Lead Academic Participating Site should ensure that it will provide the appropriate demographic data for any NCTN trial in which it participates per the protocol so that the Network Group Operations Centers and Network Group SDMCs can meet these requirements.

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 as described at: http://grants.nih.gov/grants/funding/children/children.htm. For cancer clinical research, Network Lead Academic Participating Sites participating in clinical trials for 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 Network Group devoted to pediatric cancer research, 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.

4.3.3 Resource Sharing Plans

Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and GWAS Sharing Plan) are required for all key components of the NCTN Program. However, since it is expected that all data on patients enrolled on NCTN trials by the Network Lead Academic Participating Site Center will be transmitted to the appropriate Network Group SDMCs and Operations Centers, the Resource Sharing Plans of those Operations Centers will be applied to the patient data from the Network Lead Academic Participating Sites. All Network Group Operations Center data sharing plans should comply with the NCTN Program Data Sharing Plan template as described in Part 4 - Appendices - Section VII for Network Group Operations Centers in these Guidelines.

Network Group Operations Centers should also have plans in place regarding the following types of resources, as appropriate for the clinical research it conducts: Sharing Model Organisms and Genome Wide Association Studies (GWAS). The Network Lead Academic Participating Site is required to follow and support these policies for the NCTN trials led by the applicable Network Group Operations Center.

4.3.4 Education on the Protection of Human Subjects

NIH policy requires education on the protection of human subject 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

4.3.5 Other Federal Regulations

The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central *upon acceptance for publication*. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication. More information about this policy or the submission process is available on the NIH Public Access Policy website at: http://publicaccess.nih.gov/.
Information on other federal regulations (and their associated citations/URLs) that may be applicable to the Network Lead Academic Participating Site's activities is provided in Part 4: Appendices – Section IV.B.

4.4 Conflict of Interest Policy

Network Lead Academic Participating Sites receiving NIH funding from a grant or cooperative agreement must be in compliance with all of the DHSS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: http://grants.nih.gov/grants/policy/coi. Network Lead Academic Participating Sites must also comply with the Conflict of Interest Policy of the applicable Network Group Operations Center leading an NCTN trial in which the site participates. These policies should ensure that there is no reasonable expectation that any investigator or staff member of the Network Lead Academic Participating Site involved in the design, conduct, or reporting of research will be biased by any conflict of interest (using the definition of investigator provided in the NIH grants policy). The Network Group Operation Center policies should be in compliance with the NCI/DCTD/CTEP's Conflict of Interest Policy for NCTN Phase 3 Clinical Trials found on the CTEP website at: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies.

5. Specific Awardee Rights & Responsibilities - Network Radiotherapy and Imaging Core Services Centers

Throughout these Terms and Conditions of Award, "Network Group Radiotherapy and Imaging Core Services Centers Center" refers to the organizational structure which is composed of the key personnel (including the scientific and administrative leaders of the Centers) responsible for implementing support for applicable NCTN trials related to quality assurance, credentialing, and image data management for radiotherapy and imaging as well as other support functions.

5.1 General Features and Overview

5.1.1 Governance, Organizational Structure, Policies & Procedures, & Facilities and Equipment

Governance & Organizational Structure: The Network Radiotherapy & Imaging Core Services Centers are under the leadership of one or more Principal Investigators, who coordinate all the service support for NCTN trials and related activities as well as coordination with the Network Groups. The Multiple Principal Investigator (PI) option is encouraged for the Network Radiotherapy & Imaging Core Services Centers award(s) given the team science approach of the research support effort. Information on the Multiple PI Option is available at http://grants.nih.gov/grants/multi_pi/index.htm. If this option is used, a "Contact PI" should be designated from among the multiple PIs. The Principal Investigator (or Contact Principal Investigator under the Multiple PI option) or designee is also responsible for all grant-related activities related to this award and for communication about these activities with the appropriate NCI/DCTD staff.

Network Radiotherapy & Imaging Core Services Centers are responsible for development and maintenance of a governance and organizational structure for coordinating NCTN support for applicable NCTN trials led by any of the Network Groups. The governance structure should clearly describe how activities of the Centers will be coordinated between each other and with the Network Groups, including the Information Technology (IT) systems for data and image transfer. To facilitate this coordination, the senior leadership team of each Center should include representatives from the Network Groups. The organization structure should have clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of the multiple PIs.

Standard Operating Procedures: The Network Radiotherapy & Imaging Core Services Centers are also responsible for the preparation and maintenance of Standard Operating Procedures (SOPs) that cover all aspects of the Centers' activities, including the process for prioritizing services provided to the Network Groups for their clinical trials approved for conduct in the NCTN.

Facilities & Equipment: The Network Radiotherapy & Imaging Core Services Centers' facilities (i.e., their physical plant and equipment) should provide all the necessary components to provide the applicable Core services to Network Group trials, especially with respect to information technology. This includes the ability to collect, distribute, analyze, and store/archive all appropriate imaging and radiotherapy treatment delivery data for applicable NCTN trials. The Centers should ensure basic interoperability between the radiotherapy and imaging core service components as well as with other key components of the NCTN, including electronic exchange of digital planning data and images and web-based software tools to facilitate trial-specific digital data review by Study Chairs. The Centers should also have basic interoperability with the common data management system (CDMS) used by the Network Groups to collect clinical trial data as well as the Regulatory Support System (RSS) and the Oncology Patient Enrollment Network (OPEN) used by the Network Groups for support of patient enrollment.

5.1.2 Quality Assurance/Onsite Auditing

The Core Services Centers should have policies and procedures in place to assure quality assurance and control of the data services provided for NCTN trials and any auditing the Centers

perform related to their own operations. The Centers should also have the capacity to provide data to the Network Groups if needed for onsite auditing for their members for specific clinical trials.

5.2 Radiotherapy and Imaging Core Services Centers

5.2.1 Scientific and Technical Expertise

The Network Radiotherapy & Imaging Core Services Centers should provide the scientific expertise in Advanced Medical Imaging (including PET and MR), radiotherapy, and information technology to provide appropriate quality assurance for data and image management to support applicable NCTN trials as well as for other approved NCI-supported clinical trials (e.g., NCI early phase clinical trials) evaluating advanced radiotherapy treatments and imaging techniques/procedures. The PI(s)/PD(s) and Centers' staff should also be able to provide appropriate expertise to help Network Groups in hypothesis formulation and trial design during the early stages of developing of trial proposals. The Centers should also provide expertise in information technology (IT) to facilitate collection, qualification, analysis, archive, and transfer of radiotherapy assessment and imaging data.

5.2.2 Credentialing of Institutions and Services

The Network Radiotherapy & Imaging Core Services Centers should have policies and procedures in place to provide qualification and credentialing of institutions as needed for both delivery of appropriate protocol-specified radiotherapy as well as performance of specific advanced imaging technology.

5.3 Program for Collaborations and Participation in Collective Management

The Network Radiotherapy & Imaging Core Services Centers should have the capacity to provide Core Services to NCTN trials that result from collaborations between the Network Groups and other NCI-supported programs and investigators. The Network Radiotherapy & Imaging Core Services Centers should also be able to develop collaborations with other NCI-sponsored programs and investigators (e.g., SPOREs, Cancer Centers, R01/P01 investigators) to augment and enhance the core services provided by the Centers for NCTN trials as well as to collaborate with other organizations providing these types of services to enhance services and provide best practices and/or standards for selected assessments of radiotherapy and advanced imaging techniques.

The Centers will also be responsible for providing similar services for collaborations with other NCI-supported clinical trials programs (e.g., NCI early phase clinical trials) when directed by NCI as part of the NCTN Program.

In addition, the Network Radiotherapy & Imaging Core Services Centers is also responsible for participating in the collective management of the Network including participation in appropriate NCTN Program activities and initiatives and through the NCTN Leadership Management Committee by making recommendations to NCI for modifications to the Program as well as to standard NCTN common tools and services.

5.4 Compliance with Federal Regulations for Clinical Research

The Network Radiotherapy & Imaging Core Services Centers awardee should have policies and procedures for ensuring that any work performed is in compliance with federal regulations regarding the protection of human subjects in clinical trials. In particular, policies and procedures related to confidentiality, integrity, and security of patient data should be in compliance with the Health Insurance Portability and Accountability Act (HIPAA). There should also be adequate safe-guards to ensure the technical integrity of quality assurance programs in support of NCTN clinical trial research. Policies and guidelines to be addressed include the following:

5.4.1 IRB Review of the Network Radiotherapy & Imaging Core Services Centers

Institutional Review Board (IRB) review of the Network Radiotherapy & Imaging Core Services Centers grant is required. The IRB should determine and document that the Centers have sufficient mechanisms in place to ensure appropriate data management and analysis of radiotherapy and imaging data for quality assurance and credentialing with respect to ensuring the protection of the confidentiality of patient data, given the nature of the research involved. Information on this requirement for IRB review can be obtained on the OHRP website at: http://www.hhs.gov/ohrp/.

5.4.2 Inclusion of Women, Minorities, and Children 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 at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. 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 Network 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial groups must be included in clinical trial protocols and the Network Group SDMC should ensure that it has appropriate procedures in place to address this requirement. 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 any future competitive renewal applications. The Network Radiotherapy & Imaging Core Services Centers should ensure that, when appropriate, data collected in support of NCTN trials by the Centers are incorporated into these reporting requirements by the Network Group Operations Centers and associated Network Group Statistics and Data Management Centers and have a policy in place to address this requirement.

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 as described at: http://grants.nih.gov/grants/funding/children/children.htm. Since the Network Radiotherapy & Imaging Core Services Centers may support any applicable trial conducted under the NCTN Program, the Centers will collect data to support clinical trial research in children via their association with the pediatric Network Group Operations Center and associated SDMC.

5.4.3 Resource Sharing Plans

Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and GWAS Sharing Plan) are expected for this FOA. Since it is expected that the Network Radiotherapy and Imaging Core Services Centers will follow the Resource Sharing Plans of the associated Network Groups' Operations Centers, the Network Radiotherapy and Imaging Core Services Centers should submit a Resource Sharing Plan in its application that indicates that it understands and is bound by these plans. An example of a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers for the NCTN Program is provided in Part 4 - Appendices - Section VII in the Guidelines document for the NCTN Program.

Network Group Operations Centers should also have plans in place regarding the following types of resources, as appropriate for the clinical research it conducts: Sharing Model Organisms and

Genome Wide Association Studies (GWAS) as well as a biospecimen sharing policy. Network Radiotherapy & Imaging Core Services Centers are required to follow and support these policies for the NCTN trials led by the supporting Network Group Operations Centers, if applicable.

5.4.4 Education on the Protection of Human Subjects

NIH policy requires education on the protection of human subject 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

5.4.5 Other Federal Regulations

The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central *upon acceptance for publication*. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication. More information about this policy or the submission process is available on the NIH Public Access Policy website at: http://publicaccess.nih.gov/.

Information on other federal regulations (and their associated citations/URLs) that may be applicable to the Network Radiotherapy & Imaging Core Services Centers' activities is provided in Part 4: Appendices – Section IV.B.

5.5 Conflict of Interest Policy

The Network Radiotherapy & Imaging Core Services Centers receiving NIH funding from a grant or cooperative agreement must be in compliance with all of the DHSS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: http://grants.nih.gov/grants/policy/coi. The Network Radiotherapy & Imaging Core Services Centers policy should ensure that there is no reasonable expectation that any investigator of staff member at the Core Centers involved in the design, conduct, or reporting of research conducted by the Network Group Operations Centers and their associated Network Group SDMCs will be biased by any conflict of interest (using the definition of investigator provided in the NIH grants policy). The policy should also be in compliance with the NCI/DCTD/CTEP's Conflict of Interest Policy for NCTN Phase 3 Clinical Trials found on the CTEP website at: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies.

6 Specific Awardee Rights & Responsibilities - Canadian Collaborating Clinical Trials Network

With respect to the Terms and Conditions of Award, "Canadian Collaborating Clinical Trials Network" refers to the organizational structure which is composed of the key personnel (including the scientific and administrative leaders of the organization and its scientific research and administrative committees) and the member institutions/sites (including the institution/site physicians and clinical research associates), responsible for implementing clinical trials and collaborating on research goals of the NCTN Program. In addition, throughout these Terms and Conditions of Award, "Canadian Collaborating Clinical Trials Network" refers to all of its member institutions/sites as well.

6.1 Overall Rights and Responsibilities

The Canadian Collaborating Clinical Trials Network is subject to all the Awardee Rights and Responsibilities outlined in these Guideline in Part 1 - Section IV.B.1. (Network Group Operations Centers) and Part 1 - Section IV.B.2. (Network Group SDMCs) for any NCTN trials the Canadian Network participates in and/or leads, although the volume of clinical trials, accrual, and collaborations would be expected to be more limited for the Canadian Network. There are, however, special considerations for the Canadian Collaborating Clinical Trials Network related to regulatory oversight of NCTN trials in Canada and biospecimen collection as outlined below.

6.2 Regulatory Oversight

The Canadian Collaborating Clinical Trials Network would be expected to establish relationships with U.S. Network Groups to provide appropriate regulatory oversight for U.S. Networks Group trials conducted in Canada, when needed. In some cases, this oversight may be performed by a U.S. Network Group; however, it is anticipated that the Canadian Collaborating Clinical Trials Network will play an important role in providing this type of regulatory oversight when need for both U.S. adult and pediatric Network Groups for trials open in Canada.

6.3 Biospecimen Collection and Tumor Banking

For NCTN trials led by U.S. Network Groups, biospecimens from member institutions/sites of the Canadian Collaborating Clinical Trials Network should be sent to the associated tumor bank for the U.S. Network Group or to a specified laboratory for analysis during the course of the trial (e.g., central laboratory for assessment of an integral biomarker).

For NCTN trials led by the Canadian Collaborating Clinical Trials Network, if biospecimens are collected for banking that are funded by NCI/DCTD, arrangements would be made for the biospecimens to be banked in collaboration with a tumor bank associated with a U.S. Network Group. Alternatively, these specimens may be stored in a tumor bank of the Canadian Collaborating Clinical Trials Network for an NCTN trial that the Canadian Network leads if the Canadian Network has a tumor bank and the collection and storage at that bank is approved by the Lead NCTN Program Director in consultation with the NCI Cancer Diagnosis Program Associate Director, Program Director of the NCTN Tumor Banking grant, and the CTEP Associate Director in writing (and with CTEP approval of an amendment to the trial that states that the biospecimens will go to the Canadian Collaborating Clinical Trials Network bank). The Canadian Collaborating Clinical Trials Network as part of the NCTN Program is also eligible to apply for BIQSFP funding (see http://biqsfp.cancer.gov/). Any biospecimens collected under a funded BIQSFP application that are later "banked" must also follow all the rules and regulations related to any biospecimens collected in association with an NCTN trial as outlined in the Terms and Conditions of Award for Network Group Operations Centers (see Part 1 - Section IV.B.1.5.7. of these Guidelines).

Regardless of the source of funding for collection/banking of biospecimens by the Canadian Collaborating Clinical Trials Network, study proposals for use of biospecimens collected in association with a NCTN clinical trial would be required to be reviewed by CTEP's Protocol Review Committee or an NCI/DCTD-approved NCTN Correlative Science Committee as outlined in Part 1 – Section IV.C.3. In addition, the Canadian Collaborating Clinical Trials Network is required to have a Biospecimen Sharing Policy (the same requirement as for the U.S. Network Groups) that reflects this requirement.

C. NCI/DCTD Staff Responsibilities

The role of the NCI Division of Cancer Treatment and Diagnosis (DCTD) staff, as described throughout these Terms and Conditions of Award, is to assist, facilitate, and ensure optimal coordination of NCTN activities. The NCTN is part of a larger NCI-sponsored clinical trials program that also includes investigational agent development. The Cancer Therapy Evaluation Program (CTEP) staff has very specific and well-defined responsibilities for the oversight and review of Network Group clinical trials and for investigational agent development that meets DCTD/CTEP responsibilities as sponsor of Investigational New Drug Applications (INDs) and Investigational Device Exemption (IDE) as defined in the Code of Federal Regulations (CFR) 21 Part 312. The Cancer Imaging Program (CIP) staff has similar responsibilities with respect to INDs for investigational imaging agents in applicable NCTN trials. The responsibilities of NCI/DCTD staff are described below.

1. Coordination of National Priorities

NCI/DCTD 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 planning does not occur within the Network Groups, NCI/DCTD staff with support from the Coordinating Center for Clinical Trials (CCCT) will help in coordinating the organization of Clinical Trials Planning Meetings under the auspices of the NCI Scientific Steering Committees. In addition, NCI/DCTD staff may support ad hoc scientific meetings to help achieve consensus on critical clinical problems. These Clinical Trials Planning meeting 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. NCI staff will be responsible for prompt dissemination of the recommendations from these meetings, particularly regarding statements of research priorities from Clinical Trials Planning meetings, and the Network Groups will be encouraged to address these priorities.

2. Scientific Resource and Liaison Activities

NCI/DCTD staff serves as both a resource and liaison for Network Groups and their members, as well as the other key components of the NCTN Program.

2.1 Scientific Resource for NCTN Clinical Investigations

The Lead NCTN 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), the Radiation Research Program (RRP), and the Cancer Diagnosis Program (DCP), all serve as resources available to Network Groups for specific scientific information with respect to treatment regimens, clinical trial design, investigational agent management, regulatory issues, etc. The NCI/DCTD staff also work closely with the NCI/DCP staff to coordinate operating processes and procedures for the Network Groups as well as to ensure there is a high level of integration of complementary research efforts on specific trials.

The NCI DCTD staff listed above will assist the Network Groups, their members, and other key components of the NCTN Program, as appropriate, in developing information concerning the scientific basis for specific trials, operational and regulatory issues, and will also be responsible for advising the Network 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 Network Groups on the efficacy and adverse events associated with new investigational agents supplied to Network 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 and Administrative Program Directors & Liaison Activities

The Lead NCTN Program Director is the NIH/NCI Program Official responsible for the routine scientific and programmatic stewardship of all the awards for the NCTN Program and will be named in the award notice. Co-Program Directors may also be named in the award notice for some of the key components

of the NCTN Program as these Co-Program Directors have major responsibilities in assisting the Lead NCTN Program Director for the scientific and programmatic stewardship of the awards for particular key components of the NCTN Program.

Each Network Group and key component will also have a staff physician, statistician, and/or other professional staff member from NCI/DCTD assigned to them who acts as liaison for scientific and administrative matters. These NCI/DCTD liaison (also referred to as a Project Scientist) serves as the primary contact for scientific inquiries, including information concerning the content of specific protocols, LOI, or Concept reviews, and feedback on general scientific direction of the Network Group or key component. On occasion, the Lead NCTN Program Director and Co-Program Directors may also serve as Project Scientists.

The Project Scientist monitors the Network Group's or other key component's progress, attend their meetings, and is responsible for understanding the Network Group's or key component's repertoire of studies and scientific activities, including areas of special interest, expertise, and unique resources. The Project Scientist is also responsible for providing the Lead NCTN Program Director with ongoing assessments of the key component's activity from a scientific and administrative perspective, including general information on its budget. Primary responsibility for the budgets of Network Groups and all key components of the NCTN Program, however, resides with the Lead NCTN Program Director who is assisted by the NCI/DCTD Senior Program Specialist. (See Parts 2 and 3 of these Guidelines for information on budgetary issues for the key components of the NCTN related to new applications as well as non-competing continuing applications.)

The NCI/DCTD Senior Program Specialist may be delegated by the Lead NCTN Program Director to request and receive budgetary and administrative materials from the Network Groups/key components on either an ad hoc or routine basis. The NCI/DCTD Senior Program Specialist will frequently perform liaison activities concerning budgetary and administrative matters on behalf of the responsible NCI Program Director, interfacing primarily with the primary Administrators for the Network Groups/key components.

2.3 NCI/DCTD Attendance at Meetings of the Key Components of the NCTN Program

NCI/DCTD Project Scientists and other NCI staff, as designated by the NCTN Lead Program Director, will attend the regular Network Group meetings and core scientific Network Group meetings as well as those of other key components of the NCTN Program, as appropriate. As part of their liaison responsibilities, Project Scientists, when available, will attend other Network Group and key component scientific meetings and may also attend Network Group and other key component Executive Committee meetings.

2.4 Coordination of Resources to Enhance Accrual/Completion of NCTN Trials

NCI/DCTD staff will take an active role in promoting the timely completion of important studies, for example, by encouraging and facilitating collaboration among the Network Groups and collaborations with other NCI-supported programs and investigators when appropriate or by assisting in the mobilization of other available and required resources to enhance accrual to and completion of NCTN trials.

3. Study/Trial Proposal Review & Protocol Development and Review Process

The NCI/DCTD study proposal, protocol development, and review processes are described in detail in the Investigator Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI) available at: http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm). This Handbook describes the processes for Network Groups to submit trial proposals for treatment and advanced imaging clinical trials, information related to the specific forms to be used for study proposal submissions, and description of the review or evaluation/prioritization processes used to approve study proposals for further development as clinical trials to be conducted by the NCTN.

3.1 Proposal Review

General Information: Study proposals for treatment or advanced imaging clinical trials are evaluated as either Letters of Intent (LOI) or Concepts depending on the whether the proposal is reviewed/evaluated by the NCI/DCTD Cancer Therapy Evaluation Program (CTEP) Protocol Review Committee (PRC) or by an NCI Scientific Steering Committee (i.e., disease-specific or clinical imaging Steering Committees) as described below. An illustration of the study review/evaluation process for NCTN study proposals and associated information is also provided in Part 4 – Appendices - Section III of these Guidelines. The terms NCI/DCTD PRC and CTEP PRC are used interchangeably in these Guidelines.

Trials proposals prioritized by NCI Scientific Steering Committee (SSC) undergo expedited review by CTEP before final approval is given in order to ensure significant safety, feasibility, and regulatory issues are adequately addressed, including ensuring that there are adequate resources available for the trial given the resource allocation constraints for the disease area, and to prevent duplication. However, it is expected that this final review/approval by CTEP can be accomplished in an expedited manner in most cases as designated NCI/DCTD staff participate as full members on the various NCI and significant issues in these areas are incorporated into the evaluation/prioritization discussion.

NCI/DCTD staff (i.e., 3 representatives - one representative from BRB, the Lead NCTN Program Director or his/her designee, and the physician liaison from the Clinical Investigations Branch or the Cancer Imaging Program) are full members on the disease-specific and Clinical Imaging Scientific Steering Committees. The Clinical Investigations Branch physician in the related disease area for the disease-specific Steering Committee (or Cancer Imaging Program representative for the Clinical Imaging Steering Committee) have special responsibilities on the NCI SSCs, including developing meeting agendas with the SSCs co-Chairs, preparing the Consensus Evaluations for proposals evaluated by the committees, and working with the SSC Co-Chairs on the scientific direction of the committee.

Any change in the policies and procedures of the NCI SSCs related to composition of committee membership, conflict of interest, and evaluation/prioritization procedures for NCTN clinical trials requires review and approval by the Lead NCTN Program Director and the Associate Director, CTEP, DCTD/NCI to ensure that procedures are consistent with the intent of the NCTN Program and the Terms and Conditions of Award under the Cooperative Agreements for all key components of the NCTN Program.

Proposal Review Process Based on Type of Study: Review of study proposals for the NCTN Program is based on the type of study (including intervention study, non-intervention study, trial phase), IND status, patient population (adult vs. pediatric), and sample size. The review process based on these study attributes are described below.

- **All phase 1 trial proposals, pilot studies, and any trial proposal submitted by Network Group Operations Centers in response to mass solicitations or specific solicitations from the NCI/DCTD Cancer Therapy Evaluation Program (CTEP)** are evaluated as LOIs by the CTEP's PRC.

- **All phase 3, phase 2/3, and large phase 2 trial proposals** (i.e., phase 2 trials requiring sample sizes of 100 patients or more) are first evaluated and prioritized by the appropriate NCI Scientific Steering Committee as Concepts with final expedited approval/disapproval by CTEP with consideration of the feasibility and resources available to the NCTN to conduct the study. (Note: This applies only when the study proposal is not part of a mass solicitation or other specific solicitation by NCI/DCTD or an adult pilot study).

- **All small phase 2 and phase 1/2 adult study proposals** (i.e., trials requiring a total sample size of less than 100 patients) are evaluated as LOIs by the CTEP's PRC. However, at CTEP's discretion, if these trial proposals have total sample sizes close to 100 patients (i.e., in the low 90s to 100), CTEP

may forward these for evaluation/prioritization by the appropriate NCI Scientific Steering Committee. Network Groups submitting these types of trial proposals, especially proposals with sample sizes of 90 or more patients, are encouraged to use the Concept submission form in case the proposal is forwarded to an NCI Scientific Steering Committee. **For pediatric studies (including studies for adolescents and young adults submitted from the pediatric Network Group),** it is anticipated that all pediatric phase 2 studies (regardless of the study sample size) and pediatric feasibility and pilot studies of 100 patients or more will be forwarded by CTEP to the appropriate NCI Scientific Steering Committee given the limited pediatric patient population.

- **If an appropriate NCI Scientific Steering Committee (SSC) does not exist for a disease area or is not available for evaluation of a trial proposal submitted by a Network Group Operations Center for other reasons** (e.g., significant workload or scheduling issues), the trial proposal will be reviewed by CTEP's PRC with ad hoc extramural scientific reviewers, as needed.

- **BIQSFP applications that are related to clinical treatment or advanced imaging trial proposals submitted by the Network Group Operation Centers** are initially evaluated by the appropriate NCI SSC (or by CTEP with ad hoc extramural scientific reviewers) with the reviewer recommendations forwarded to the NCI Clinical and Translational Research Operations Committee (CTROC) for a final decision on the BIQSFP application and budget.

- **Correlative science studies embedded in NCTN clinical trial studies at the time of initial proposal submission** should be appropriately designed as integral and/or integrated studies with robust statistical designs and analysis plans that address specific and important scientific hypotheses. Exploratory studies without a specific hypothesis and robust statistical analysis plan will not be approved. Although optional collection of biospecimens without an approved research plan may be approved for a trial (e.g., adjuvant study), use of the specimen must be approved by CTEP and must be based on studies with specific hypotheses and statistical analysis plans (i.e., biospecimens cannot be "reserved" for future unspecified research without a subsequent study proposal being reviewed and approved).

- **Correlative science studies requesting use of biospecimens** from any NCTN clinical trial that **has not** yet reported out primary results is evaluated by CTEP's PRC (usually as an amendment during the course of the conduct of the study). At CTEP's discretion, depending on the timing of the request, the correlative science study may be sent for evaluation to an NCI/DCTD-approved NCTN Correlative Science Committee.

  All correlative science studies requesting use of biospecimens from any NCTN clinical trial that **has** reported out primary results (i.e., request for use of "banked" biospecimens) is reviewed by CTEP's PRC or sent by CTEP for evaluation to an NCI/DCTD-approved NCTN Correlative Science Committee.

  It is anticipated that all requests for use of "banked" biospecimens collected in associated with any NCTN clinical trial (regardless of funding source) will be submitted to a central NCI/DCTD "Triage Committee" in order to assess the appropriateness of the request for use of these scarce resources that are linked to annotated clinical trial data, including outcome data, as well as determining with the Network Group based on its biospecimen inventory and the status of the clinical trial data, whether the request could be addressed. If the central NCI/DCTD "Triage Committee" determines that the request is appropriate, the request will then be sent to NCI/CTEP's Protocol Information Office (PIO) for evaluation via CTEP's PRC or an NCI/DCTD-approved NCTN Correlative Science Committee. Correlative science studies requesting use of "banked" biospecimens should be appropriately designed with robust statistical designs and analysis plans that address specific and important scientific hypotheses (and with the statistician named as part of the study proposal on its title page).

The NCI/DCTD-approved Correlative Science Committee(s) will be constituted in a similar manner to that of the NCI Scientific Steering Committees with appropriate representation from the extramural oncology community (including experts in pathology, translational science, and statistics) as well as with Network Group and NCI/DCTD representatives and representatives in applicable disease areas. The committee representation will be approved by NCI/DCTD and will be constituted so that Network Group representation does not constitute a majority of the committee – similar to the NCI Scientific Steering Committees.

These requests may also require approval or review/comment by a CTEP collaborator if the study is/was conducted under a CTEP binding collaborating agreement per requirements of the CTEP IP option (see information on the CTEP IP Option available at: http://ctep.cancer.gov/industryCollaborations2/default.htm).

All correlative science studies require CTEP review and approval by one of the procedures described above regardless of the number of patient specimens requested. It is anticipated that requests for a small number of specimens that do not constitute an important subset (e.g., specimens from only patients with a particular outcome when the outcome was a rare event) and do not require approval and/or comment by a CTEP collaborator will undergo an expedited review/approval process; however, review and approval is required (there are no "file-only" studies).

NOTE: All requests for biospecimens collected in conjunction with or tied to an NCTN trial that are "banked" must undergo review and approval even if the collection or storage of specimens was funded from sources outside the NCTN Program as the NCTN clinical trial was supported by the NCI/DCTD under these Terms and Conditions of Award which requires review under a process approved by NCI/DCTD unless a specific exemption to the review policy is granted by NCI/DCTD. This requirement reflect NCI's interest as a scientific matter and a substantial public policy interest in assuring biospecimen collections that are tied to publicly funded NCTN trials are made available to the general research community through an NCI-approved review process for meritorious use.

Banked biospecimens in NCI-funded or other tumor banks tied to NCTN trials cannot be released without an approval letter from NCI/DCTD authorizing release for a specific research proposal that has been approved by the procedures described above. There are **no** exceptions to this policy.

- **Requests for use of clinical data only** from an NCTN clinical trial is subject to the CTEP-approved data-sharing policy of the Network Group Operations Center that leads/led the trial. These requests may also require approval or review/comment by a CTEP collaborator if the study is/was conducted under a CTEP binding collaborating agreement per requirements of the CTEP IP option (see information on the CTEP IP Option at: http://ctep.cancer.gov/industryCollaborations2/default.htm).

Evaluation/Review Outcome: In general, CTEP's PRC (or the appropriate NCI SSC) discusses the submitted LOI (Concept) with all assigned reviewers and committee members and makes a decision on the study proposal from one of the 3 options provided below. A similar process is followed for review of non-intervention study proposals (i.e., correlative science studies requesting use of biospecimens collected in association with an NCTN trial) by CTEP's PRC or a NCI/DCTD-approved NCTN Correlative Science Committee.

Approved as written or with recommendations – The investigators are requested to give serious consideration to any recommendation included in the consensus review/evaluation but they are not obligated to amend the study proposal. 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. Approval-on-Hold is given initially for studies requiring

review/approval by a CTEP collaborator (e.g., collaborator providing investigational agent for the trial) and if/when the CTEP collaborator gives official approval, CTEP issues a final full approval for the study with or without recommendations. On occasion, an approval may come with a required modification specified in the approval letter and/or attached Consensus Evaluation/Consensus Review that will need to be incorporated into the study proposal at the time of protocol review. This is done for minor modifications so that the trial proposal does not need to go back as a pending when the modification is straightforward.

Pending – The CTEP PRC or NCI SSC 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/evaluation adequately (i.e., comments requiring a response).

Disapproved – In the judgment of CTEP's PRC or the NCI SSC, the study cannot be approved.

In addition, all Concepts and non-intervention study proposals that are prioritized for further development by NCI SSCs or an NCI/DCTD-approved NCTN Correlative Science Committee must undergo expedited review by CTEP before final approval is given in order to ensure significant safety, feasibility, and regulatory issues are adequately addressed, including ensuring that there are adequate resources available for the study proposal or trial given the resource allocation constraints for the disease area, and to prevent duplication. However, it is expected that this final review/approval by CTEP can be accomplished in an expedited manner in most cases as designated NCI/DCTD staff participate as full members on the various NCI SSCs or NCI/DCTD-approved NCTN Correlative Science Committees and significant issues in these areas are incorporated into the evaluation/prioritization discussion.

Also, any approved NCTN Concept for a phase 3 or phase 2/3 trial is submitted to FDA for comment and any approved NCTN LOI/Concept with an investigational device/biomarker for the particular clinical setting may also be submitted to FDA for comment even if the study is not identified as being specifically designed for a licensing indication for an agent or device.

3.2 Protocol Development Review/Approval and Amendment Review/Approval

The protocol document must be reviewed and approved by NCI/DCTD prior to distribution by a Network Group to its sites for local IRB review (or NCI Central IRB review) and trial activation (i.e., opening the study to patient enrollment after approval of the study by at least one IRB). All approved adult phase 3 study protocols also require approval by the NCI Adult Central Institutional Review Board (CIRB) **after** approval of the protocol document by CTEP; however, distribution of the trial may proceed to sites using other IRBs **prior** to final CIRB approval. Any changes/modifications requested by the NCI CIRB at the time of its initial review may require an amendment to the study after distribution if CTEP believes any of the requested changes/modifications should be in master protocol document (either in the informed consent or in other sections of the protocol document). Minor changes in the informed consent document may be limited to the approved CIRB version of the informed consent document (IRB) for its sites only. After the trial is activated, all protocol amendments submitted on the trial require NCI CIRB approval prior to final approval of the amendment by CTEP. In select cases, phase 2 trials may also be required by NCI/DCTD to be reviewed by the NCI CIRB, especially those phase 2 studies that may be opened widely across the entire NCTN.

All pediatric study protocols (except phase 1 study protocols - although these may be included in the future) require approval by the NCI Pediatric CIRB **prior** to final approval of the study protocol document by NCI/DCTD.

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. Additional information on the procedures for protocol amendment can be found in the Investigator's Handbook.

3.3 Study/Trial 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).

All NCTN phase 3 trials (and phase 2/3 trials) are subject to CTEP's Slowly Accruing Guidelines for Phase 3 Trials as described in Part 4 – Appendices - Section I.G. of these Guidelines. In addition, the Lead NCTN Program Director may at any time request that a Network Group's DSMB consider closing a phase 3, phase 2/3, or other phase 2 protocols 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 if appropriate). In future, slowly accruing guidelines for phase 1 and phase 2 trials may also be instituted by NCI/DCTD for the NCTN Program.

3.4 Data and Safety Monitoring Boards (Data Monitoring Committees)

The Lead NCTN Program Director, assisted by the Co-Program Directors and the Biometric Research Branch (BRB) staff, will assess Network Group compliance with NCI established policies on Data and Safety Monitoring Boards (DSMBs), also known as Data Monitoring Committees (DMCs), for Network Group phase 3 trials as well as phase 2/3 and any other phase 2 trials monitored by the DSMB. These policies must address both the membership of the DSMB/DMC and its operational policies. One or more CTEP staff or other NCI/DCTD staff (designated by the Chief of the Clinical Investigations Branch/Lead NCTN Program Director at CTEP) and one BRB staff (designated by the Chief of BRB) will serve as non-voting members at each Network Group DSMB/DMC meeting.

The membership of the Group's DSMB/DMC and its policy must be approved by Lead NCTN Program Director. In addition, Lead NCTN Program Director, assisted by the Co-Program Directors and the BRB staff, must review and approve each Network Group Operations Center's policy (developed in conjunction with the associated Network Group Statistics and Data Management Center) 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 by the *following URLs:*

http://grants.nih.gov/grants/guide/notice-files/not98-084.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines

Information on CTEP's policy on monitoring of phase 3 trials and randomized phase 2 trials by Network Group DSMBs/DMCs is provided in Part 4 – Appendices – Section VIII of these Guidelines.

Because NCI/DCTD staff serve as non-voting members of the Network Group Operation Center DSMBs/DMCs to ensure compliance with NIH/NCI policies and protocol requirements, NCI/DCTD staff members recuse themselves from NCI/DCTD 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/DMC of which they are members, if confidential outcome data on that study have been previously presented to the DSMB/DMC. When this situation arises, the amendment is reviewed by NCI/DCTD staff members who are not members of that DSMB/DMC.

4. Quality Assurance and Onsite Auditing

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 Network 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 onsite audits, CTMB staff or its designee(s) may attend certain onsite audits.

The CTMB has developed the CTMB Audit Information System which permits the on-line submission by the Network Group Operations Centers of all data related to quality assurance onsite. 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 member institutions/sites in each Network Group Operations Center. This roster information is used for determining compliance with monitoring requirements.

The Network Group Operations Center is responsible for ensuring that all member institutions/sites have 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) at: http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm 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 Network Group Operations Center member institution/site fails to comply with these guidelines, the CTMB may, in consultation with the Network Group Operations Center, suspend the member institution/site immediately from participating in any NCTN trials led by the Network Group Operations Center or all NCTN trials regardless of the Center leading the study. The suspension will remain in effect until the Network Group Operations Center conducts the required audit and the audit report or remedial action is accepted by the Network Group and the NCI.

The Network Group Operations Center will be responsible for notifying any affected the member institution/site of the suspension. During the suspension period, no funds from this award may be provided to the member institution/site for new accruals, and no charges to the award for new accruals will be permitted. The NCI will also notify a Lead Academic Participating Site that is the direct recipient of a Cooperative Agreement award under the NCTN Program if it is necessary to suspend accrual at the Academic Participating Site or at an affiliate site supported under that Lead Academic Participating Site's Cooperative Agreement based on the Network Group's audit.

The CTMB staff will review and provide advice regarding mechanisms established by the Network Group Operations Center and its associated Network Group SDMC for quality control of therapeutic and diagnostic modalities employed in its trials. The CTMB staff reviews and approves the mechanisms established by the Network Group Operations Center and its associated Network Group SDMC for study monitoring including its onsite auditing program. CTEP and/or its contractor staff may attend, as observers, the onsite audits conducted by the Network Group Operations Center. The frequency of participation by an NCI representative as observer will be determined by the NCI.

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 Network Group Operations Center, 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 the NCTN Program's clinical trials. It should be emphasized that the irregularity/misrepresentation does not need to be proven, a reasonable level of suspicion suffices for CTEP

CTMB notification. It is also essential that involved individual(s) and/or institutions follow their own institutional misconduct procedures in these matters.

5. Data Management and Analysis Review & Use of Standard NCTN Tools and Services

At the request of CTEP, the Biometric Research Branch (BRB) staff, in consultation with other NCI/DCTD staff, will review mechanisms established by the Network 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 Network Group data although the data remain the property of the awardee institution under 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.

During the approval process for study protocols and amendments, NCI/DCTD ensures that these standard NCTN tools and services are used. In addition, Network Group trial protocols will be periodically audited by NCI/DCTD to ensure that the tools related to common data elements in compliance with the NCTN Program approved sections of the data dictionary for common data elements in caDSR are used in the data collection instruments for the NCTN trials. If issues with compliance are identified, the NCI/DCTD will work with the Network Group to develop a corrective action plan.

6. Investigational Agent Development and Regulations

The clinical development of new anticancer agents is a highly important use of Network Group resources. The Network Groups are a vital component of the research apparatus necessary for the clinical development of the many new investigational agents sponsored by NCI/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 Clinical Trials Branch in the Clinical Imaging Program (CIP) is responsible for: (1) planning, within CIP as well as with members of the extramural community, overall strategies for studies of new imaging agents in specific tumor types and (2) coordinating and monitoring trials of new/novel imaging agents under evaluation by NCTN Network Groups.

- 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 ongoing 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 Network 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 Network Groups to the quality assurance procedures of investigational agent trials.

- The Cancer Diagnosis Program with other NCI/DCTD staff may be involved in planning and oversight of trials that require an investigational device exemption (IDE).

As previously stated, NCI/DCTD (including CTEP and CIP) uses a system of Letters of Intent (LOIs) as a mechanism for developing rational strategies for investigational drug/agent development studies as described in the Investigator Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI) available at: http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm) which includes a full description of the process for the clinical development of investigational agents and summary of the responsibilities of investigators conducting these trials.

7. 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 Network Groups to meet FDA regulatory requirements for studies involving DCTD/CTEP-sponsored investigational agents and OHRP requirements for the protection of human subjects.

8. Budget Levels for Per Case Management Funding & Budget Adjustments for the NCTN Program

Although the collective management team (i.e., NCTN Leadership Management Committee) composed of the senior leadership from the NCTN key components and the NCI/DCTD recommend priorities for trials to receive special per case management funding as well as other categories of "per case management" funding as described in Part 1 – Section III.D.2. of these Guidelines, the final decision regarding funding for the all NCTN awards, administrative supplements, and amounts selected for all "per case management" funding, including "special per case management" funding and" biospecimen per case management" funding for specific trials, rests with the NCI/DCTD. NCI/DCTD also sets the threshold levels for accrual for "high-performance" sites for the NCTN Program (i.e., for Lead Academic Participating Sites, CCOPs/MB-CCOPs, and pediatric institutions as well as other sites, depending on the availability of funding).

In addition, because of the integrated nature of the NCTN Program, applications from Network Group Operations Centers may include budgets that request "per case management" funding for patients enrolled on study from member institutions/sites that eventually receive a Network Lead Academic Participating Site award based on a Type 1 new application (or potentially Type 2 competing applications in the future). In order to adjust budgets appropriately, the Lead NCTN Program Director approves the final budgets for all key components for the NCTN Program after consultation with the Associate Director, CTEP, and DCTD Division Director, with final adjustments made to Network Group Operations Center budgets based on which institutions/sites are awarded Network Lead Academic Participating Site awards and the projected accrual across the Network for those institutions/sites.

9. Changes in Principal Investigator(s) for Any Key Component of the NCTN Program

The Lead NCTN Program Director must approve any proposed changes in the Principal Investigator (PI) for any key component for the NCTN under the Cooperative Agreement. The institution's business office should forward the name of the proposed Principal Investigator in a memorandum to the Lead NCTN Program Director requesting approval, with a copy to the NCI/DCTD Senior 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.

10. Changes in Awardee Institution for Any Key Component of the NCTN Program

Only under exceptional circumstances will NCI permit transfer of a Cooperative Agreement from one institution to another for Network Group Operations Centers and Network Group Statistics and Data Management Centers as the recipient institution would not have undergone peer review. Any such request should be approved in accordance with the Network 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 Lead NCTN Program Director and the NCI/DCTD Senior Program Specialist should be consulted

for further advice if the Network 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, resources, etc., and approval and oversight by the responsible Lead NCTN Program Director and Associate Director, CTEP.

Approval of requests for transfer by NCI/DCTD of a Cooperative Agreement form one institution to another for the other key components of the NCTN Program would also require exceptional circumstances and follow the same general process as described above.

D. Joint Responsibilities (Key Components of the NCTN Program and NCI/DCTD)

1. General Study Development and Conduct

Because of the significant resource, regulatory, and general administrative issues involved in NCTN key component activities and to ensure required compliance with other federal regulations and federal agencies, the NCTN Network Groups and other key components of the NCTN should collaborate closely with NCI/DCTD staff. This collaboration should occur early on in the development of phase 3 trials well as in the development of other trials, general research strategies, and new initiatives. In particular, when new avenues of cancer therapy involving investigational drugs are pursued, the trial should be designed such that the clinical information obtained should be acceptable to the FDA for inclusion in a potential licensing application. Therefore, the NCI/DCTD staff and the Network Group should work collaboratively to develop protocols meeting that standard. All parties (Network Groups, NCI/DCTD staff, and company collaborators should be involved in any conference calls and/or meeting involving the FDA during the development and conduct of any approved NCTN trial with licensing potential, regardless of whether the study is being conducted under CTEP IND or a Network Group IND in order to ensure that all sponsors are involved in discussion regarding the trial.

Both the Network Groups and NCI/DCTD share the responsibility to ensure that study proposals are reviewed/evaluated, protocols developed, and trials activated in a timely manner per the timelines established and approved by the Operational Efficiency Working Group (OEWG), including target and absolute deadlines for opening trials to patient enrollment. A description of the OEWG process, requirements, and required timelines are available at: http://ctep.cancer.gov/SpotlightOn/OEWG.htm.

Both the Network Groups and NCI/DCTD also share the responsibility to collaborate on initiatives to promote accrual to NCTN trials.

2. Data and Safety Monitoring Boards (Data Monitoring Committees)

The appropriate conduct of Network Group Data and Safety and Monitoring Boards (DSMBs), sometimes called Data Monitoring Committees (DMCs), is a collaborative responsibility of the Network Group (Operations Center and associated Statistics and Data Management Center) and NCI/DCTD staff. Information on the CTEP policy for DSMBs/DMCs is available in Part 4 – Appendices – Section VIII of these Guidelines. The Network Group's Data and Safety Monitoring Policy must be submitted to and approved by the Lead NCTN Program Director. All DSMB/DMC members, including the DSMB/DMC Chair, must be approved by the Lead NCTN Program Director prior to their inclusion in DSMB/DMC meetings. Any changes to the Network Group DMSB/DMC policy and/or membership must be reviewed and approved by the Lead NCTN Program Director prior to implementation. The Lead NCTN Program Director also names the NCI/DCTD staff who represent NCI/DCTD as non-voting members on the Network Group's DSMB/DMC. If the Network Group DSMB/DMC includes oversight of studies funded by the Division of Cancer Prevention, all changes in membership and policy are also reviewed by the appropriate staff in DCP as applicable and DCP also names the non-voting NCI/DCP staff person to represent the Division on the Network Group DSMB/DMC.

3. Development of Collaborative Trials and International Trials

The Clinical Investigations Branch staff at CTEP work with the NCTN Network Groups to facilitate international participation in trials when appropriate. When institutions outside the U.S. are members of a U.S. Network Group and wish to participate in a U.S Group Trial, the institution and its investigators must meet ALL the same Network Group membership requirements as U.S. institutional members and their associated investigators, including being audited by the Network Group per CTMB guidelines for international Participating Sites, filing FDA 1572 Forms, etc. However, when trials call for collaboration with a separate international clinical trial organization for its participation in a U.S. Network 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/CIB staff in

advance for general advice and guidance regarding whether the advantages of international collaboration will outweigh the expected resource costs.

Network Group Operations Centers are required to have a binding collaborative agreement in place with the international clinical trial organization that addresses the major components of clinical trial conduct by the international organization to ensure that the conduct is consistent with all appropriate federal and other appropriate regulations for the clinical research trial. This agreement must be reviewed and approved by the Lead NCTN Program Director in consultation with the Associate Director of CTEP and the Chief, CTEP Regulatory Affairs Branch, and all appropriate U.S. State Department approvals must be in place for countries that will be participating in the research as well as other appropriate approvals (e.g., company partner approvals for trials being conducted under an NCI/DCTD binding collaborative agreement or CRADA).

With respect to participation of U.S. Network Groups in trials led by a non-U.S. organization (other than the Canadian Collaborating Clinical Trials Network of the NCTN), there are also numerous logistical, regulatory, and company-sponsor issues that must be addressed in addition to approval of the non-U.S. trial by the NCI via the appropriate NCI Scientific Steering Committee (if applicable) and NCI/DCTD/CTEP. Again, it is critical for any proposal for participation of a U.S. Network Group in a non-U.S. trial to be discussed in advance with CTEP staff to determine whether participation in such a study is feasible. These trials are required to have a U.S. Network Group Operations Center identified as the primary or lead sponsor for the trial for the NCTN Program. A binding collaborative agreement is also required with the international clinical trial organization that addresses the major components of clinical trial conduct by the international organization to ensure that the conduct is consistent with all appropriate federal and other appropriate regulations for a clinical research trial sponsored by the NCTN Program. This will usually also require a trial specific Steering Committee be in place to address oversight of the trial conduct with respect to regulatory compliance for the U.S. Network Group Operations Centers participating in the trial as well as to address issues related to data ownership and biospecimen collection.

In addition, the lead U.S. Network Group Operations Center that is the primary or lead sponsor for the trial in the U.S. must have U.S. State Department approvals in place for countries that will be participating in the research even though federal funds will only be used to support the participants from the NCTN Program enrolling patients on study. The research agreement between the U.S. Network Group Operations Center that is the primary or lead sponsor for the trial in the U.S. and the international organization leading the trial that governs the conduct of the study must be reviewed and approved by the Lead NCTN Program Director in consultation with the Associate Director of CTEP and the Chief, CTEP Regulatory Affairs Branch.

A guidance document from NCI/DCTD/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: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies. This document addresses the various regulatory issues involved in the conduct of international trials that involve participation/leadership of Network Groups under the NCTN Program.

4. Collective Management of the Network

In order to provide for collaboration and coordination of policies and procedures for the NCTN, collective management of the Network is needed. To achieve this goal, a core collective management team (i.e., the NCTN Leadership Management Committee) composed of senior leadership from each of the following key components of the NCTN Program (i.e., 1 representative from each of the Network Group Operations Centers, 1 representative from each of the Network Group Statistics and Data Management Centers, 2 representatives from the Canadian Collaborating Clinical Trials Network Organization representing Operations and Statistics/Data Management, and 1 representative from the Radiotherapy Core Service Center and 1 representative from the Imaging Core Service Center) and key NCI/DCTD staff (Director Division DCTD, Associate Director CTEP, Chief and Associate Chiefs of the Clinical Investigations Branch CTEP, Cancer Diagnosis Branch Associate Director, Tumor Banks Program Director) and the project scientists/program directors involved in the NCTN Program and key NCI/DCP staff (Deputy Director DCP,

Program Director of the CCOP and MB-CCOP) will meet regularly to discuss major policy issues and address concerns about the NCTN. The Committee will make recommendations to senior NCI leadership on the Program. It is anticipated that the Committee will meet on at least a quarterly basis by teleconference and/or in-person. Additional representatives from the NCTN may be invited to participate in meetings depending on the issues to be discussed. It is also anticipated that there may be meetings held specific to the Network Group Statisticians and Network Group Directors of Operations/Group Administrators on a periodic basis to discuss significant issues, as appropriate.

Specific areas that will require recommendations from the NCTN Leadership Management Committee include but are not limited to the following:

- Identification, and recommended prioritization, of NCTN clinical trials that should receive "special per case management" funding because of trial complexity and/or because the trial addresses a rare cancer or rare subset of a more common cancer
- Recommendations regarding how development of trials in rare cancer should be integrated into the Network Groups scientific research committees
- Identification of trial categories and/or specific trials that should be prioritized to receive funding for biospecimen collection
- Prioritization of trials for receipt of services from the Network Radiotherapy and Imaging Core Services Centers if the Centers encounter resource limitations
- Establishment of harmonized or standard policies for Network Group Member Performance Evaluations related to data quality and data timeliness for NCTN clinical trials as well as other Network-wide issues such as human subjects training for clinical trials
- Harmonized or standard policies for institutional membership in Network Groups so that institutions are encouraged to participate in trials across the NCTN (i.e., ensure that requirements for membership do not preclude sites from crediting different Network Groups to which they belong)
- Address important coordination issues between the NCTN and NCI Scientific Steering Committees
- Address recommendations from the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) on strategic directions for the NCTN Program
- Establishment and coordination of NCTN Correlative Science Committee(s) and procedures to review requests for use of "banked" biospecimens collected in conjunction with or tied to NCTN clinical trials
- Procedures for establishing public data sets from NCTN clinical trials that have reported out primary results
- Improvements to general NCTN policies/procedures to promote standardization/harmonization for the entire Network and recommendations for new policy and procedural initiatives as well as identification of needs for new tools, services, and resources

5. Network-Wide Common Services, Tools, and Resources

The Network Groups are required to use specific NCTN common services and tools, including but not limited to those listed below, for all NCTN trials in order for the trials to be approved for activation:

- NCTN Common Data Management System for data collection
- NCTN System for tracking biospecimen collection from NCTN trials (in development)
- NCTN Oncology Patient Enrollment Network (OPEN) via the Cancer Trials Support Unit (CTSU)

- NCTN Regulatory Support Services (RSS) via the Cancer Trials Support Unit (CTSU)
- NCTN Specification for appropriate designation of per case funding for trials prior to activation
- NCI CIRB Review for studies as required under these Guidelines

6. Legacy Studies

Legacy studies supported by the NCTN Program will be conducted under the same NCTN Terms and Conditions of Award as are those studies that commence under the NCTN Program. Hence, the awardees of any of the key components of the NCTN Program (i.e., Network Group Operations Centers, Network Group Statistics and Data Management Centers, Network Integrated Translational Science Awards, Network Lead Academic Participating Sites, Network Radiotherapy and Imaging Core Services Centers, and Canadian Collaborating Clinical Trials Network) are bound by the Terms and Conditions of their Award under the NCTN Program when working on legacy studies that are supported by the NCTN Program.

E. Appeals Process for Decisions Regarding Study Proposals & Types of Studies Performed by NCTN Program

This appeal process is only for disagreements related to scientific merit decisions made on study proposals for the NCTN Program or the programmatic definition of study types supported under the NCTN Program.

1. Decisions on Study Proposals

The appeals process for decisions related to study proposals supported under the NCTN Program (including both intervention and non-intervention studies) is described below.

- For NCTN phase 3 and phase 2 Concepts evaluated by NCI Scientific Steering Committees (or the CTEP Protocol Review Committee for disease areas without an NCI Scientific Steering Committee or in lieu of an NCI Scientific Steering Committee because of scheduling/workload issues) that are not approved for development based on scientific merit, the Network Group Operations Center may "appeal" the decision to the Director, Division of Cancer Treatment and Diagnosis, if the Network Group Operations Center believes that there were factual errors in the evaluation that led to the disapproval. If the Director agrees with the appeal request by the Network Group Operations Center, the Director will direct the appropriate NCI disease-specific Steering Committee to re-evaluate the study proposal. The result of the re-evaluation will be considered final.

- For NCTN phase 1 and phase 2 Letter of Intent (LOI) proposals evaluated by NCT/CTEP's Protocol Review Committee for trials proposals that **would be conducted under CTEP IND**, the Network Group Operations Center may appeal an LOI not approved for development based on scientific merit by requesting that the Investigational Drug Steering Committee (IDSC) review the LOI. The result of the review of the LOI by the IDSC will be considered final.

- For NCTN phase 1 and phase 2 LOIs reviewed by NCI/CTEP's Protocol Review Committee for trials proposals that **would NOT be conducted under CTEP IND**, the Network Group Operations Center may appeal an LOI not approved for development based on scientific merit to the Director, Division of Cancer Treatment and Diagnosis, if the Network Group Operations Center believes that there were factual errors in the review that led to the disapproval. If the Director agrees with the appeal by the Center, the Director will direct CTEP's Protocol Review Committee to re-evaluate the study proposal. The result of the re-evaluation will be considered final.

- For NCTN non-intervention studies (i.e., correlative science studies that request use of biospecimens collected in association with an NCTN trial) reviewed by NCI/CTEP's Protocol Review Committee or evaluated by an NCI/DCTD-approved NCTN Correlative Science Committee, the Network Group Operations Center may appeal a study proposal not approved for development based on scientific merit to the Director, Division of Cancer Treatment and Diagnosis, if the Network Group Operations Center believes that there were factual errors in the review that led to the disapproval. If the Director agrees with the appeal by the Center, the Director will direct CTEP's Protocol Review Committee or the NCI/DCTD-approved NCTN Correlative Science Committee to re-evaluate the study proposal. The result of the re-evaluation will be considered final.

Any approval of a Concept, LOI, or non-intervention study proposal, even after appeal, is subject to feasibility/resource considerations as determined by NCI/DCTD.

2. Decisions on Types of Studies Funded Under the NCTN Program

The Associate Director, NCI/CTEP makes decisions regarding any questions regarding the interpretation of the types of studies funded under the NCTN Program in consultation with the Chief of the Clinical Investigations Branch and Lead NCTN Program Director. The Network Group Operations Center may appeal this decision to the Director, Division of Cancer Treatment and Diagnosis for a particular study, if the Network Group Operations Center believes the type of study is within the scope of the NCTN Program as described in these Guidelines. If the Director agrees with the appeal by the Network Group Operations

Center, the Director will direct NCI/DCTD to consider the proposal under the appropriate evaluation or review procedures for the NCTN Program as described in Part 1 – Section IV.C.3.1. of these Guidelines.

V. Other NCI Administrative Considerations

A. Program Staff Administration of the NCTN Program

Within NCI/DCTD, major scientific policy and programmatic decisions concerning the NCI National Clinical Trials Network (NCTN) Program are made only after appropriate consultation with and involvement by the responsible Lead NCTN Program Director, the Co-Program Directors of the NCTN Program, the Project Scientists, NCI/DCTD Branch Chiefs and Program Chiefs that are involved in the Program, and the Associate Director, CTEP, DCTD, as necessary and appropriate. Routine programmatic administration is the responsibility of the responsible Lead NCTN Program Director, who assures uniformity of implementation across the various key components in conjunction with the Co-Program Directors of the NCTN Program and the Project Scientists.

The Lead NCTN Program Director or his/her designee has responsibility for addressing and approving non-competitive award (Type 5) budget requests, any supplemental budget requests, and new/competitive award (Type 1) budgets, as well as future Type 2 applications. The responsible Lead NCTN 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 Co-Program Directors of the NCTN Program and the Project Scientists for the key components of the NCTN Program as well as the NCI/DCTD Senior Program Specialist for the Program.

B. Senior Program Specialist for the NCTN Program

The NCI/DCTD Senior Program Specialist for the NCTN Program works closely with the responsible Lead NCTN Program Director in reviewing administrative materials supporting Group requests, performing budget analyses, and facilitating the completion of action items involving coordination between NCI/DCTD, the NCI Office of Grants Administration (OGA), and the awardees under the Program. The NCI/DCTD Senior Program Specialist exchanges information with the Network Group Directors of Operations for the key components of the NCTN Program and OGA staff on administrative changes and priorities.

C. 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 Lead NCTN Program Director and NCI/DCTD Senior Program Specialist 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. 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 ongoing expense.

2. Requests for Non-competing Supplemental Funding

Informal discussions about the possibility of receiving non-competing supplemental funding for special needs and/or additional funding to cover data collection and management and biospecimen collection on a per case basis may be initiated by the awardee for the key component of the NCTN Program. 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(s). Electronic facsimile signatures on documents transmitted via email are acceptable. 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 Lead NCTN Program Director, in care of the NCI/DCTD Senior Program Specialist.

Part 2: Guidelines for Submission of Competing New Applications & Description of Review Process

I. Pre-Application Consultation and Application Submission Instructions

A. General Considerations and Due Dates

All competing new applications (Type 1) for support through the NCI National Clinical Trials Network (NCTN) Program must be submitted under the appropriate Funding Opportunity Announcement (FOA) for each of the 6 key components of the Program as listed below. The FOAs contain essential information on various aspects of the components including the eligibility requirements for the applicant institution/organization and Principal Investigator(s).

NCTN Program Key Component	Funding Opportunity Announcement (FOA)
Network Group Operations Centers	**RFA-CA-12-010 (U10)**
Network Group Statistics & Data Management Centers	**RFA-CA-12-011 (U10)**
Network Group Integrated Translational Science Centers	**RFA-CA-12-012 (U10)**
Network Lead Academic Participating Sites	**RFA-CA-12-013 (U10)**
Network Radiotherapy & Imaging Core Services Centers	**RFA-CA-12-014 (U24)**
Canadian Collaborating Clinical Trials Network	**RFA-CA-12-504 (Limited Competition U10)**

All new applications 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 the Cooperative Agreements supported under this Program (i.e., Network Group Operations Centers, Network Group Statistical and Data Management Centers, Network Translational Science Support Centers, Network Lead Academic Participating Sites, Network Radiotherapy and Imaging Core Services Centers, and Canadian Collaborating Clinical Trials Network). The major components of the PHS 398 as described in these Guidelines for the NCTN 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 application. The PHS 398 is available at: http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact: **GrantsInfo,** Telephone (301) 435-0714, **Email: GrantsInfo@nih.gov**. Once the SF424 is required for applications submitted for the NCTN Program, applicants will be

notified by the NCI/DCTD Program Specialist and applicants should use the appropriate NIH website references available at: http://grants.nih.gov/grants/funding/424/index.htm 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 National Clinical Trials Network (NCTN) 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 these applications). If an issue is not explicitly included in these Guidelines, then applicants should follow** the information and guidance given in the PHS 398/SF424.

Applications not prepared using the current version of the PHS 398 application forms (or SF424 electronic application when it replaces the PHS 398) or not adhering to the format and preparation instructions contained in these Guidelines and the appropriate NCI NCTN Funding Opportunities Announcement (FOA) may be returned without review or just not reviewed. Organizations submitting new applications for any of the key components of the NCTN supported under the Program MUST apply for five (5) years of support. Applications requesting less or more than 5 years of support may be returned without review.

The receipt dates & review schedule for all new competing applications for 5 years of support should be submitted in response to the Funding Opportunities Announcements for the key components of the NCTN Program are summarized below:

Application Submission & Review Activity	Due Date
Pre-consultation with NCI/DCTD	4 to 6 months prior to Application Due Date
Letter of Intent Due Date	December 15, 2012
Application Due Date	January 15, 2013
Post Submission Application Materials	30 Days Prior to Scientific Merit Review Meeting
Scientific Merit Review	June, 2013
Advisory Council Review (NCAB)	October, 2013
Earliest Start Date	March 1, 2014
Just-in-Time Information	Prior to Start Date

Please Note: It is anticipated that new applications for the Network Lead Academic Participating Site award may be accepted for 3 years of funding after the first 2 years of the NCTN Program's initial 5-year funding period have been completed. This time point and award project period would be selected for additional new Network Lead Academic Participating Site applications so that the award funding would be synchronized with the next potential funding cycle for all Lead Academic Participating Site grants (i.e., so that all the Lead Academic Participating Sites would come in for potential competitive renewal at the same time at the next 5-year funding cycle). The schedule for submission and review of those applications would be specified in an anticipated future Funding Opportunity Announcement (FOA).

It is also anticipated that when competing continuation applications (Type 2) and competing supplemental applications (Type 3) become part of the Program in the future, the submission requirements for Type 2 and Type 3 applications will be the same as those detailed in this section for competing new applications (Type 1) with the due dates specified in the associated FOAs.

B. Initial Communications and Letter of Intent

Initial Communications with NCI/DCTD Staff – 4 to 6 Months Before Application Due Date:
Although it is not required, it is strongly recommended that prospective applicants schedule a pre-application consultation with NCI/DCTD Program Staff including the Lead NCTN Program Director and appropriate Scientific Program/Project Officers (i.e., Co-Program Directors for specific components of the NCTN) approximately four (4) to six (6) months in advance of the application due date. This consultation is intended to help the Principal Investigator (along with multiple Principal Investigators and/or co-investigators) to clarify the NCTN application and discuss all relevant aspects of the application process. NCI/DCTD staff will clarify the intent of the Guidelines and current NCI budget allocations, and describe the peer-review process. To schedule the pre-application consultation, prospective applicants should send a request to the NCI/DCTD Senior Program Specialist for the NCTN electronically or by mail:

NCI/DCTD Senior Program Specialist for the NCTN:
Elise Kreiss, MSW, MBA
Office of the Associate Director, Cancer Therapy Evaluation Program
National Cancer Institute
6130 Executive Boulevard, Room 7018, MSC 7340
Bethesda, MD 20892-7340 (for U.S. Postal Service regular or Express Mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: 301-496-6138
Email: ncictepanalyst@mail.nih.gov

Letter of Intent – 30 Days Before Application Due Date:
Although a Letter of Intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NCI staff to estimate the potential review workload and plan the review. By the date listed in the table provided under **"General Considerations and Due Dates" in Part 2 – Section I.A in these Guidelines,** prospective applicants are asked to submit a Letter of Intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Program Director(s)/Principal Investigator(s)
- Names of other key personnel
- Participating institutions
- Number and title of the Funding Opportunity Announcement/Request for Application

The Letter of Intent should be sent to:

NCTN Lead Program Director:
Meg Mooney, MD
Clinical Investigations Branch, Cancer Therapy Evaluation Program
National Cancer Institute
6130 Executive Boulevard, Room 7024, MSC 7340
Bethesda, MD 20892-7340 (for U.S. Postal Service regular or Express Mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: 301-496-2522
Email: ncictepanalyst@mail.nih.gov

C. Application Submission Procedures

Applications must be prepared using the PHS 398 research grant application forms and instructions (unless they have converted to electronic submission) for preparing a research grant application. Submit a signed, typewritten original of the application, including the checklist, and three (3) signed

photocopies in one package to the Center for Scientific Review at the address listed below. **The original must be signed by the Project Director/Principal Investigator (PD(S)/PI(S)) 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 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two (2) identical, single-sided paper copies of the original application and one (1) CD containing appendix material (if allowed for the NCTN key component) must be sent to the address listed below. Please Note: One of the two copies of the application sent to the NCI Referral Office may be a CD with a bookmarked PDF file (as outlined in the PHS 398). All appendix material (if allowed for the NCTN key component) must be prepared as bookmarked PDF files on a CD following the instructions in the PHS 398 form.

Referral Officer
Division of Extramural Activities
National Cancer Institute
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329 (for U.S. Postal Service regular or express mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: ncirefof@dea.nci.nih.gov

D. Appendix Material for All Key Components of the NCTN Program

Per the NIH/NCI policy on what may be submitted as appendix materials (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-077.html), **the information provided below specifies if appendix materials are allowed as part of the application for the key component of the NCTN Program as well as the type of appendix material that may be included.** All appendix materials for paper applications submitted on the PHS 398 form must be submitted as book marked PDF files on CDs. A summary listing of all the items included in the appendix is encouraged but not required. When including a summary, it should be the first file on the CD.

Follow the standard instructions for preparing the CDs:

- Use PDF format only. The files should prepared as PDF version no higher than 1.4 for compatibility with NIH programs and software.
- Where possible, applicants should avoid creating PDF files from scanned documents. NIH recommends producing the documents electronically using text or word-processing software and then converting the document to PDF format. Scanned document images should be checked for legibility.
- Label each disk with the date, Principal Investigator's Name, Grant Number (if available), grant title, and applicant institution.
- If burning CD-ROM disks on a Mac, select the ISO 9660 format.
- Do not use compression techniques for the electronic files.
- Do not use password protection, encryption, digital signature and/or digital certification in the PDF files.

Applications for key components of the NCTN Program are scanned by central NIH offices to produce black and white images and black and white double sided copies for the reviewers. Figures in the

application that do not reproduce well in black and white may be included in the application and allowed Appendix material. However, all figures included in the appendix material must be included in the application, although they may be reduced in size in the application. Images not included in the application cannot be included in the appendix.

If your application contains a large number of color illustrations or charts and graphs that will not reproduce well in black and white, you may also submit a CD with a bookmarked PDF file of the entire application as one of the two copies of the application sent to the NCI Referral Office on the due date. Such CDs will be accepted only at the time of application submission. The PDF file should be bookmarked at major subdivisions of the application so that reviewers can navigate through the file and find individual components easily. The files should be saved as PDF version no higher than 1.4 for compatibility with NIH programs and software.

Appendix materials must be included with the copies of the application sent to the NCI Referral Office on the due date as specified above in Part 2 – Section I.C of these Guidelines. Additional copies of the collated sets of Appendix material may be requested by the Scientific Review Officer (SRO) from the Division of Extramural for the peer review of the application and the number of additional copies and timing of submission should be discussed at the time of the pre-application consultation with NCI Program Staff and the SRO. Appendix material cannot be used to circumvent page limitations of the research plan.

All the key components of the NCTN Program can provide the following information (and only the following information) in the appendix material for their respective applications as described below.

Applicants may submit up to 3 of the following types of publications:

- Manuscripts and/or abstracts accepted for publication but not yet published that are referenced in the Research Plan of the application.
- Published manuscripts and/or abstracts that are referenced in the Research Plan of the application **only** when a free, online, publicly available journal link is not available.
- Patents materials directly relevant to the application.

Other Information:

- Paper PHS 398 applications **only** may include full-sized glossy photographs of material such as electron micrographs or gels in the Appendix; however, an image of each (may be reduced in size but readily legible) must also be included within the page limitations of the Research Plan.

- Any additional appendix material that is allowed for a specific key component of the NCTN Program will be listed in the corresponding "Appendix Material and Post Submission Materials" sub-section in Part 2. II of these Guidelines for that key component.

E. Notification of International Involvement in NCTN Trials

The NCTN key component should alert the NCI/DCTD Senior Program Specialist when the new competing application involves any international (non-US) component. In such cases, advance clearance from the U.S. Department of State is required for each non-US component prior to the award. The information required by U.S. 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

F. Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in NOT-OD-10-115. **Note:** Because applications submitted in response to the Request for Applications (RFAs)/Funding Opportunity Announcements (FOAs) for all the key components of the NCTN Program have only one due date, applicants may submit materials per the exceptions list in NOT-OD-10-115 using the specified page limits (see: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-115.html).

II. New Applications Format and Budget Considerations

A. General Information and Common Budget Outline for Network Group

All applications for key components of the NCTN Program must follow the PHS 398/SF424 format for new applications, including formatting and page limitations except as modified below. The applications 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 the main activities of the NCTN component 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 each application. Key Personnel will usually include the PI (and multiple PIs, if applicable), other significant scientific, technical and administrative officers as well as major committee chairs and vice-chairs. Consultants should also be included if they meet the definition of "Key Personnel." 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 (see "Just-in-Time" information is this section of the Guidelines).

Please Note: All pages must be numbered sequentially within a submitted application. All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the internet sites. Furthermore, reviewers are cautioned that their anonymity may be compromised when they directly access an internet site. **The exception to this is the URL for published manuscripts and abstracts via PubMed as only the public internet references for these publications are accepted in the application.**

The Network Group Operations Center applicant, in conjunction with its associated Network Group Statistics and Data Management Center (SDMC), is required to submit a Common Budget Outline (see Part 4: Appendices – Section IX) as part of its application.

Rationale for the Common Budget Outline: The Common Budget Outline was designed to provide budget information in a standard format that allows the reviewers to understand how the total Network Group budget is allocated among the various components of the Group to support its basic functions and so the reviewers can compare budgets received across the NCTN Program.

Total Budget for a Network Group: The budget of a Network Group (i.e., Network Group Operations Center and Network Group Statistics and Data Management Center) is dependent on accrual to the trials led by the Network Group as well as the accrual to other Network Group trials. The estimated total cost used to generate budgets for a Network Group as defined above should be based on funding for (1) infrastructure support for the Network Group Operations Center and Network Group Statistics and Data Management Center to develop, conduct and analyze NCTN clinical trials and (2) costs to cover data collection and management and biospecimen collection associated with patient enrollment to NCTN trials by member institution/sites.

B. Network Group Operations Center Application

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

1. Detailed Budget for the Initial Budget Period

1.1 Estimation of Total Cost Budget Request

The total cost budget requested by the Network Group Operations Center in its application should be based on 2 components described below, using guidelines provided in Part 4 – Appendices – Section IV of these Guidelines:

(1) an algorithm used to estimate the cost of the data collection/management and biospecimen collection (i.e., "per case management" funding) that will be provided to the Network Group Operations Center's member institutions/sites enrolling patients on NCTN trials that do not receive "per case management" funding via grants (e.g., Lead Academic Participating Sites grants, CCOP or MB-CCOP grants)

(2) an algorithm used to estimate the total cost of developing and conducting NCTN trials (i.e., infrastructure costs) that the Network Group Operations Center leads and collaborates on.

Guidelines for amounts to use in developing the total cost budget request for Type 1 applications are provided in Part 4 – Appendices - Section IV. of these Guidelines. These guidelines include total cost amounts or ranges for the categories of:

- "per case management" funding for participating sites;
- infrastructure financial management coordination for the site by the Network Group based on type of "per case management" funding being provided ; and
- other infrastructure costs for the Network Group Operations Center and its associated Network Group SDMC to conduct NCTN trials led by the Network Group based on estimated accrual to the trials (with separate estimated ranges related to intervention accrual *versus* non-intervention accrual).

Applicants must use the amounts specified in these Guidelines for the different categories of "per case management" funding that are to be provided to member sites in preparing their budget. Applicants are not required to use the specific estimated ranges for infrastructure costs provided in these guidelines (i.e., estimated ranges for infrastructure costs may be adjusted by the applicant to fit its particular funding needs). However, total cost Network Group budgets that include infrastructure costs based on estimated ranges that are in significant excess of the estimated ranges provided in these Guidelines for infrastructure costs are unlikely to be supported. These guidelines also provide a total cost range for scientific leadership/coordination at "high-performance" pediatric sites based on accrual as these sites do not have the option of applying for the Lead Academic Participating Site awards.

1.2 General Information and Cost Categories

Since the organizational framework of each Network Group may be different, the Operations Center budget should be presented in logical, discrete units, with specific budgets for each unit (e.g., "per case management" funding for member sites, support for scientific

leadership, infrastructure cost categories such as administration, regulatory oversight, protocol development). A specific budget page covering the Network Group's quality assurance and study monitoring activities, onsite audit program, and must be included.

Funds for correlative science research and/or reference laboratories are not supported under the NCTN Program and should not be included in the application. Funding for integral and integrated laboratory and/or biomarker studies for NCTN trials can be covered by BIQSFP applications (see information on the BIQSFP at: http://biqsfp.cancer.gov/) as well as through other sources of funding (e.g., R01/P01 grants, industry and charitable support), and potentially through administrative supplements for specific trials under the NCTN Cooperative Agreement.

The following budget guidelines apply specifically to the Network Group Operations Center budget. The categories listed below (with the exception of "Mechanisms for Per Case Data Management Funding") refer to those contained in the section of the PHS 398/SF424 pertaining to the detailed budget for initial budget period. **NOTE:** Specific job descriptions and qualifications for funded personnel (administrative as well as scientific leadership) should be covered in this budget section and not repeated in the research plan narrative.

a) Personnel: A staffing plan for the Network Group Operations Center, including position descriptions and qualifications should be provided. Precise justification for the amount of effort requested for each position is essential, including the following:

- **Scientific Leadership:** Research costs include the time and effort involved in developing the Network Group's research strategy and its repertoire of trials/protocols as well as the trial monitoring, analysis of results, and publication of those results of Network Group research in peer reviewed journals. These costs also include funding for scientific research and administrative committee chairs and/or chairs as well as study chairs, if applicable.

- **Scientific Services:** Research costs include the time and effort involved in providing scientific services such as scientific review (toxicity review, pathology review, surgical review) specific to the research goals of a Network Group study (i.e., not associated with conventional patient care or for educational purposes). As noted above, correlative science research outside of biospecimen and/or special image collection approved for specific trials is not funded under the NCTN. Funding for integral and integrated laboratory and/or biomarker assessment for NCTN trials can be covered by BIQSFP applications or other funding sources as described in Section 1.1 above.

  Network Group Operations Center budgets also should not include scientific services related to development of innovations in advanced imaging and radiotherapy treatments unless it is a specific, essential component of the Network Group's overall research strategy. It is anticipated that services for developmental work in these areas would only be funded in 1 Network Group and would need to be requested as a specific budget item in the appropriate categories in the PHS 398 budget pages and as a specific budget line item in the Common Budget Outline. General quality assurance for imaging and radiotherapy for clinical trials should be part of the Network Radiotherapy and Imaging Core Services Centers.

- **Protocol Development/Management:** Research costs include the time and effort of the Operations Center staff that support the scientific leadership of the Network Group in development of study proposals and study protocols as well as the management of trials after activation (e.g., protocol amendment processing).

- **Administration:** Research costs include the time and effort involved in the overall management/administration of the Network Group's resources, regulatory activities, quality assurance, study monitoring procedures, etc.

- **Data and Safety Monitoring Boards (Required Funding in Application as Separate Line Item as Funding is Restricted for this Purpose):** Research costs include the time and effort involved in the overall management/administration by the Network Group Operations Center for the Data and Safety Monitoring Board for the Network Group's phase 3 and randomized phase 2 trials.

- **Auditing (Required Funding in Application as Separate Line Item as Funding is Restricted for this Purpose):** Personnel costs and travel for the Network Group Operations Center to support the Network Group auditing program.

- **Tumor Bank Coordination (Required Funding in Application as Separate Line Item as Funding is Restricted for this Purpose):** Personnel costs to support coordination of the activities of the Network Group Operations Center and the associated Network Group SDMC with those of the Tumor Bank for the Network Group (i.e., coordination support for linking biospecimens and clinical data so there is an accurate inventory of available biospecimens and requests for "banked" biospecimens for approved studies can be appropriately supported).

b) **Consultant Costs:** Reasonable consultant costs are allowed if the consultant is contributing in a substantial way to the conduct or development of Network Group's research strategy, although clear and quantifiable justification is required. Most of a Network Group's consultant costs should appear in the Operations Center budget. These costs include travel, per-diem and consultant fees, if applicable and within institutional policy.

c) **Equipment:** Only those equipment items that are required to conduct Network Group studies should be included. Justification should include percent of time used for Network Group business as well as necessity for purchase. The amount of funds requested should be based on percent of use.

d) **Supplies:** Research costs for appropriate supplies with quantitative justifications based on actual use should be provided.

e) **Travel:** The importance of meetings to the achievements of any Network Group's overall research strategy 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:

- Trips by the Network Group's leadership and investigators on behalf of the Network Group to the NCI and other national organizations where the results

of Network Group research are presented or where Network Group research strategies are to be discussed;

- Travel for Network Group scientific and administrative committee members to committee meetings held separately from major Network Group meetings;
- Travel for protocol chairs and others who must perform quality assurance functions away from their home institution;
- Travel for persons on the Operations Center staff who must attend the Network Group's meetings;
- Travel for the Network Group senior leadership to attend NCI/DCTD – Network Group NCTN Leadership Management Committee meetings for the NCTN Program;
- Travel associated with onsite audit program (see Auditing under Personnel above); and
- A reasonable number of carefully justified trips for provisional Network Group members or other associated stakeholders (e.g., patient advocates) to attend Network Group meetings in order to encourage participation and assure input from all relevant modalities and stakeholders in clinical trial research.

f) Alterations and Renovations: Costs for alterations and renovations are not allowable under the NCTN Program.

g) Other Expenses: Research costs due to other expenses include those related to communication and information dissemination among other components of the Network Group as well as with sites accruing patients to Network Group trials. 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.

h) Consortium/Contractual Costs: Research costs include financial support to Network Group members who are responsible for committees or scientific services and this financial support is usually provided through consortium/contractual arrangements. Consortium/contractual cost for each participant require a separate budget page, with appropriate justification. Indirect costs to consortium/contractual participants are included in the direct costs for the Network Groups Operations Center budget.

Network Groups are encouraged to structure their organization in a manner which minimizes the burden of indirect costs on the overall Network Group budget. The "per case management" funding described in Part 2 – Section II.B.1.4 below) should also be included in the category of consortium/contractual costs for the Network Group Operations Center budget.

1.3 Patient Care Costs

NCI will not support costs associated with routine patient care. Only in the most unusual circumstances would a Network Group clinical trial require interventions beyond those considered appropriate for the care of cancer patients. In those circumstances, a Network

Group may make a case for reimbursement of patient care costs associated with the particular research element as an administrative supplement. The justification should be presented at the level of the Network Group Chair(s) to the Lead NCTN Program Director with a specific request from each institution based upon likely accrual to the specific study. This request would need to be approved/funded by NCI/DCTD for the specific trial prior to activation of the study. Alternatively, the Network Group could seek other sources of funding for these costs (e.g., company collaborators, other NIH/NCI grant funding, charitable foundation funding).

In the case such funding was approved by NCI for a specific NCTN trial, it would be expected that the Network Group Operations Centers would provide this funding as per case "special per case management" funding to their respective member institutions/sites that enrolled patients on the trial and credited the Network Group Operations Center with the accrual. At its discretion, for the Lead Academic Participating Sites, the NCI/DCTD could decide to provide such funding directly to Lead Academic Participating Sites (and the affiliates included in its award) that are enrolling patients on the trial via an administrative supplement to their grants if it was expected that enrollment to the trial would be concentrated primarily at these sites. NCI/DCTD would specify, at the time such funding was approved for an NCTN trial, how the funding would be provided to the Lead Academic Participating Sites awardees.

Rationale for patient care cost policy: This policy is based on the observation that Network Group NCTN trials always involve treatment or imaging 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.

1.4 Per Case Management Funding - Adult Network Group Operations Center Budgets (Restricted)

This category of funding must be included in the budget of the Network Group Operations Center and must be restricted for this purpose. The Network Group Operations Center's budget for per case data collection and management and biospecimen collection funding (also called "per case management" funding) should be estimated based on accrual projections for patient enrollment by its member institutions/sites to all NCTN trials that the institutions/sites credit to the Network Group Operations Center. This funding amount is based on the amounts and funding algorithm specified in Part 4: Appendices – Section IV (Total Cost Figures for Budget Preparation) using the definitions provided below for the various categories of "per case management" funding.

The amount for these funding categories as specified in Part 4: Appendices – Section IV reflect the total cost that must be provided to the participating site that is a member of the Network Group Operations Office and which does not receive its funding via a grant as a Lead Academic Participating Site, COOP, or MB-CCOP, or as a pediatric site via the Pediatric Network Group's grant. These amounts are based on the "category" of funding as defined below and are set at the same level across the entire NCTN regardless of the Network Group Operations Center leading the trial. Only these amounts should be used in creating the application budget. These amounts are paid by the Network Group Operations Center based on accrual to any NCTN trial for which the member credits the Network Group Operations Center regardless of which Network Group is leading the trial.

The various categories of NCI/DCTD supported "per case management" funding that should be included in an adult Network Group Operations Center budget for its member

institutions/sites are described below. **Note:** "Special per case management" funding is not part of the Network Group Operations Center budget as it will be provided periodically as administrative supplements for specific trials, if needed, and "High-Performance intervention per case Management" funding is not part of the budget for adult Network Group Operations Centers as their member institutions/sites that qualify for that funding will receive it either via direct grant funding in a Network Lead Academic Participating Site award, CCOP/MB-CCOP award, or via a special initiative program administered by the NCI Cancer Trials Support Unit (CTSU) at NCI/DCTD's direction.

- **Screening Per Case Management Funding:** Funding to cover data management costs for patients enrolled on a trial that require specific screening with informed consent as part of the trial (e.g., investigational molecular test of their tumor) and who do not subsequently undergo the study treatment/intervention and/or randomization because of the screening results.

- **Basic Intervention Per Case Management Funding:** Funding to cover data management costs for enrolled patients who undergo the study treatment/intervention and/or randomization. Basic intervention funding is divided into therapeutic (treatment intervention or pilot studies) or advanced imaging interventions. This base amount is set at the same level for all treatment trials; however, the base amount for advanced imaging trials may be different. This funding category also includes funding for average follow-up per case data management for an NCTN trial (i.e., separate payments for follow-up are not provided). Please note that the basic intervention per case cost includes any screening performed (i.e., per case funding is provided for an enrolled patient for either screening or intervention but not both). Likewise, intervention per case management funding is provided at either the basic level or the high-performance level, but not both – see the information on high-performance intervention per case management funding below.

- **Advanced Imaging Trial Per Case Management Funding:** Funding to cover data management and imaging costs for complex imaging used in advanced imaging trials (above the base intervention per case amount described above) would be provided to all NCTN participating sites by the Network Group Operations Center with a specialty focus in this area that leads these trials (including providing the funding to other Network Group Operations Centers for their members which participate in the trials) as these studies are expected to be limited in number relative to the number of treatment trials. This funding is provided on a trial by trial basis as approved by NCI/DCTD.

- **Biospecimen Collection Per Case Management Funding:** Funding to cover biospecimen collection and any associated management costs for patients enrolled on study who undergo the study treatment/intervention and/or randomization for trials with required or optional biospecimen collections – this category of funding would not be expected to be given in association with screening per case funding except in unusual circumstances. This funding is provided on a trial by trial basis as approved by NCI/DCTD.

- **Quality of Life Per Case Management Funding:** Funding to cover data collection/management costs associated with patient enrollment in quality of life sub-studies incorporated into NCTN treatment or advanced imaging clinical trials is not provided by NCI/DCTD except in special circumstances as described below.

  "Quality of Life Per Case Management" funding is provided by the NCI Division of Cancer Prevention (DCP) through the CCOP/MB-CCOP grants and to other member

institutions/sites of the Network Groups (including the Network Lead Academic Participating Sites) through DCP grants to the Network Groups as CCOP Research Bases. If a Network Group in the NCTN Program (including the Canadian Collaborating Clinical Trials Network) does not have a CCOP Research Base grant from DCP, "quality of life per case management" funding for approved quality of life studies incorporated into NCTN trials, which are led by other Network Groups, can be provided in the grant to the Network Group Operations Center and/or the Canadian Collaboration Clinical Trials Network by NCI/DCTD for participation in these studies by the member institutions/sites of that Network Group which is not a CCOP Research Base.

Note: This exception is provided in order to ensure that approved quality of life studies incorporated into NCTN trials are available to all members of the Network participating in the NCTN trial. However, NCI/DCTD funding cannot be used, under any circumstances, by a Network Group that does not have a CCOP Research Base grant to develop quality of life studies or provide "quality of life per case management" for NCTN trials that it leads as the NCI/NIH peer-review for such research activities is part of the CCOP Research Base grants (i.e., it is not part of the NCI/NIH peer review of the NCTN Program grants). In this situation, a Network Group that does not have a CCOP Research Base grant may wish to collaborate with a Network Group which does have a grant and can conduct the quality of life study.

1.5 Per Case Management Funding - Pediatric Network Group Operations Center Budget (Restricted)

NCI/DCTD funding given to the pediatric Network Group Operations Center for its member institutions/sites which are not CCOPs or MB-CCOPs is provided to these sites through purchase service agreements or subcontracts using a special algorithm for either "Basic intervention per case management" or "High-Performance per case management" funding to a site as well as other funding "per case" categories as described above for adult Network Group Operations Centers. The amounts to be used for budget requests for Type 1 applications are specified in Part 4: Appendices – Section IV for these Guidelines. The "High-Performance per case management" funding is based on a different threshold for patient accrual than that used for adult patient accrual given the smaller pediatric patient population and more limited sources of private funding available for pediatric trials. Guidelines for this threshold as a percentage of all interventional accrual (anticipated therapeutic accrual and ½ of advanced imaging interventional accrual) is provided in the same section.

1.6 Infrastructure Funding for Pediatric Network Group Member Institutions/Sites

The pediatric Network Group Operations Center may also provide additional infrastructure support to "high-performance" pediatric sites based on the overall level of patient accrual at those sites since they are not eligible for the adult Network Academic Participating Site awards which provide this type of support to high-performance sites engaged in NCTN trials that enroll adult cancer patients. Guidelines for this component of the pediatric Network Group Operations Center budget are also provided in Part 4 – Appendices – Section IV of these Guidelines. The pediatric Network Group Operations Center application may also include a specification/algorithm with justification for distributing this infrastructure support over a broader range of sites (i.e., distribute this funding over a wider group of sites and/or at more than 1 set dollar level). This justification can be presented in the Budget Section of the application.

1.7 Consortium Arrangements

Consortium arrangements and all other contractual arrangements, including all mechanisms for providing per case management funding, must be formalized in writing in accordance

with applicable NIH Grants Policy requirements, which are provided on the NIH website at: http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch15.htm. 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.

1.8 Common Budget Outline & Accrual Input by Member Institution/Site for Budget Request

The Network Group Operations Center must submit a Common Budget Outline as described in Part 2 – Section II.A. of these Guidelines. A sample table for the Common Budget Outlines is provided in Part 4 – Appendices - Section IX of these Guidelines. In addition to the Common Budget Outline, the Network Group Operations Center must also submit a breakdown of the accrual it anticipates from each of its member institutions/sites to all NCTN trials over the project period that it used as input to generate its budget request. A suggested format for a table to provide this information is presented in Part 4 – Appendices – Section X of these Guidelines.

2. Research Plan

In the "Research Plan" section of the Network Group Operation Center's application, a Specific Aims page should be provided as well as separate PHS 398 Research Strategy Sections for the 5 sub-sections listed below within the corresponding specified page limits (and the Table of Contents for the Research Plan section of the application should be modified accordingly). The 5 sub-sections listed below consist of an Operations Center Overview and 4 required functional components of an Operations Center (i.e., clinical trial development, member site accrual, operational management, and collaborations and collective management of the NCTN Program).

Table of Contents for the Network Group Operations Center application only

Specific Aims (including Impact Statement) - 1 page

Research Strategy Section for the Network Group Operations Center Application
This section must consist of the sub-sections A-E described below.

A. Operations Center Overview - 12 pages
B. Clinical Trial Development Program - 30 pages
C. Member Site Accrual Program - 12 pages
D. Operational Management - 12 pages
E. Program for Collaborations and Participation in Collective Management - 12 pages

Other sections of the PHS 398 Research Plan (398 application instructions Part I, Section 5.5), such as the sections for Letters of Support (e.g., Letter of Support from the institution or organization sponsoring the Network Groups Operations Center) and Multiple Program Director/Principal Investigator (PD/PI) Leadership Plan, remain unmodified and must be completed following standard instructions.

***2.1 Sub-Section A. Overview of the Operations Center* (up to 12 pages)**

In this sub-section, applicants are expected to provide a general overview of the proposed Operations Center and describe the general features and operations of the Center. Include a diagram illustrating the organizational structure of the proposed Operations Center and outline how the Operations Center would interact with the other key components of the NCTN Program.

***2.2 Sub-section B. Clinical Trial Development Program* (up to 30 pages)**

In this sub-section, applicants are expected to address the following aspects:

Research Directions. Define the overall research directions for the development of clinical trials in specific disease areas and patient populations over a broad range of cancer types. In particular, the applicant team must identify the diseases that the proposed Operations Center will pursue in its research and outline how its particular research objectives will benefit the NCTN Program as a whole. The applicant team should also address how its research strategy will address unmet clinical needs in rare cancers.

Capabilities and Experience. Summarize the capabilities and experience of the applicant team in successfully developing, organizing, and coordinating large-scale, definitive clinical trials as well as experience in leveraging resources from multiple funding sources for the conduct of ancillary studies (e.g., correlative science studies) associated with clinical trials. Outline the most important achievements in these areas over the past 5-6 years.

Promising Directions. Identify the most promising current and future research initiatives and clinical trials as an indication of the potential of the applicant team to contribute to the NCTN Program. It is expected that applicants' emphasis will be placed on studies with potential to change clinical practice and the importance of the overall research strategy being pursued and not on individual disease clinical trial portfolios.

Role of Senior Members of Research Teams. Include information on the current participation of senior members of applicant's research teams in relevant committees (e.g., scientific research committees and administrative committees). Outline the current situation and plans for the involvement of senior members in the mentoring of new/junior investigators in clinical trial research.

NOTE: Information on the applicant's scientific leadership in clinical trial development as well as achievements of its past (over the prior 5 to 6 years) and current clinical trial development program may be summarized in tables. ***Use of template Tables #1, #2, #3, and #4 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.3 Sub-Section C. Member Site Accrual Program (up to 12 pages)

This functional component is critical for the role of the Operations Center. Include in this sub-section a well-defined plan for robust accrual of patients to NCTN clinical trials. In this plan, describe how the Operations Center will work with the member institutions/sites of clinical trials that are or will be affiliated with the applicants. This plan must encompass accrual to clinical trials led by the applicant as well as trials that may be led by other Network Groups. **Emphasis should be placed on overall accrual to the NCTN not on accrual specific to trials led by the Network Group Operations Center.** Summarize the potential of the proposed Operations Center to accrue (via its member institutions/sites) patients to oncology clinical treatment trials and advanced imaging trials in a publicly funded clinical trials system across a broad range of diseases, including rare cancers.

NOTE: In this sub-section, the applicants are expected to highlight the track record of the applicant team and its member sites for accrual over the past 5-6 years with accrual summarized in tables. ***Use of template Tables #5, #6, and #7 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.4 Sub-Section D. Operational Management (up to 12 pages)

In this sub-section, address the organizational structure of the proposed Operations Center, its governance, standard operating procedures, and operational efficiency program. All

these elements are expected to be designed to optimize the applicant's capability to develop, activate, and conduct clinical trials in a timely manner. Specifically, address the following aspects:

Governance & organizational structure of leadership team for the Operations Center. Define the roles and responsibilities of the PD(s)/PI(s), including responsibilities for human subjects in clinical studies. If applicable, outline in this sub-section a rationale and the general benefits of choosing a multiple PD(s)/PI(s) approach. **NOTE:** Applicants designating multiple PD(s)/PI(s) must also complete the dedicated Section 12 of PHS 398 Research Plan "Multiple PD(S)/PI(S) Leadership Plan."

Scope and authority of the applicant's leadership team. Delineate the roles of other key members of the leadership team in terms of scientific, administrative, and/or technical responsibilities, as appropriate, such as the Director of Operations position and the Executive/Advisory Committee. Outline communication plans, processes for making decisions on scientific directions, and procedures for resolving conflicts. Include succession plans for key leadership positions and describe the relationship/rules for institutional membership in the Network Group as well as financial management policies.

Operational efficiency. Describe plans to optimize the operational efficiency in both study development and clinical trial activation, including providing appropriate training programs for protocol chairs, institutional site PD(s)/PI(s), and clinical research associates (CRAs). Indicate how the proposed Center will take advantage of the available, NCI-supported standard tools and services for the conduct of clinical trials (e.g., Clinical Data Management System, Oncology Patient Enrollment System, and Regulatory Support System for the NCTN). Address how the proposed Center will assure the compliance with NCI/NIH and other Federal regulations regarding study monitoring and clinical research (e.g., explain how these aspects are covered by the applicants' policies on Data and Safety Monitoring, Data Sharing, Biospecimen Sharing, and Onsite Auditing).

The applicant should also present a plan and demonstrate its ability to adhere to regulations regarding trial registration in the NCI Clinical Trials Reporting Program and in the U.S. National Library of Medicine (NLM) (www.clinicaltrials.gov) along with results reporting, as applicable. The applicant should also describe its plan to ensure that results from clinical trials will be published in peer-reviewed manuscripts in a timely manner consistent with NCTN Program requirements and demonstrate its potential to do so. The applicant should also describe its plans for and demonstrate its capability to make data and biospecimens from clinical trials accessible to the public for further research or explain why sharing is not possible.

The applicant's key standard operating procedures for the conduct of clinical trials related to the following should be provided in the Resource section of the application:

- Data & Safety Monitoring Board Policy for Phase 3 Trials & Randomized Phase 2 Trials
- Data and Safety Monitoring Plan for Phase 1 and Phase 2 Trials
- Conflict of Interest Policies
- Onsite Auditing Policy and Procedures
- Constitution & By-laws for Institution/Site Membership and Individual Participant/Investigator Membership (including Scientific and Administrative Committee Membership)
- Standard Template for the Informed Consent Document

NOTE: The applicants' capabilities and potential to conduct large-scale operations related to developing, activating, and conducting clinical trials are essential and will be a factor in the application merit evaluation. In this sub-section, the applicants are expected to highlight their most relevant achievements over the past 5-6 years which may be summarized in tables. ***Use of template Tables #8, #9, #10, and #11 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.5 Sub-section E. Program for Collaborations & Participation in Collective Management (up to 12 pages)

In this sub-section, address the following aspects:

- Highlight the current collaborative interactions of the applicant team related to clinical trials and translational research with investigators at other clinical trial organizations as well as other NCI-sponsored programs;
- Define specific plans for future joint activities and potential collaborations between investigators at the proposed Operations Center and investigators at other Network Groups; and
- Outline potential collaborative interactions with other NCI-sponsored investigators and programs (e.g., SPORE awardees, NCI Cancer Centers, R01/P01 investigators);

In addition, address the potential of the applicant team to participate in the collective management of the NCTN and relevant experience in the past 5-6 years:

- Outline expectations of how your team will participate in the collective management of the NCTN;
- Provide specific examples of participation by member investigators of the Network Group Operations Centers in the NCI Scientific Steering Committees (SSC) and associated Task Forces and Working Groups, Planning Committees for SSC Clinical Trials Planning, and NCI Central Institutional Review Board (Central IRB) (including membership of institutional members of the Network Group on the NCI Central IRBs) and/or examples of similar collaborative activities involving other clinical trial networks; and
- Discuss the ability of the team to complete development of study proposals and conduct future clinical trials that may originate outside the Network Group Operations Center if they are approved by the NCI disease-specific SSCs.

2.6 Protection of Human Subjects

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 Network Group Operations Center application must address the inclusion of women and minorities and inclusion of children in its clinical research as required per NIH/NCI Policy. **Information on the targeted/planned enrollment table for minorities and members of both genders (as well as children, if applicable), should be based on accrual summarized across all diseases for the planned project period in the competing new application (Type 1), not on a study or disease-specific basis.**

Information on the policies for inclusion of women and minorities is available at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Information on the policies for inclusion of children is available at:
http://grants.nih.gov/grants/funding/children/children.htm
http://www.nih.gov/grants/guide/notice-files/not98-024.html

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 as described at: http://grants.nih.gov/grants/funding/children/children.htm. For cancer clinical research, Network Group Operations Centers 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 Network Group devoted to pediatric cancer research, 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.

2.7 Resource Sharing Plans

Applicants are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS) as provided in the PHS 398 Application Guide with the following modifications:

- Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and Genome Wide Association Studies (GWAS) are expected in this application.

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan. An example of a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers for the NCTN Program is provided in Part 4 – Appendices – Section VII in these Guidelines.

The Data Sharing Plan and other resource plans (or rationale for not providing sharing certain resources) should be provided in the research application; however, prior to funding of an award, all resource sharing plans/policies will also need to be reviewed and approved by NCI/DCTD program staff prior to funding any award in order to ensure that the plans/policies are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

3. Appendix Material & Post Submission Materials

Information on the Appendix material that should be provided in the Network Group 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 – Section I.D. of these Guidelines.

In addition to the information that can be included in the Appendix material described in that section, copies of up to 3 protocol documents described or referenced in the narrative of Sub-section B (Clinical Trial Development Program) of the research plan for the proposed Network Group Operations Center illustrating the Center's overall research directions may be submitted in the Appendix. The applicant may not submit copies of all protocols being conducted or in development by the applicant in the Appendix.

Information on post submission materials that may be provided for the Network Group Operations Center application is described in Part 2 – Section I.F of these Guidelines.

4. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement for the Network Group Operations Center.

4.1 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.

4.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Network Group Operations Center 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

4.3 Onsite Auditing Activities

The NCI-CTMB Guidelines for 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. In order for the NCI to review the Network Group Operations Center's compliance with this requirement, the Network Group Operations Center should conduct a comprehensive review of its membership and provide **updated** auditing information for all Participating Sites and affiliates to the NCI/DCTD Senior 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 Network Group Operations Center; (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 Part 4 – Appendices – Section II.A.9.

4.4 Provision of Funds to Member Institution/Sites for Per Patient Data Management

If the Network Group Operations Center provides funds to member institutions/sites for accruals (non-Lead Academic Participating Sites and non-CCOP/MB-CCOP institutions) via per-accrual reimbursement mechanisms (e.g., purchased service agreements or subcontracts), the following information must be provided as Just-In-Time information by a scheduled date to be specified by NCI/DCTD:

- For the upcoming budget period: (1) the estimated number of per patient accruals by category (screening, intervention, and biospecimen accruals) by major disease area and within each disease area by trial led by the Network Group Operations Center; (2) the

estimated number of per patient accruals by category (screening, intervention, and biospecimen accruals) by major disease area for trials that will not be led by the Network Group Operations Center; and (3) the estimated total costs (direct and indirect) that the Network Group Operations Center anticipates providing to member institutions/sites, with corresponding NCI institution codes, via this award.

4.5 Data and Safety Monitoring Boards/Plans and Updates

The Network Group Operations Centers should have a Data and Safety and Monitoring Board (Data Monitoring Committee) policy for randomized phase 2 and phase 3 NCTN trials that complies with the "NCI NCTN Program Data and Safety Monitoring Board Policy" as provided in Part 4 – Appendices – Section VIII of these Guidelines. In addition, the Network Group Operations Center must have Data and Safety Monitoring plans for all other Network Group studies (e.g., phase 1 and phase 2 studies, pilot studies, etc.) that comply with the NIH policy for data and safety monitoring, posted on the NIH website at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html, with additional description at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.

These policies/plans should be provided in the research application; however, prior to funding of an award, all Data and Safety Monitoring Board (Data Monitoring Committee) policies/plans (and any updates to these policies/plans) will also need to be reviewed and approved by NCI/DCTD program staff prior to funding of an award to ensure that they are in compliance with NCI/NIH regulations.

C. Network Group Statistics & 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 total cost budget requested by the Network Group Statistics and Data Management Center (SDMC) in its application should be based on an algorithm used to estimate the total cost of developing and conducting NCTN trials by both the SDMC and its associated Network Group Operations Center that leads those trials (i.e., infrastructure costs).

Guidelines for amounts to use in developing the total cost budget request for Type 1 applications are provided in Part 4 – Appendices - Section IV. of these Guidelines. The cost guidelines are presented as ranges for total infrastructure costs for the Network Group Operations Center and its associated Network Group SDMC to conduct NCTN trials led by the Network Group **based on estimated accrual** (with separate estimated ranges related to intervention accrual *versus* non-intervention accrual).

Applicants are not required to use the specific estimated ranges for infrastructure costs provided in these guidelines (i.e., estimated ranges for infrastructure costs may be adjusted by the applicant to fit its particular funding needs). However, total cost Network Group budgets that include infrastructure costs based on estimated ranges that are in significant excess of the estimated ranges provided in these Guidelines for infrastructure costs are unlikely to be supported.

In addition, the Network Group Operations Center must submit a Common Budget Outline as described in Part 2 – Section II.A. of these Guidelines in conjunction with input from its associated Network Group Statistics and Data Management Center. A sample table for the Common Budget Outlines is provided in Part 4 – Appendices - Section IX. of these Guidelines.

The following budget guidelines apply specifically to the Network Group 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." **NOTE:** Specific job descriptions and qualifications for funded personnel (administrative as well as scientific leadership) should be covered in this budget section and not repeated in the research plan narrative.

a) Personnel: A staffing plan for the SDMC, including position descriptions and qualifications should be provided. Precise justification for the amount of effort requested for each position is essential, including but not limited to the following:

- **Statistics:** Time and effort involved in developing statistical designs and analysis plans for associated Network Group Operations Center clinical trials as well as providing statistical analyses, interpretations, and conclusions with regard to study data and supporting required results reporting per federal regulations in www.clinicaltrials.gov as well as publication of those results in peer-review journals.

- **Data Management:** Time and effort involved in the development of case report forms using NCTN–approved common data elements and the NCTN Common Data Management System (CDMS) for trials, central registration and randomization of patients onto clinical trials, collection and monitoring of primary patient data, compliance with relevant data reporting and other regulatory requirements, and conducting and/or supporting quality assurance activities for all NCTN trials the

SDMC supports.

- **Administration:** Time and effort involved in the overall management/ administration of the SDMC.

- **Data and Safety Monitoring Boards (Required Funding in Application as Separate Line Item as Funding is Restricted for this Purpose):** Research costs include the time and effort involved in the overall management/administration by the Network Group SDMC for the Data and Safety Monitoring Board for the Network Group's phase 3 and randomized phase 2 trials.

- **Auditing (Required Funding in Application Restricted for this Purpose):** Personnel and travel costs to support the auditing function of the associated Network Group Operations Center auditing program (as well as those of other Network Group Operations Centers and institutions for NCI approved non-Network Group trials the SDMC supports) should be included as a separate line item as the funding for this activity is restricted.

- **Creation and Coordination of Trial Datasets for Data Sharing (Required Funding in Application Restricted for this Purpose):** Personnel costs to support the creation and coordination of trial data sets for data sharing in a timely manner after the primary results of a clinical trial are published.

- **Coordination with Tumor Banks (Required Funding in Application Restricted for this Purpose):** Personnel costs to support coordination of the activities of the Network Group Statistics and Data Management Center and the associated Network Group Operations Center with the Network Tumor Bank activities (i.e., coordination support for linking biospecimens and clinical data so that there is an accurate inventory of available biospecimens and so requests for "banked biospecimens" for approved studies can be appropriately supported).

b) **Consultant costs:** Reasonable consultant costs are allowed if the consultant is contributing in a substantial way to the SDMC's support for the conduct or development of NCTN trials. Clear and quantifiable justification is required. These costs include travel, per-diem, and consultant fees, if applicable and within institutional policy.

c) **Equipment:** Requests for computer systems or other major equipment must be very carefully documented with supporting justification and cost analysis**.** Justification for equipment costs should include percent of time used for SDMC business as well as necessity for purchase. The amount of funds requested should be based on the percent of usage.

d) **Supplies:** Research costs for appropriate supplies with quantitative justifications based on actual use should be provided.

e) **Travel:** The importance of meetings to the achievements of any NCTN 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:

- Trips by the SDMC's leadership and investigators to the NCI and other national organizations where the results of SDMC supported research must be presented or where SDMC support of research strategies are to be discussed.

- Travel for persons on the SDMC staff who must attend the associated Network Group Operations Center regular meetings.

- Travel for SDMC members to appropriate scientific research and administrative committee meetings meeting held by the associated Network Group Operations Center outside of regular meetings.

- Travel for SDMC leadership to attend NCI/DCTD – Network Group NCTN Leadership Management Committee meetings for the NCTN Program or other NCI/DCTD meetings on special initiatives of the NCTN Program.

f) **Other Expenses:** Research costs due to other expenses include those related to communication and information dissemination with other key components of the NCTN Program as well as with member institutions/sites of the NCTN Program. 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.

g) **Consortium/Contractual Costs***:* If 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 costs of the SDMC. The SDMCs is encouraged to structure its organization in a manner that minimizes the burden of indirect costs on the overall SDMC budget.

2. Research Plan

In the "Research Plan" section of the Network Group Statistics and Data Management Center's application, a Specific Aims page should be provided as well as separate PHS 398 Research Strategy Sections for the 3 sub-sections listed below within the corresponding specified page limits (and the Table of Contents for the Research Plan section of the application should be modified accordingly). The 3 sub-sections listed below consist of a Center Overview and 2 required functional components of a Center - i.e., (1) Statistical Analysis Program & Collaborative Research and Collective Management and (2) Data Management Program.

Table of Contents for Network Group Statistics and Data Management Center application only

Specific Aims (including Impact Statement) - 1 page

Research Strategy Section for the Network Group Statistics and Data Management Center Application – This section must consist of the sub-sections A-C described below.

A. Statistics and Data Management Center Overview - 12 pages
B. Statistical Analysis Program & Collaborative Research/Collective Management - 30 pages
C. Data Management Program - 30 pages

Other sections of the PHS 398 Research Plan (398 application instructions Part I, Section 5.5), such as the sections for Letters of Support (e.g., Letter of Support from the institution or organization supporting the Statistical and Data Management Center, Letter of Support from the associated Network Groups Operations Center PD(s)/PI(s)) and Multiple Program Director/Principal Investigator (PD(s)/PI(s)) Leadership Plan, remain unmodified and must be completed following standard instructions.

2.1 Sub-section A. Statistics and Data Management Center Overview (up to 12 pages)

This sub-section should provide a general overview of the Statistics and Data Management Center (SDMC) and describe the general features and operations of the SDMC**.** The applicant should provide a diagram illustrating the organizational structure of the SDMC in this sub-section, particularly the relationship between the Statistical Analysis Program and the Data Management Program and describe how the SDMC would interact with the other key components of the NCTN Program**.**

The applicant's key standard operating procedures for the conduct of clinical trials related to the following should be provided in the Resource section of the application:

- Procedures for Statistical Analysis (e.g., guidelines for interim monitoring, general procedures for sample size estimation, accrual rate estimation, and choice of testing and estimation procedures)
- Data Management and Monitoring Policies & Procedures for Clinical Trials
- Procedures to Ensure Security and Confidentiality of Patient Data
- Conflict of Interest Policy
- Onsite Auditing Policy and Procedures
- Model Statistical Analysis Template for Clinical Trials
- Sample of Trial Reports (i.e., 3 trials) from the SDMC Report of Studies

2.2 Sub-section B. Statistical Analysis Program & Collaborative Research and Collective Management (up to 30 pages)

Statistical Analysis Program: This functional component should consist of a well-defined organization, approaches, policies, and procedures for statistical analysis of clinical trials in specific disease areas and patient populations. The applicant should describe the organizational structure, governance, and standard operating procedures in order to demonstrate the applicant's capability to design, monitor, and analyze clinical trials in a timely manner. The expertise and experience as well as the scope and authority of the applicant's statistical leadership team, including how the team directs the Data Management Program and how the team interacts with the Director of Operations position for the associated Network Group Operations Center should be described, including succession planning for key leadership positions in the statistical program.

For applications designating multiple PD(s)/PIs(s), a leadership plan related to the multiple PD/PI designation must be included in the appropriate section of the application (i.e., Multiple Program Director(s)/Principal Investigator(s) (PD(s)/PIs(s), Leadership Plan section of the PHS 398). A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team for the SDMC should be described including communication plans, process for making decisions and procedures for resolving conflicts. The roles and administrative, technical, and statistical responsibilities for the SDMC should be delineated for the PD(s)/PIs(s), including responsibilities for protection of information on human subjects in clinical studies. If budget allocation is planned, the distribution of resources to specific components of the SDMC and/or the individual PD(s)/PIs(s) should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote of the Notice of Award.

The applicant should describe the general approach to statistical trial design and analysis plans for multi-institutional clinical trials, including guidelines for interim monitoring and general procedures for sample size estimation and choice of testing and estimation procedures. Examples of robust statistical trial designs and statistical support should be

described as well as how the SDMC provides statistical leadership in design and analysis, including incorporating new, integral and integrated, molecular and imaging biomarkers and laboratory studies into the overall evaluation of NCTN trials. The applicant should also describe how the SDMC ensures that final study analyses are performed in a manner to provide timely publication of study results and results reporting per NCI and federal regulations.

Collaborative Research: The applicant should highlight its current collaborations and future plans for collaborations/initiatives with other clinical trials organization on the statistical design and analysis of clinical trials as well as with other NCI-sponsored programs and investigators on ancillary studies (e.g., translational research, laboratory studies) associated with clinical trials as an indication of the applicant's potential to be a collaborative partner in the NCTN Program. In particular, the applicant should describe the capability of the SDMC to provide statistical design and analysis for non-Network Group trials. While independent statistical research is not required (or funded under this FOA), involvement in research related to the design, conduct, and analysis of cancer clinical trials is considered a strength, and the applicant should therefore describe research being conducted by the SDMC statisticians using Network Group SDMC and Operations Center resources, including their clinical databases.

Collective Management: The applicant should address how it can contribute to the collective management of the NCTN Program through examples of participation in the NCI Scientific Steering Committees (SSC) and associated Task Forces and Working Groups, Planning Committees for SSC Clinical Trials Planning, and NCI CIRB or examples of similar activities in other clinical trial networks as indications of its potential to participate in the collective management of the NCTN. The applicant should also describe how it coordinates with the Tumor Bank(s) associated clinical trials organization to ensure that clinical data is provided in a timely and user-friendly format for public access to data from clinical trials and for studies approved for use of biospecimens as an indication of the applicant's potential to provide these services efficiently for the NCTN Program. In addition, the applicant should describe its track record in and potential to implement initiatives and new standards for clinical trial conduct and data management in a timely fashion.

2.3 Sub-section C. Data Management (up to 30 pages)

This functional component should consist of a well-defined plan for data management of NCTN trials, both trials led by the applicant's associated Network Group Operations Center including approved multi-center phase 2 and phase 3 trials that originate from outside the associated Network Group Operations Center.

The applicant should provide a detailed description of the data management and study monitoring practices of the SDMC, including the flow and review of data following submission from individual institutions/sites and investigators. The applicant should describe the data management systems employed and how the SDMC would use standard NCTN tools including the NCTN Common Data Management System (CDMS) and use of NCTN-approved Common Data Element (CDEs) from the Cancer Data Standards Registry and Repository (ca-DSR), the NCTN Regulatory Support System (RSS), the NCTN Oncology Patient Enrollment Network (OPEN), the NCI/DCTD Clinical Data Update Systems (CDUS/CDS), the NCI Expedited Adverse Event Reporting System (AdEERs), the NCI Common Terminology Criteria for Adverse Events (CTCAE) for data management for NCTN trials, and trial registration in the NCI National Clinical Trials Reporting Program (CTRP) and in the U.S. National Library of Medicine (NLM) (www.clinicaltrials.gov) along with results reporting, as applicable. The applicant should describe how it coordinates with the associated Network

Group Operations Center to ensure that data and biospecimens can be made available to the public for future research.

Descriptions of SDMC training for investigators, Clinical Research Associates, and study chairs related to data management and study monitoring for clinical trials should be provided. The applicant should also describe procedures for study monitoring as well as for data quality control and accuracy verification, including how the SDMC works with the associated Network Group Operations Center on auditing activities. The applicant's method for active trial monitoring, including procedures for accrual and biospecimen collection tracking, assessing case, eligibility and evaluability, ensuring timely medical review and assessment of patient data, monitoring of data timeliness, and facilitating SDMC staff interactions with study chairs should be described. The applicant should describe the SDMC's guidelines for institutions/sites for data timelines, including a summary of data quality and timeliness as an indication of its potential to operate efficiently within the NCTN Program.

The applicant should also describe the facilities and equipment available as well as the information technology (IT) support for central storage, security, analysis and retrieval of clinical data. The applicant should describe how it complies with the Constitution & By-laws of the associated Network Group Operations Center as well as its conflict of interest policy and guidelines for good clinical practice. The applicant should describe how it complies with federal/DHHS/NIH/NCI regulations for clinical research involving human subjects as well as with NCI/NIH administrative requirements for conduct of clinical trials with respect to NCI/DCTD's IP Option and NCI/DCTD's collaborative binding agreements for NCI/DCTD IND studies.

Appropriate summary documentation of the track record of the applicant team with respect to key statistical leadership staffing and timely data management and data collection for clinical trials over the past 5 to 6 years may be presented in summary tables. ***Use of template Tables #1, #2, and #3 as described in Part 4 - Appendices – Section II.B. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.4 Letter of Support from Network Group Operations Center

In addition to general Letters of Support (e.g., Letter of Support from the institution or organization supporting the Statistical and Data Management Center), the SDMC application should also include a Letter of Support from the Network Group Operations Center applicant PD(s)/PI(s) supporting the Network Group SDMC senior leadership (PD(s)/PI(s)).

2.5 Protection of Human Subjects

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 SDMC application must address the inclusion of women and minorities and inclusion of children in its clinical research as required per NIH/NCI Policy. Information on the policies for inclusion of women and minorities is available at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Information on the policies for inclusion of children is available at:

http://grants.nih.gov/grants/funding/children/children.htm
http://www.nih.gov/grants/guide/notice-files/not98-024.html

2.6 Resource Sharing Plans

Applicants are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS) as provided in the PHS 398 Application Guide with the following modifications:

- Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and Genome Wide Association Studies (GWAS) are expected in this application.

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan. An example of a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers for the NCTN Program is provided in Part 4 – Appendices – Section VII in these Guidelines.

The Data Sharing Plan and other resource plans (or rationale for not providing sharing certain resources) should be provided in the research application; however, prior to funding of an award, all resource sharing plans/policies will also need to be reviewed and approved by NCI/DCTD program staff prior to funding any award in order to ensure that the plans/policies are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

3. Appendix Material & Post Submission Materials

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 should be provided is described in Part 2 – Section I.D of these Guidelines.

In addition to the information that can be included in the Appendix material described in that section, copies of up to 3 protocol documents described/referenced in the narrative of Sub-section B - Statistical Analysis Program of the research plan as illustrating the proposed Network Group Statistics and Data Management Center's robust statistical trial designs and statistical analyses may be submitted in the Appendix. The applicant may not submit any other copies of protocols being conducted or in development by the applicant in the Appendix

Information on post submission materials that may be provided for the Network Group SDMC application is described in Part 2 – Section I.F of these Guidelines.

4. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement for the Network Group SDMC.

4.1 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.

4.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Network Group SDMC 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

4.3 Data and Safety and Monitoring Boards/Plans Updates

The Network Group Operations Centers should have a Data and Safety and Monitoring Board (Data Monitoring Committee) policy for randomized phase 2 and phase 3 NCTN trials that complies with the "NCI NCTN Program Data and Safety Monitoring Board Policy" as provided in Part 4 – Appendices – Section VIII of these Guidelines. In addition, the Network Group Operations Center must have Data and Safety Monitoring plans for all other Network Group studies (e.g., phase 1 and phase 2 studies, pilot studies, etc.) that comply with the NIH policy for data and safety monitoring, posted on the NIH website at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html, with additional description at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.

These policies/plans should be provided in the research application; however, prior to funding of an award, all Data and Safety Monitoring Board (Data Monitoring Committee) policies/plans (and any updates to these policies/plans) will also need to be reviewed and approved by NCI/DCTD program staff prior to funding of an award to ensure that they are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

D. Network Group Integrated Translational Science Center Application

Specific instructions are provided on the following pages for the Network Group Integrated Translational Science Center 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 Integrated Translational Science Support Application budget. The categories listed below refer to those contained in the section of the PHS 398/SF424 entitled "Detailed Budget for Initial Budget Period." **The total cost that can be requested for this award is limited to $800,000 per year.**

NOTE: Specific job descriptions and qualifications for funded personnel (administrative as well as scientific leadership) should be covered in this budget section and not repeated in the research plan narrative.

a) Personnel: A staffing plan for the award, including position descriptions and qualifications, should be provided. Precise justification for the amount of effort requested for each position is essential, including the following:

- **Translational Science Support:** Time and effort involved in developing and designing research strategies for incorporating translational science studies into NCTN trials and designing pilot studies to collect preliminary data for further research and analyze the results from those pilot studies. **NOTE:** Any clinical pilot study requiring patient enrollment and clinical data management would be conducted by the associated Network Group Operations Center(s) and Network Group Statistics and Data Management Center(s) and covered in the budgets for those entities; however, assay studies/analysis could be conducted by the recipient of this award.

- **Data Management:** Time and effort involved in the analysis of data associated with any pilot laboratory or assay performance studies conducted to support incorporation of specific translational science studies into NCTN trials.

- **Administration:** Time and effort involved in the overall management of the resources under the Integrated Translational Science Center award, regulatory activities, and quality assurance/monitoring for any pilot laboratory or assay performance studies conducted in support of NCTN trials.

b) Consultant Costs: Reasonable consultant costs are allowed if the consultant is contributing in a substantial way to the development of translational research studies associated with NCTN trials. These costs include travel, per-diem, and consultant fees, if applicable and within institutional policy.

c) Equipment & Supplies: Only those equipment items (including computer hardware and software) and supplies that are required to conduct assays/tests for pilot studies should be included. Requests must be very carefully documented with supporting justification and cost analysis. The amount of funds requested should be based on the percent of usage.

d) Travel: Travel expenses are limited to trips by the Integrated Translational Science Center leadership team to meet with investigators of the associated supporting Network Group Operations Center(s) and Network Group Statistics and Data Management Centers at regular meetings and other trial-specific or scientific committee meetings of these Centers.

e) Other Expenses: Research costs due to other expenses include those related to communication and information dissemination about translational research studies in development or underway. Also included are costs of equipment rental and maintenance (e.g., copiers, telephones, computers), postage, copying and printing, etc., justified quantitatively on the basis of previous experience, where relevant.

f) Consortium/Contractual Costs: If 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 this award. Integrated Translational Science Centers are encouraged to structure their organization in a manner that minimizes the burden of indirect costs on the overall budget.

2. Research Plan

In the "Research Plan" section of the Network Group Integrated Translational Science Center's application, a Specific Aims page should be provided as well as separate PHS 398 Research Strategy Sections for the 3 sub-sections listed below within the corresponding specified page limits (and the Table of Contents for the Research Plan section of the application should be modified accordingly).

Table of Contents for Network Group Integrated Translational Science Center application only

Specific Aims (including Impact Statement) - 1 page

Research Strategy Section for the Integrated Translational Science Center Application
This section must consist of the sub-sections A-C described below.

A. Integrated Translational Science Center Overview - 6 pages
B. Translational Science Program - 12 pages
C. Pilot Studies and Collaborative Projects - 12 pages

Other sections of the PHS 398 Research Plan (398 application instructions Part I, Section 5.5), such as the sections for Letters of Support (e.g., Letter of Support from the institution or organization supporting the Integrated Translational Science Center, Letter of Support from the associated Network Groups Operations Center PD(s)/PI(s)) and Multiple Program Director/Principal Investigator (PD/PI) Leadership Plan, remain unmodified and must be completed following standard instructions.

2.1 Sub-section A. Integrated Translational Science Center Overview (up to 6 pages)

This sub-section of the research plan should provide an overview of the governance and organizational facilities and commitment relevant to the award, and the general translational science research strategy and approach for the award, including the expertise of the senior leadership team. This sub-section should also present information demonstrating the ability and commitment of the investigators to function as a coordinated research team and to work efficiently and expeditiously with the supporting Network Group Operations Center(s) and Network Group Statistics and Data Management Center(s) to integrate translational science into NCTN trials. This sub-section should also describe the institution's conflict of interest policy with respect to this award and the policies and procedures in place for ensuring compliance with all federal/DHHS/NIH/NCI policies and regulations regarding the use of data from clinical trials involving human subjects, including regulations concerning the confidentiality, integrity, and security of patient data.

For applications designating multiple PD(s)/PI(s), a leadership plan related to the multiple PD(s)/PI(s) designation must be included in the appropriate section of the application (i.e.,

Multiple Program Director(s)/Principal Investigator(s) (PD(s)/PI(s))Leadership Plan section of the PHS 398). A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team for the Integrated Translational Research Center should be described including communication plans, process for making decisions and procedures for resolving conflicts. The roles and administrative, technical, and statistical responsibilities for the Integrated Translational Research Center should be delineated for the PD(s)/PI(s), including responsibilities for protection of information on human subjects in clinical studies. If budget allocation is planned, the distribution of resources to specific components of the Integrated Translational Research Center and/or the individual PD(s)/PI(s) should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote of the Notice of Award.

2.2 Sub-Section B. Translational Science Program (up to 12 pages)

This sub-section of the research plan should provide a more detailed description of the specific technical expertise of the leadership team and the proposed strategies and approaches that will be pursued for integrating translational research into the NCTN trials. In particular, this sub-section should describe the disease areas and focus of the translation research to be pursued and how the translational studies will be coordinated with collection of associated clinical data and biospecimens. This sub-section should discuss how the aims of the research program for integrating translational science studies into NCTN trials will maximize the utility of NCTN clinical trial data and biospecimens and how the translational science research program will benefit the research aims of the entire NCTN Program. This sub-section should also describe how the translational science investigators will participate in scientific meetings of the supporting Network Group Operations Center(s) and Network Group Statistics and Data Management Center(s) and other activities of the NCTN Program (e.g., NCI Scientific Steering Committees and associated task forces and working groups, Clinical Trials Planning Meetings) as well as other NIH/NCI translational science programs and initiatives.

2.3 Sub-section C. Pilot Studies and Collaborative Projects (up to 12 pages)

This sub-section of the research plan should provide a description of pilot studies to be performed to enable collection of preliminary data required to effectively incorporate specific translational science studies into late phase, definitive NCTN trials. This sub-section should also describe plans for collaborating with other NCTN Program components as well as other NCI-sponsored programs (e.g., SPOREs, NCI Cancer Centers) to facilitate hand-offs of translational science discoveries and/or early phase clinical trial results into later phase, NCTN trials. This sub-section should detail how institutional resources, especially laboratory resources, and other independently funded resources will be leveraged to support the development of translational research studies to be incorporated into NCTN trials and help support any pilot studies.

2.4 Letter of Support from Network Group Operations Center(s) and Network Group SDMCs

In addition to general Letters of Support (e.g., Letter of Support from the institutions or organizations supporting the Integrated Translations Science Center), the application should also include Letters of Support from the Network Group Operations Center applicant PD(s)/PI(s) and Network Group SDMC(s) supporting the Integrated Translations Science Center senior leadership (PD(s)/PI(s)).

2.5 Protection of Human Subjects

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 Integrated Translational Science Support

application must address the inclusion of women and minorities and inclusion of children in its clinical research as required per NIH/NCI Policy. Information on the policies for inclusion of women and minorities is available at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Information on the policies for inclusion of children is available at:

http://grants.nih.gov/grants/funding/children/children.htm
http://www.nih.gov/grants/guide/notice-files/not98-024.html

2.6 Resource Sharing Plans

Applicants are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS) as provided in the PHS 398 Application Guide with the following modifications:

- Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and Genome Wide Association Studies (GWAS) are expected in this application. Since it is expected that the Network Group Integrated Translational Science Center will follow the Resource Sharing Plans of the associated Network Group Operations Center(s) it works with, the proposed Network Group Integrated Translational Science Center should indicate in its application that it is bound by these plans (i.e., the resource sharing plans that may have been submitted by the associated Network Group Operations Centers which the applicant will work with). An example for a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers for the NCTN Program is provided in Part 4 – Appendices – Section VII in these Guidelines.

The Data Sharing Plan and other resource plans (or rationale for not providing sharing certain resources) should be provided in the research application; however, prior to funding of an award, all resource sharing plans/policies will also need to be reviewed and approved by NCI/DCTD program staff prior to funding any award in order to ensure that the plans/policies are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

3. Appendix Material & Post Submission Materials

Information on the Appendix material that should be provided in the Integrated Translational Science 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 – Section I.D. of these Guidelines. Information on post submission materials that may be provided for the Network Group Operations Center application is described in Part 2 – Section I.F of these Guidelines.

4. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement to the Network Group Integrated Translational Science Center applicants.

4.1 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.

4.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Network Group Integrated Translational Science Center 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

E. Network Lead Academic Participating Site Application

Specific instructions are provided on the following pages for the Network Lead Academic Participating Site application. In general, except where noted below, all applications should conform to the instructions in the PHS 398/SF424.

An application must be submitted by an academic institution/organization defined as a hospital and/or clinic program providing direct medical care to patients that is considered one integral organizational entity under a single financial management system and governance structure. Academic centers for the purposes of this award are distinguished from large medical centers whose primary mission is patient care. In addition to patient care, academic centers have comprehensive medical training programs and have preclinical laboratories that perform basic research.

Hospitals, clinics, military or VA hospitals or treatment facilities, and health care organizations that may provide services in collaboration with the applicant institution in a network, but which are not an integral component of the organization under a single financial management system and governance structure that comprises the applicant institution (i.e., Network Lead Academic Participating Site consisting of an academic center and its essential components), may not be considered part of that institution for the purposes of this award with respect to how the budget request for the application should be estimated, as described in Part 2 - Section II.E.1 in these Guidelines. These other organizations may be considered "affiliates" of the Lead Academic Participating Site and be included in the application under that designation (i.e., "affiliate"), if the Lead Academic Participating Site will provide complete management services for the affiliate site related to enrollment of patients on NCTN trials. Any budget request in the application related to these affiliates should follow the outline provided in the section of the Guidelines referenced above.

Other applicant organizations that are not eligible to apply for the Network Lead Academic Participating Site awards include Community Clinical Oncology Program Groups (CCOPs) and Minority-based Clinical Oncology Program Groups (MB-CCOPs) funded by the NCI Division of Cancer Prevention (DCP).

Applications must come from academic institutions/organizations that meet the eligibility definition of a Lead Academic Participating Site. In addition, however, all prospective formally eligible applicants must be alerted that they will be expected to convincingly demonstrate the potential to accrue at least 55 to 70 patients per year to treatment interventions and/or advanced imaging interventions (excluding pilot studies) on adult cancer clinical trials. Applications that fail to do so would be unlikely to be competitive at the time of peer review.

1. Detailed Budget for the Initial Budget Period

1.1 Estimation of Total Cost Budget Request Based on Potential Accrual to NCTN Trials

The total cost budget that can be requested by the Lead Academic Participating Sites in its application should be based on 2 components: (1) an algorithm used to estimate the cost of the data collection/management and biospecimen collection (i.e., "per case data management" funding associated with enrolling patients on NCTN trials for the academic center and any affiliates for which it provided complete management services related to patient enrollment and (2) an algorithm used to estimate the cost for scientific leadership activities at the academic center for NCTN trials. Guidelines for amounts to use in developing the total cost budget request for Type 1 applications are provided in Part 4-Appendices-Section IV of these Guidelines.

Applicants must use the amounts specified in these Guidelines for the different categories of "per case management" funding for participating sites in preparing their budget. Applicants

are not required to use the specific estimated ranges for infrastructure costs provided in these guidelines (i.e., estimated ranges for infrastructure costs may be adjusted by the applicant to fit its particular funding needs). However, Network Lead Academic Participating Site total cost budgets that include infrastructure costs based on estimated ranges that are in significant excess of the estimated ranges provided in these Guidelines for infrastructure costs are unlikely to be supported.

The various categories of NCI/DCTD supported "per case management" funding that should be included in a Network Lead Academic Participating Site application are described below.

Note: "Special per case management" funding is not part of the Lead Academic Participating Site application budget as it will be provided periodically as administrative supplements for specific trials, if needed. "High performance" per case funding is provided for the academic center only (not affiliates). Affiliates may be eligible for administrative supplements on an annual basis if they are selected as a high performing site based on accrual and data quality for a particular year (see Part 1 – Section III.D.2. of these Guidelines).

- **Screening Per Case Management Funding:** Funding to cover data management costs for patients enrolled on a trial that require specific screening with informed consent as part of the trial (e.g., investigational molecular test of their tumor) and who do not subsequently undergo the study treatment/intervention and/or randomization because of the screening results.

- **Basic Intervention Per Case Management Funding:** Funding to cover data management costs for enrolled patients who undergo the study treatment/intervention and/or randomization. Basic intervention funding is divided into therapeutic (treatment intervention or pilot studies) or advanced imaging interventions. This base amount is set at the same level for all treatment trials; however, the base amount for advanced imaging trials may be different. This funding category also includes funding for average follow-up per case data management for an NCTN trial (i.e., separate payments for follow-up are not provided). Please note that the basic intervention per case cost includes any screening performed (i.e., per case funding is provided for an enrolled patient for either screening or intervention but not both). Likewise, intervention per case management funding is provided at either the basic level or the high-performance level, but not both – see the information on high-performance intervention per case management funding below. Basic interventional per case management would be provided for affiliates included in the Network Lead Academic Participating Site application because the academic center provides all management services for affiliate enrollment of patients to NCTN trials.

- **Advanced Imaging Trial Per Case Management Funding:** Funding to cover data management and imaging costs for complex imaging used in advanced imaging trials (above the base intervention per case amount described above) would be provided to all NCTN participating sites by the Network Group Operations Center with a specialty focus in this area that leads these trials (including providing the funding to other Network Group Operations Centers for their members which participate in the trials) as these studies are expected to be limited in number relative to the number of treatment trials. This funding is provided on a trial by trial basis as approved by NCI/DCTD.

- **Biospecimen Collection Per Case Management Funding:** Funding to cover biospecimen collection and any associated management costs for patients enrolled on study who undergo the study treatment/intervention and/or randomization for trials with required

or optional biospecimen collections – this category of funding would not be expected to be given in association with screening per case funding except in unusual circumstances. This funding is provided on a trial by trial basis as approved by NCI/DCTD.

- **High-Performance Intervention Per Case Management Funding for Lead Academic Participating Sites:** Funding to cover additional data management costs/workload and follow-up at institutions (with acceptable audit standings) that enroll a large number of patients. It is anticipated that this funding will be provided to Lead Academic Participating Sites for accrual at the main academic center if the threshold accrual level for Lead Academic Participating Site awardees is sustained, and it covers all follow-up data management costs for these patients. "High-Performance" per case funding for affiliates that are included in a Lead Academic Participating Site grant award (i.e., if complete management services for the affiliates is provided by the Lead Academic Participating Sites) may be possible, pending funds availability based on whether the affiliates meet special threshold accrual levels for this category of sites set by NCI/DCTD each year.

Total costs for scientific leadership and coordination activities at the academic center (i.e., personnel, consultants, supplies, equipment, travel, and consortium/contractual costs) should be based on a percentage of the total costs related to the estimated "intervention per case management" funding plus a percentage of the total costs related to the estimated "intervention per case management" funding for all patients enrolled to NCTN trials each year at the academic center and affiliates. See Part 4 – Appendices – Section IV for guidelines on the percentage to be used in the Type 1 application. Network Lead Academic Participating Site budgets in significant excess of these guidelines are unlikely to be supported.

The total amount of funding (i.e., the total cost budget request based on the algorithms for "per case management" funding and scientific leadership and coordination for the Network Lead Academic Participating Site application) should then be distributed to cover the "level of effort" required to provide management services for patient enrollment on NCTN trials in the categories listed below at the academic center and affiliates for which it provides complete management services. If patients are accrued to study interventions in excess of the "per case management" funding categories used to estimate the total cost budget for the academic center, the center should submit an administrative supplement to cover the additional patients accrued at the academic center and affiliates based on the "per case management" funding categories for those patients.

1.2 Budget Categories for Funding "Level of Effort" Total Cost Budget Request

Once the Lead Academic Participating Site applicant has determined the amount of its total cost budget request using the guidelines specified above, the applicant should provide a "level of effort" budget based on the budget categories allowed for the application as described below.

a) **Personnel:** A staffing plan for the Lead Academic Participating Site, including position descriptions and qualifications should be provided. NOTE: Specific job descriptions and qualifications for funded personnel (administrative as well as scientific leadership) should be covered in this budget section and not repeated in the research plan narrative. Precise justification for the amount of effort requested for each is essential, including the following:

- **Investigator Efforts:** Research costs include the time and effort involved in developing the research repertoire of NCTN trials to be activated at the Lead

Academic Participating Site (and affiliates if the Lead Academic Participating Site provides complete management services for the affiliates related to enrollment of patients on NCTN trials) and in preparing the results of the academic site's research contribution to NCTN trials for publication. Research costs 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 at the academic site and affiliates.

NOTE: Funding for positions within the senior leadership of a Network Group Operations Center (i.e., Executive Committee positions, Scientific and Administrative Committee Chair/Co-Chair positions, Study Chair positions) should be funded by the Network Group Operations Center via its grant to its senior leadership team). The same is true for positions investigators at the academic site hold in other key components of the NCTN Program – i.e., funding for those senior leadership positions should be funded via the key component's grant.

- **Data management:** Research costs include the time and effort involved in accurate data collection and submission at the by the Lead Academic Participating Site.

- **Scientific Services:** Research costs include the time and effort related to providing specific services such as pathology and radiology at the Lead Academic Participating Site.

- **Administration:** Research costs include the time and effort involved in coordinating NCTN related research activities at the Lead Academic Participating Site including regulatory activities, implementation of quality assurance and study monitoring procedures and participation in Network Groups' onsite audit programs. If a Lead Academic Participating Site provides complete management services for affiliates, its budget should include the resources required to assure proper monitoring of the affiliates.

b) **Consultant Costs:** Consultant costs are not usually appropriate in this award, so requests should be justified in detail. These costs include travel, per-diem, and consultant fees, if applicable and within institutional policy.

c) **Supplies, Equipment, and Other Costs:** Research costs for appropriate supplies, with quantitative justifications based on actual use, should be provided. Significant equipment costs are unusual in this award, and such costs must be justified in detail. 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 various Network Groups' offices, 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).

d) **Travel:** Travel for a reasonable number of the institution's participating investigators, data managers, and nurses to attend the regular meetings of the various Network Groups should be included in the Lead Academic Participating Site's budget. Attendance of investigators at meetings on behalf of the Network

Groups, or at special (i.e., non-routine) meetings of committees of the various Network Groups, should generally be funded through the respective Network Group Operations Center or Network Group Statistics and Data Management Center, rather than through this award.

e) **Patient care costs:** NCI will not support costs associated with routine patient care. Only in the most unusual circumstances would a Network Group clinical trial require interventions beyond those considered appropriate for the care of cancer patients. In those circumstances, a Network Group may make a case for reimbursement of patient care costs associated with the particular research element as an administrative supplement. The justification should be presented at the level of the Network Group Chair(s) to the Lead NCTN Program Director with a specific request from the PD(s)/PI(s) and grantee institution of each applicable Network Group Operations Center based upon likely accrual to the specific study. This request would need to be approved/funded by NCI/DCTD for the specific trial prior to activation of the study. In the case such funding was approved by NCI for a specific NCTN trial, it would be expected that the Network Group Operations Centers would provide this funding as per case "special intervention" management funding to their respective member institutions/sites that enrolled patients on the trial and credited the Network Group Operations Center with the accrual. Alternatively, the NCI/DCTD could decide to provide such funding directly to Lead Academic Participating Sites enrolling patients on the trial via an administrative supplement if it was expected that enrollment to the trial would be concentrated primarily at these sites. NCT/DCTD would specify, at the time such funding was approved, how the funding would be provided to the Lead Academic Participating Sites.

Rationale for patient care cost policy: This policy is based on the observation that Network Group NCTN trials always involve treatment or imaging 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.

f) **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.

g) **Consortium/ Contractual Arrangements:** Consortium arrangements and all other contractual arrangements, including mechanisms for reimbursement for administration management/data management for patient accrual, must be formalized in writing in accordance with applicable NIH Grants Policy requirements available at: http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch15.htm. 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 NCI, NIH, DHHS, and 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.

1.3 Rationale for Budget Policy

Lead Academic Participating Sites considered "high performance" sites and receive a higher rate for per case data management funding because of the institutional burden of the large number of patients accrued and the efforts of the academic center's investigators in the scientific development of trials across the NCTN. Thus, the academic site performs two

primary activities - it contributes scientific expertise to the Network Groups and it accrues patients to NCTN trials. The Lead Academic Participating site should request those costs required for scientific/administrative contributions to NCTN activities and for attendance of a reasonable number of investigators at the Network Group meetings to which the site belongs. The budget of a typical Lead Academic Participating Site application should be largely devoted to personnel, reflecting investigator support and the costs associated with data management for patient enrollment and monitoring on NCTN trials at the site (and its affiliates, if appropriate). Data management support and other costs related specifically to the costs of follow-up of previously accrued patients should not be requested in this application. Instead, these costs are covered by the "high performance" per case data management rate the site receives for all patients enrolled on study interventions in NCTN trials.

1.4 Accrual Input by Academic Participating Site for Budget Request

The Network Lead Academic Participating Site must also submit a breakdown of the anticipated accrual from each of its integral components (as well as any affiliates for which it provides complete management services that are included in the application) over the planned project period that was used to generate the budget request. A suggested format for a table to provide this information is presented in Part 4 – Appendices – Section X of these Guidelines.

2. Research Plan

In the "Research Plan" section of the Network Lead Academic Participating Site application, a Specific Aims page should be provided as well as separate PHS 398 Research Strategy Sections for the 3 sub-sections listed below within the corresponding specified page limits (and the Table of Contents for the Research Plan section of the application should be modified accordingly). The 3 sub-sections listed below consist of an Overview and 2 required functional components of a Network Lead Academic Participating Site - i.e., (1) Clinical Trial Program and the (2) Site Accrual Program - related to clinical treatment trials and advanced imaging trials for **adult** cancer patients only:

Table of Contents for Network Lead Academic Participating Site application only

Specific Aims (including Impact Statement) - 1 page

Research Strategy Section for the Network Lead Academic Participating Site Application:
This section must consist of the sub-sections A-C described below.

A. Lead Academic Participating Site Overview - 6 pages
B. Clinical Trial Program - 12 pages
C. Site Accrual Program - 12 pages

Other sections of the PHS 398 Research Plan (398 application instructions Part I, Section 5.5), such as the sections for Letters of Support (e.g., Letter of Support from the institution or organization supporting the Network Lead Academic Participating Site, Letters of Support from the associated Network Groups Operations Center PD(s)/PI(s)) and Multiple Program Director/Principal Investigator (PD/PI) Leadership Plan, remain unmodified and must be completed following standard instructions.

2.1 Sub-section A. Lead Academic Participating Site Overview (up to 6 pages)

This sub-section of the research plan should provide an overview of the governance and organizational facilities and commitment relevant to the award, and the general expertise of the senior leadership team. This sub-section should also present information demonstrating the ability and commitment of the investigators at the institution to function as a

coordinated research team and to work efficiently and expeditiously with the supporting Network Group Operations Center(s) and Network Group Statistics and Data Management Center(s) to enhance the research goals of the NCTN Program and to enroll NCTN trials across the Network. This sub-section should also describe the institution's conflict of interest policy with respect to this award and the policies and procedures in place for ensuring compliance with all federal/DHHS/NIH/NCI policies and regulations regarding the use of data from clinical trials involving human subjects, including regulations concerning the confidentiality, integrity, and security of patient data.

For applications designating multiple PD(s)/PI(s), a leadership plan related to the multiple PD(s)/PI(s) designation must be included in the appropriate section of the application (i.e., Multiple Director(s)/Principal Investigator(s) (PD(s)/PI(s)) Leadership Plan section of the PHS 398). A rationale for choosing a multiple PD(s)/PI(s) approach should be described. The governance and organizational structure of the leadership team for the Operations Center should be described including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the Lead Academic Participating Site should be delineated for the PD(s)/PI(s), including responsibilities for human subjects in clinical studies. If budget allocation is planned, the distribution of resources to specific components of the Lead Academic Participating Site and/or the individual PD(s)/PI(s) should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote of the Notice of Award.

2.2 Sub-section B. Clinical Trial Program (up to 12 pages)

This functional component should consist of a well-defined plan by the applicant for its participation in scientific leadership for NCTN trials across the Network as well as for coordination activities at the main academic institution/site regarding participation in the NCTN Program, including the use of the NCI Central Institutional Review Board and other NCTN Program initiatives and activities.

This sub-section should concisely describe the academic centers scientific leadership in development of NCTN clinical trials and in the scientific activities of the NCTN, including activities with all the Network Groups to which the academic center belongs as well as activities related to NCI initiatives for the NCTN Program such as participating as members on the NCI CIRB and the NCI Scientific Steering Committees. This sub-section should also describe how institutional activities related to the NCTN across various disciplines and departments at the institution are coordinated and how activities and responsibilities will be carried out among the multiple PD(s)/PI(s), if applicable. The academic center should address how it would select NCTN clinical trials to activate at the center and how it would mesh clinical research activities at the center with that of the NCTN Program. In particular, application should clearly describe how funding associated with patient enrollment and clinical data collection and management will be distributed to the various disciplines and clinical departments involved in the conduct of NCTN trials at the center.

The academic center should highlight in this narrative section its most important achievements over prior project period in activities that show its potential for achievement in the NCTN (these achievements can include those from the former NCI Clinical Trials Cooperative Group Program or an equivalent non-profit clinical trial network organization). In addition, the academic center should also describe how it mentors junior investigators in clinical trial research.

The academic center's senior leadership team, including representation of its investigators on executive/advisory committees as well as on scientific and administrative committees for

clinical trial network organizations (either committees from the former NCI Clinical Trials Cooperative Group Program or an equivalent non-profit clinical trial network organization) as well as the clinical productivity of the academic center should be summarized in tables. ***Use of template Tables #1, #2, #3, and #4 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.3 Sub-section C. Site Accrual Program (up to 12 pages)

This sub-section should consist of a well-defined plan for robust accrual to NCTN trials across the Network, including accrual to rare cancers, by the applicant's academic institution/site and any affiliate site(s) for which it will provide complete management services for patients enrolled on NCTN trials.

This sub-section of the research plan should describe both the accrual potential of the academic institution/site and the operational efficiency of trial activation and conduct by the academic center (including the timeliness of data submission and auditing results as well as how quickly it activates clinical treatment trials). This information can be provided from participation in the former NCI Clinical Trials Cooperative Group Program or an equivalent non-profit clinical trials network organization).

Use of template Tables #5, #6, #7, and #8 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.

2.4 Letters of Support from Network Group Operations Centers

The Lead Academic Participating Site application should also include letters of support from potential Network Group Operation Center applicants to which the academic center belongs. These letters of support should be for investigators at the academic center that are members of the Network Group scientific research committees and/or senior leadership that will also be part of the senior leadership team at the Lead Academic Site (or a PD/PI on the application if the institution employs the multiple PD/PI option for the grant application).

2.5 Protection of Human Subjects

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. **Information on the targeted/planned enrollment table for minorities and members of both genders (as well as children, if applicable), should be based on accrual summarized across all diseases for the planned project period in the competing new application (Type 1), not on a study or disease-specific basis.**

The Network Lead Academic Participating Site application must address the inclusion of women and minorities and inclusion of children in the clinical research it participates in as required per NIH/NCI Policy. Information on the policies for inclusion of women and minorities is available at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Information on the policies for inclusion of children is available at:

http://grants.nih.gov/grants/funding/children/children.htm
http://www.nih.gov/grants/guide/notice-files/not98-024.html

2.6 Resource Sharing Plans

Applicants are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS) as provided in the PHS 398 Application Guide with the following modifications:

- Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and Genome Wide Association Studies (GWAS) are expected in this application. Since it is expected that the Network Lead Academic Participating Site will follow the Resource Sharing Plans of the associated Network Group Operations Center(s) it works with, the proposed Network Lead Academic Participating Site should indicate in its application that it is bound by these plans (i.e., the resource sharing plans that may have been submitted by the associated Network Group Operations Centers of which the applicant is a member). An example for a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers for the NCTN Program is provided in Part 4 – Appendices – Section VII in these Guidelines.

The Data Sharing Plan and other resource plans (or rationale for not providing sharing certain resources) should be provided in the research application; however, prior to funding of an award, all resource sharing plans/policies will also need to be reviewed and approved by NCI/DCTD program staff prior to funding any award in order to ensure that the plans/policies are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

3. Appendix Material & Post Submission Materials

Information on the Appendix material that should be provided in the Network Lead Academic Participating Site 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 – Section I.D. of these Guidelines. Information on post submission materials that may be provided for the Network Lead Academic Participating Site application is described in Part 2 – Section I.F of these Guidelines.

4. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement for the Network Lead Academic Participating Site.

4.1 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.

4.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Network Lead Academic Participating Site 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

5. Applications for New Network Lead Academic Participating Sites

It is anticipated that new applications for the Network Lead Academic Participating Site award may be accepted for 3 years of funding after the first 2 years of the NCTN Program's initial 5-year funding period has been completed. This time point and award project period would be selected for additional new Network Lead Academic Participating Site applications so that the award funding would be synchronized with the next potential funding cycle for all Lead Academic Participating Site grants (i.e., so that all the Lead Academic Participating Sites would come in for potential competitive renewal at the same time at the next 5-year funding cycle). The schedule for submission and review of those applications would be specified in an anticipated future Funding Opportunity Announcement (FOA).

F. Network Radiotherapy & Imaging Core Services Centers Application

Specific instructions are provided on the following pages for the Network Radiotherapy and Imaging Core Services Centers 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 Network Radiotherapy and Imaging Core Services Centers budget. **A separate budget should be prepared for the 2 core services centers (i.e., Radiotherapy Core and Imaging Core), including coordination activities, as this award will be made with restricted budget allocations for each core.** The categories listed below refer to those contained in the section of the PHS 398/SF424 entitled "Detailed Budget for Initial Budget Period." **NOTE:** Specific job descriptions and qualifications for funded personnel (administrative as well as scientific leadership) should be covered in this budget section and not repeated in the research plan narrative.

a) Personnel: A staffing plan for the award, including position descriptions and qualifications, should be provided. Precise justification for the amount of effort requested for each position is essential, including the following:

- **Scientific/Technical Support:** Time and effort involved in providing scientific and technical expertise in radiotherapy, advanced medical imaging (e.g., PET, MRI), and information technology (IT) in support of quality assurance and image data management core services for NCTN trials, including appropriate study monitoring for applicable NCTN trials, and in assisting Network Groups (i.e., Network Group Operations Centers and associated Network Group Statistics and Data Management Centers) as well as other NCI-sponsored investigators and programs involved in collaborations (including the NCI/DCTD early phase clinical trials program) in hypothesis formulation and trial design.

- **Data Management:** Time and effort involved in the central collection, computerization, and analysis of primary patient data associated with radiotherapy and imaging quality assurance and credentialing needed for appropriate/applicable NCTN clinical trials.

- **Administration:** Time and effort involved in the overall management of the Network Radiotherapy and Imaging Core Services Centers' resources, including regulatory compliance, quality assurance, and IT.

b) Consultant Costs: Reasonable consultant costs are allowed if the consultant is contributing in a substantial way to quality assurance, credentialing, and image data management core services support needed by NCTN trials. Clear and quantifiable justification is required. These costs include travel, per-diem, and consultant fees, if applicable and within institutional policy.

c) Equipment: Only those equipment items (including computer systems) that are required to support NCTN trials and/or collaborations should be included. Requests must be carefully documented with supporting justification and cost analysis and the amount of the funds requested should be based on the percent of use.

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

e) **Travel:** The importance of meetings to the coordination of the Network Radiotherapy and Imaging Core Services Centers for NCTN trials 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:

- Trips by the Core Services Center's leadership and investigators to the Network Groups' regular meetings and other trial-specific or scientific research planning meetings held by the Network Groups in order to coordinate radiotherapy and imaging services for applicable trials and to discuss the development of new trial proposals that may need support from the Core Services Centers.

- Travel for staff of the Imaging Core Service Center and the Radiotherapy Core Service Center to meet to coordinate activities and services between the 2 Cores, if needed (i.e., various staff are located at different geographic locations).

- Travel for Core Services Centers' leadership to attend NCI/DCTD – Network Group NCTN Leadership Management Committee meetings for the NCTN Program as well as to other meetings on initiatives for the NCTN Program.

f) **Other Expenses:** Research costs due to other expenses include those related to communication and information dissemination with other components of the NCTN Program. 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.

g) **Consortium/Contractual costs:** If 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 Network Radiotherapy and Imaging Core Services Centers. The Centers are encouraged to structure their organization in a manner that minimizes the burden of indirect costs on the overall Centers' budget.

2. Research Plan

In the "Research Plan" section of the Network Radiotherapy and Imaging Core Services Centers application, a Specific Aims page should be provided as well as separate PHS 398 Research Strategy Sections for the 4 sub-sections listed below within the corresponding specified page limits (and the Table of Contents for the Research Plan section of the application should be modified accordingly). The 4 sub-sections listed below consist of a Center Overview and 3 required functional components of a Center - i.e., (1) Radiotherapy Core Services Center Program, (2) Imaging Core Services Center Program, and (3) Program for Collaborations and Participation in Collective Management.

Table of Contents for Network Radiotherapy and Imaging Core Services Centers application only

Specific Aims (including Impact Statement) - 1 page

Research Strategy Section for the Network Radiotherapy and Imaging Core Services Centers Application – This section must consist of the sub-sections A-D described below.

A. Network Radiotherapy and Imaging Core Services Centers Overview **-** 12 pages
B. Radiotherapy Core Services Center Program - 12 pages
C. Imaging Core Services Center Program - 12 pages
D. Program for Collaborations and Participation in Collective Management – 12 pages

Other sections of the PHS 398 Research Plan (398 application instructions Part I, Section 5.5), such as the sections for Letters of Support (e.g., Letter of Support from the institution or organization supporting the Network Radiotherapy and Imaging Core Services Centers, and Multiple Program Director/Principal Investigator (PD/PI) Leadership Plan, remain unmodified and must be completed following standard instructions.

2.1 Sub-section A. Network Radiotherapy and Imaging Core Services Centers Overview (up to 12 pages)

This sub-section of the research plan should give an overview of the scientific and technical expertise provided by the Core Service Centers' staff for radiotherapy and imaging, including its senior leadership team. A brief overview of the facilities of the Cores should be presented. This sub-section of the research plan should also give a detailed description of the organizational structure and governance policy for the core centers for radiotherapy and imaging, especially if multiple PD(s)/PI(s) are involved. This sub-section should describe how the Cores will interact with various Network Group Operations Centers and associated SDMCs and the Cores' plan for how to have these organizations represented on the senior leadership team to enhance coordination of services for all NCTN trials.

For applications designating multiple PD(s)/PI(s), a leadership plan related to the multiple PD/PI designation must be included in the appropriate section of the application (i.e., Multiple Program Director/Principal Investigator (PD/PI) Leadership Plan section of the PHS 398). A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team for the Core Services Centers should be described including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the Core Services Centers should be delineated for the PD(s)/PI(s), including responsibilities for human subjects in clinical studies. If budget allocation is planned, the distribution of resources to specific components of the Core Services Centers and/or the individual PD(s)/PI(s) should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote of the Notice of Award.

This sub-section should also describe how the Cores will prioritize services for NCTN trials as well as how they will ensure that their input is incorporated so as to ensure operational efficiency in study development and completion of studies as well as how the applicant will comply with NCI/NIH and other federal regulations regarding study monitoring and clinical research (e.g., human subjects protection especially with respect to the confidentiality of patient data and coordination with the Network Groups to provide data for their onsite auditing programs) should be addressed in this sub-section.

In addition, the application should describe how the activities of the radiotherapy core will be coordinated with the imaging core, especially with respect to IT services and image management. This sub-section should also describe key collaborations between the 2 Cores as well as between Cores and the Network Groups, especially with respect to development of standards and harmonization of processes and data collection.

The applicant's key standard operating procedures for the conduct of clinical trials related to the following should be provided in the Resource section of the application:

- Key Standard Operating Procedures for Radiotherapy and Imaging Quality Assurance, Image Data Management, and Credentialing
- Procedures to Ensure Security and Confidentiality of Patient Data
- Conflict of Interest Policy

2.2 Sub-section B. Radiotherapy Core Services Center (up to 12 pages)

This sub-section should consist of a well-defined plan outlining the general approaches to be used and the specific services that will be provided by the radiotherapy core for NCTN trials, including the policies and procedures for the types of quality assurance & credentialing provided by the core. A detailed description of the special facilities and equipment used by the core should also be provided. Key accomplishments related to services provided for clinical trials should be highlighted in this sub-section.

NOTE: Narrative information may be supplemented by an optional table that details the applicant's track record in providing specific clinical trials with core services. Appropriate summary documentation of the applicant team's track record over the past 5 to 6 years may be summarized in tables. ***Use of template Table #1 as described in Part 4 - Appendices – Section II.D. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.3 Sub-Section C. Imaging Core Services Center (up to 12 pages)

This sub-section should consist of a well-defined plan outlining the general approaches to be used and the specific services that will be provided by the imaging core for NCTN trials, including the policies and procedures for the types of quality assurance, credentialing, and imaging data management provided by the core. In the description, include plans for participation in the development of NEMA DICOM-RT standards (http://medical.nema.org/) and in support of trials which merge imaging from different platforms such as FDG PET, CT, MRI, and other platforms. Also, provide a detailed description of the special facilities and equipment used by the Core team and highlight key accomplishments related to the services provided for clinical trials.

NOTE: Narrative information may be supplemented by an optional table that details the applicant's track record in providing specific clinical trials with core services. Appropriate summary documentation of the applicant team's track record over the past 5 to 6 years may be summarized in tables. ***Use of template Table #2 as described in Part 4 - Appendices – Section II.D. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.4 Sub-section D. Program for Collaborations and Participation in Collective Management (up to 12 pages)

This sub-section should consist of a well-defined plan for key collaborations between the 2 Cores, especially with respect to development of standards and harmonization of processes and data collection. The Cores should also describe how they plan to work with Network Group Operations Centers and associated Statistics and Data Management Centers with respect to development of standards and harmonization of processes and data collection for NCTN trials. This description should also explain the following aspects:

- The applicant's capacity for interoperability with the common data management system (CDMS) of the NCTN Program to collect clinical trial data and link information to clinical data collected by other key components of the NCTN Program (i.e., Network Group Operations Centers and associated Network Group Statistics and Data Management Centers, and

- The applicant's ability and plans to work with the NCTN Program tools and services employed for regulatory support and patients enrollment (i.e., the Regulatory

Support System (RSS) and the Oncology Patient Enrollment Network (OPEN) for all NCTN clinical trials.

The Network Radiotherapy & Imaging Core Services Centers applicant should also describe its capacity to provide core services to NCTN trials that result from collaborations between the Network Groups and other NCI-supported programs and investigators. The Network Radiotherapy & Imaging Core Services Centers applicant should also be able to describe plans for collaborations with other NCI-sponsored programs and investigators (e.g., SPOREs, Cancer Centers, R01/P01 investigators, NCI/DCTD early phase clinical trials programs) to augment and enhance the core services provided by the Centers for NCTN trials as well as how to collaborate with other organizations providing these types of services to enhance services and provide best practices and/or standards for selected assessments of radiotherapy and advanced imaging techniques.

In addition, the Network Radiotherapy & Imaging Core Services Centers applicant should describe its plans for participation in the collective management of the Network including participation in appropriate NCTN Program activities and initiatives.

2.5 Protection of Human Subjects

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 Network Radiotherapy and Imaging Core Services application must address the inclusion of women and minorities and inclusion of children in its clinical research program support, if appropriate, as required per NIH/NCI Policy. Information on the policies for inclusion of women and minorities is available at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Information on the policies for inclusion of children is available at:

http://grants.nih.gov/grants/funding/children/children.htm
http://www.nih.gov/grants/guide/notice-files/not98-024.html

2.6 Resource Sharing Plans

Applicants are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS) as provided in the PHS 398 Application Guide with the following modifications:

- Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and Genome Wide Association Studies (GWAS) are expected in this application. Since it is expected that the Network Radiotherapy and Imaging Core Services Centers will follow the Resource Sharing Plans of the associated Network Group Operations Center(s) it works with, the proposed Radiotherapy and Imaging Core Services Centers should submit a Resource Sharing Plan in its application that indicates that it understands and is bound by these plans. An example for a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers for the NCTN Program is provided in Part 4 – Appendices – Section VII in these Guidelines.

The Data Sharing Plan and other resource plans (or rationale for not providing sharing certain resources) should be provided in the research application; however, prior to funding of an award, all resource sharing plans/policies will also need to be reviewed and approved by NCI/DCTD program staff prior to funding any award in order to ensure that the

plans/policies are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

3. Appendix Material & Post Submission Materials

Information on the Appendix material that should be provided in the Network Radiotherapy & Imaging Core Services Centers 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 – Section I.D. of these Guidelines. Information on post submission materials that may be provided for the Network Radiotherapy & Imaging Core Services Centers application is described in Part 2 – Section I.F of these Guidelines.

4. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement for the Network Radiotherapy & Imaging Core Services Centers award.

4.1 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.

4.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Network Radiotherapy and Imaging Core Services Centers 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

G. Canadian Collaborating Clinical Trials Network Application

The budget and research plan for this component are essentially the same as for the Network Group Operations Center and associated Statistics and Data Management Centers s (Operations Center and SDMC) although the volume of clinical trials, accrual, and collaborations would be expected to be more limited. In addition, the Canadian partner would be expected to establish relationships with U.S. Network Group Operations Centers to provide appropriate regulatory oversight for U.S. Networks trials conducted in Canada when needed and this budget component should be explained and justified in the application budget.

1. Detailed Budget for the Initial Budget Period

Applicants for the Canadian Collaborating Clinical Trials Network should prepare their budgets following the budget section for the Network Group Operations Center provided in Part 2 – Section II.B.1. of these Guidelines and the budget section for the Network Group Statistics and Data Management Center provided in Part 2 – Section II.C.1. of these Guidelines, with appropriate adjustments.

2. Research Plan

In the "Research Plan" section of the Canadian Collaborating Clinical Trials Network 's application, a Specific Aims page should be provided as well as separate PHS 398 Research Strategy Sections for the 5 sub-sections listed below within the corresponding specified page limits (and the Table of Contents for the Research Plan section of the application should be modified accordingly). The 5 sub-sections listed below consist of an Operations Center Overview and 4 required functional components of an Operations Center & SDMC - i.e., (1) Clinical Trial Development & Member Site Accrual Program, (2) Operational Management, (3) Statistics Analysis Program and Data Management, and (4) Program for Collaborations and Participation in Collective Management).

Table of Contents for the Network Group Operations Center application only

Specific Aims (including Impact Statement) - 1 page

Research Strategy Section for the Canadian Collaborating Clinical Trials Network Application
This section must consist of the sub-sections A-E described below.

A. Operations, Statistics, and Data Management Center Overview - 6 pages
B. Clinical Trial Development & Member Site Accrual Program- 12 pages
C. Operational Management – 12 pages
D. Statistics Analysis Program and Data Management - 12 pages
E. Program for Collaborations and Participation in Collective Management - 12 pages

Other sections of the PHS 398 Research Plan (398 application instructions Part I, Section 5.5), such as the sections for Letters of Support (e.g., Letter of Support from the institution or organization sponsoring the Network Groups Operations Center) and Multiple Program Director/Principal Investigator (PD(s)/PI(s) Leadership Plan, remain unmodified and must be completed following standard instructions.

2.1 Sub-section A. Operations, Statistics, and Data Management Center Overview (up to 6 pages)

This sub-section should provide a general overview of the Operations, Statistics, and Data Management Center of the Canadian Collaborating Clinical Trials Network organization and describe the general features and operations of the organization. The applicant should provide a diagram illustrating the organizational structure of the organization in this sub-

section and describe how the Canadian Collaborating Clinical Trials Network would interact with the other key components of the NCTN Program.

The applicant's key standard operating procedures for the conduct of clinical trials related to the following should be provided in the Resource section of the application:

- Data and Safety Monitoring Board Policy for Phase 3 Trials & Randomized Phase 2 Trials
- Data and Safety Monitoring Plan for Phase 1 and Phase 2 Trials
- Conflict of Interest Policy
- Onsite Auditing Policy and Procedures
- Constitution & By-laws for Institution/Site Membership and Individual Participant/Investigator Membership (including Scientific and Administrative Committee Membership)
- Standard Template for the Informed Consent Document
- Procedures for Statistical Analysis (e.g., guidelines for interim monitoring, general
- procedures for sample size estimation, accrual rate estimation, and choice of testing and estimation procedures)
- Data Management and Monitoring Policies & Procedures for Clinical Trials
- Procedures to Ensure Security and Confidentiality of Patient Data
- Model Statistical Analysis Template for Clinical Trials
- Sample of Trial Reports (i.e., 3 trials) from the SDMC Report of Studies

2.2 Sub-section B. Clinical Trial Development & Member Site Accrual Program (up to 12 pages)

This sub-section should consist of a well-defined research strategy by the applicant for the development of clinical trials with a specific research focus and patient populations that complement the research strategy of the U.S. NCTN Program. In particular, the applicant should address how its research agenda will complement the NCTN Program as a whole even though the applicant would be expected to participate in only a limited portion of the NCTN Program. The applicant should address how it decides what research collaborations to pursue with the NCTN Program. The applicant should highlight its most important achievements over the past 5 to 6 years as well as its most promising current and future research initiatives and trials as an indication of its potential to contribute to the NCTN Program. This sub-section should also include information on the applicant's senior research teams (for scientific research committees and administrative committees) and the applicant should also describe how it will mentor new/young investigators in clinical trial research.

NOTE: Information on the applicant's scientific leadership in clinical trial development as well as achievements of its past (over the prior 5 to 6 years) and current clinical trial development program may be summarized in tables. ***Use of template Tables #1, #2, #3, and #4 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

This sub-section should also consist of a well-defined plan for accrual to NCTN trials by the applicant's member institutions/sites. This plan should encompass accrual to the occasional trial led by the applicant as well as trials that will be led by U.S. Network Groups Operations Centers. Emphasis should be placed on overall accrual across the entire NCTN. This sub-section should present information on the potential of the applicant to accrue patients to oncology clinical treatment trials and advanced imaging trials in a publicly funded clinical trials system across a broad range of diseases, including rare cancers, via its member institutions/sites.

NOTE: The applicants are expected to highlight the track record of the applicant team and its member site for accrual over the past 5 to 6 years, summarized in tables. ***Use of template Tables #5, #6, and #7 as described in Part 4 - Appendices – Section II.A. of these Guidelines document for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.3 Sub-section C. Operational Management (up to 6 pages)

This sub-section should describe the applicant's organizational structure, governance, standard operating procedures, and operational efficiency program in order to demonstrate the applicant applicant's capability to develop, activate, and conduct clinical trials in a timely manner.

The scope and authority of the applicant's leadership team for operations, statistics, and data management, the Director of Operations position, and the Executive/Advisory Committee should be described, including succession planning for key leadership positions. This description should also include the relationship/rules for institutional membership in the Canadian Collaborating Clinical Trials Network as well as financial management policies.

For applications designating multiple PD(s)/PI(s), a leadership plan related to the multiple PD/PI designation must be included in the appropriate section of the application (i.e., Multiple Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) Leadership Plan section of the PHS 398). A rationale for choosing a multiple PD(s)/PI(s) approach should be described. The governance and organizational structure of the leadership team for the Canadian Collaborating Clinical Trials Network should be described including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the organization should be delineated for the PD(s)/PI(s), including responsibilities for human subjects in clinical studies. If budget allocation is planned, the distribution of resources to specific components of the organization and/or the individual PD(s)/PI(s) should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote of the Notice of Award.

The applicant's plan for operational efficiency in study development, trial activation, and timely completion of studies it leads as well as timely activation within Canada for NCTN trials that the Canadian Collaborating Network decides to participate in. The applicant team should describe how it will provides regulatory support for Canadian sites to participate in NCTN trials led by U.S. Network Groups

Also, explain how the Canadian team will use the NCI standard tools and services for the conduct of clinical trials (e.g., Clinical Data Management System, Oncology Patient Enrollment System, and Regulatory Support System for the NCTN). Address how the Canadian Collaborating Network will assure compliance with NCI, NIH, and HHS policies and all applicable U.S. federal regulations regarding the protection of human subjects in clinical research. Explain how the Canadian Collaborating Network will address study monitoring and reporting (e.g., explain how these aspects are covered by the applicant’s policies on Data and Safety Monitoring, Data Sharing, Biospecimen Sharing, Onsite Auditing, and Clinical Trial Registration and Reporting. Describe the applicant’s plan to ensure that results from clinical trials will be published in peer-reviewed manuscripts in a timely manner consistent with NCTN Program requirements.

NOTE: The applicant’s capabilities and potential to conduct large-scale operations related to developing, activating, and conducting clinical trials is essential and will be a factor in the

application merit evaluation. In this sub-section, the applicants are expected to highlight their most relevant achievements over the past 5 to 6 years, in addition to details presented in summary tables. ***Use of template Tables #8, #9, #10, and #11 as described in Part 4 - Appendices – Section II.A. of these Guidelines for the NCTN Program is highly recommended and may be included in the Resources section of the application.***

2.4 Sub-section D. Statistics Analysis Program and Data Management (up to 12 pages)

This sub-section should consist of a well-defined organization, approaches, policies, and procedures for statistical analysis and data management of clinical trials led by the applicant (including any approved, multi-center Phase 2 and Phase 3 trials that originated from investigators outside the applicant's organization).

The applicant should provide a **brief** description of the general approach to statistical trial design and analysis plans for multi-institutional clinical trials, including guidelines for interim monitoring and general procedures for sample size estimation and choice of testing and estimation procedures. Examples of robust statistical trial designs and statistical support should be described as well as how the organization provides statistical leadership in design and analysis, including incorporating new, integral and integrated, molecular and imaging biomarkers and laboratory studies into the overall evaluation of NCTN trials. The applicant should also describe how the organization ensures that final study analyses are performed in a manner to provide timely publication of study results and results reporting per NCI and federal regulations.

The applicant should provide a **brief** description of the data management and study monitoring practices of the SDMC, including the flow and review of data following submission from individual institutions/sites and investigators. The applicant should describe the data management systems employed and how the SDMC would use standard NCTN tools including the NCTN Common Data Management System (CDMS) and use of NCTN-approved Common Data Element (CDEs) from the caDSR, the NCTN Regulatory Support System (RSS), the NCTN Oncology Patient Enrollment Network (OPEN), the NCI/DCTD Clinical Data Update Systems (CDUS/CDS), the NCI Expedited Adverse Event Reporting System (AdEERs), the NCI Common Terminology Criteria for Adverse Events (CTCAE) for data management for NCTN trials, and trial registration in the NCI Clinical Trials Reporting Program (CTRP) and in the U.S. National Library of Medicine (NLM) (www.clinicaltrials.gov) along with results reporting, as applicable.

Brief descriptions of training for investigators (including mentorship for junior investigators), Clinical Research Associates, and study chairs related to data management and study monitoring for clinical trials should be provided. The applicant should also describe procedures for study monitoring as well as for data quality control and accuracy verification, including how the organization conducts auditing activities. The applicant's method for active trial monitoring, including procedures for accrual and biospecimen collection tracking, assessing case, eligibility and evaluability, ensuring timely medical review and assessment of patient data, monitoring of data timeliness, and facilitating staff interactions with study chairs should be described briefly. The applicant should describe the organization's guidelines for institutions/sites for data timelines, including a summary of data quality and timeliness as an indication of its potential to operate efficiently within the NCTN Program. This information may be summarized in a table. Information on the Statistics Analysis and Data Management Program may be summarized in a series of tables. Use of template Tables #1, #2, and #3 as described in Part 4 – Appendices – Section II.B. of these Guidelines is highly recommended and may be included in the Resources section of the application.

The applicant should also describe the facilities and equipment available as well as the information technology (IT) support for central storage, security, analysis and retrieval of clinical data. The applicant should describe how it complies with guidelines for good clinical practice and with federal/DHHS/NIH/NCI regulations for clinical research involving human subjects as well as with NCI/NIH administrative requirements for conduct of clinical trials with respect to NCI/DCTD's IP Option and NCI/DCTD's collaborative binding agreements for NCI/DCTD IND studies.

2.5 Sub-section E. Program for Collaborations and Participation in Collective Management (up to 6 pages)

This functional component should consist of a well-defined plan for potential collaborations by the applicant with U.S. Network Groups and NCI-sponsored investigators and programs as well as how the applicant plans to participate in the collective management of the NCTN.

The applicant should address how it can contribute to the collective management of the NCTN Program through examples of participation in the NCI Scientific Steering Committees (SSC) and associated Task Forces and Working Groups, and Planning Committees for SSC Clinical Trials Planning Meetings, or examples of similar activities in other clinical trial network as indications of its potential to participate in the collective management of the NCTN. The applicant should also discuss its ability to complete development of study proposals and conduct future trials that may originate outside the NCTN Program if they are approved by the NCI disease-specific SSCs.

2.6 Protection of Human Subjects

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. **Information on the targeted/planned enrollment table for minorities and members of both genders (as well as children, if applicable), should be based on accrual summarized across all diseases for the planned project period in the competing new application (Type 1), not on a study or disease-specific basis.**

The Canadian Collaborating Clinical Trials Network application must address the inclusion of women and minorities and inclusion of children in its clinical research as required per NIH/NCI Policy. Information on the policies for inclusion of women and minorities is available at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

Information on the policies for inclusion of children is available at:

http://grants.nih.gov/grants/funding/children/children.htm
http://www.nih.gov/grants/guide/notice-files/not98-024.html

2.7 Resource Sharing Plans

Applicants are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS) as provided in the PHS 398 Application Guide with the following modifications:

- Generally, Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms if applicable, and Genome Wide Association Studies (GWAS) are expected in this application.

- All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan. An example of a Data Sharing Plan for Network Group Operations Centers and associated Network Group Statistics and Data Management Centers (or Canadian Collaborating Clinical Trials Network) for the NCTN Program is provided in Part 4 – Appendices – Section VII in these Guidelines.

The Data Sharing Plan and other resource plans (or rationale for not providing sharing certain resources) should be provided in the research application; however, prior to funding of an award, all resource sharing plans/policies will also need to be reviewed and approved by NCI/DCTD program staff prior to funding any award in order to ensure that the plans/policies are in compliance with NCI/NIH regulations and the Terms of the Award for the applicable key component of the NCTN Program.

3. Appendix Material & Post Submission Materials

Information on the Appendix material that should be provided in Canadian Collaborating Clinical Trials Network 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 – Section I.D. of these Guidelines as well as in Part 2 – Section II.B.3 for the operations center component of the application and Part 2 – Section II.C.3 for the statistical component of the application. Information on post submission materials that may be provided for the Network Group Operations Center application is described in Part 2 – Section I.F of these Guidelines.

4. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement for the Canadian Collaborating Clinical Trials Network.

4.1 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.

4.2 Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the Canadian Collaborating Clinical Trials Network 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: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

4.3 Onsite Auditing Activities

The NCI-CTMB Guidelines for 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. In order for the NCI to review the Canadian Collaborating Clinical Trials Network's compliance with this requirement, the Canadian

Collaborating Clinical Trials Network should conduct a comprehensive review of its membership and provide **updated** auditing information for all Participating Sites and affiliates to the NCI/DCTD Senior 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 Canadian Collaborating Clinical Trials Network; (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 Part 4 – Appendices – Section II.A.9.

4.4 Provision of Funds to Member Institution/Sites for Per Patient Data Management

If the Canadian Collaborating Clinical Trials Network provides funds to member institutions/sites for accruals (non-Lead Academic Participating Sites and non-CCOP/MB-CCOP institutions) via per-accrual reimbursement mechanisms (e.g., purchased service agreements or subcontracts), the following information must be provided as Just-In-Time information:

- For the upcoming budget period: (1) the estimated number of per patient accruals by category (screening, intervention, and biospecimen accruals) by major disease area and within each disease area by trial led by Canadian Collaborating Clinical Trials Network; (2) the estimated number of per patient accruals by category (screening, intervention, and biospecimen accruals) by major disease area for trials that would not be led by the Canadian Collaborating Clinical Trials Network; and (3) the estimated total costs (direct and indirect) that the Canadian Collaborating Clinical Trials Network anticipates providing by member institution/site via this award.

4.5 Data and Safety Monitoring Boards/Plans

The Canadian Collaborating Clinical Trials Network should have a Data and Safety and Monitoring Board (Data Monitoring Committee) policy for randomized phase 2 and phase 3 NCTN trials that complies with the "NCI NCTN Program Data and Safety Monitoring Board Policy" as provided in Part 4 – Appendices – Section VIII of these Guidelines. In addition, the Network Group Operations Center must have Data and Safety Monitoring plans for all other Network Group studies (e.g., phase 1 and phase 2 studies, pilot studies, etc.) that comply with the NIH policy for data and safety monitoring, posted on the NIH website at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html, with additional description at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.

These policies/plans should be provided in the research application; however, prior to funding of an award, all Data and Safety Monitoring Board (Data Monitoring Committee) policies/plans will also need to be reviewed and approved by NCI/DCTD program staff prior to funding of an award to ensure that they are in compliance with NCI/NIH regulations.

III. Description of Review Process and Review Criteria for New and Competing Applications

A. General Information

1. Role of Peer Review and Review Policies

All applications for the key components of the NCTN Program are submitted and reviewed in the same award cycle. The role of peer review is to assess the extent to which each key component of the NCTN Program has and/or is likely to promote excellence in the conduct of clinical treatment and advanced imaging studies that may lead to a reduction in the incidence of morbidity and mortality attributable to cancer. The focus of the review is on the ability of each key component of the NCTN Program to help develop, implement, and conduct meritorious clinical trials, especially definitive late phase, multi-institutional trials. All applications will be reviewed based on individual review criteria categories for each of the key components of the NCTN Program which include an assessment of the application's strength to contribute to the Network as a whole. In particular, applications for Network Group Operations Centers and their associated Statistics and Data Management Centers, will be reviewed not only for their overall research strategy and scientific impact, but also on their contributions to the science of and accrual to clinical trials conducted across the entire NCTN and the strength of their collaborations with other NCTN key components and other NCI-sponsored programs and investigators.

The NCI Scientific Review Officer (SRO) serves as the Designated Federal Official (DFO) with legal responsibility for managing the review and ensuring that the review is conducted according to relevant laws, regulations, policies, and established NIH and NCI policies and procedures. The SRO provides guidance and direction with respect to review policies, procedures and criteria; the functions of the NCI staff; conflict of interest policies; implications of the Privacy Act; the need for confidentiality of the proceedings; the necessity of addressing gender, minority, and children representation in clinical study populations; and other policy and logistical matters. During the review, the NCTN Lead Program Director serves as a resource, as needed, concerning the history and development of the NCTN Program and other relevant programmatic matters.

- The NCI is committed to the conduct of impartial, high-quality peer review of grant applications submitted by the scientific community and to the maintenance of an objective review process.

- The Division of Extramural Activities, NCI, which is responsible for managing the peer review of the NCTN Program applications, is organizationally independent from the NCI extramural program units. The Division of Extramural Activities has responsibility for and autonomy in the conduct of review activities.

- The conduct of peer review of the NCTN Program applications shall be in all particulars consistent with, and subject to, applicable NIH and PHS peer review practices and policies.

- NCI SROs are responsible for managing the scientific and technical review of the NCTN Program applications, including the selection of reviewers; management of Special Emphasis Panels (SEPs); and the documentation of review panel findings and recommendations.

- The responsibility for communications between the applicant and NCI staff changes during the various phases of the application process. Prior to submission of the application, NCI/DCTD staff members are the appropriate contact. From submission of the application until the peer review has been completed, all contacts should be made through the SRO.

- Following the peer review, NCI/DCTD staff members again become the contact for communications with the applicant.

- Efforts are made to avoid both real and apparent conflicts of interest in review of the NCTN Program applications. In addition, the confidentiality of both review materials and reviewer deliberations is maintained. Direct contact between applicants and reviewers is prohibited. Instead, any questions or concerns should be brought to the attention of appropriate NCI staff as indicated above.

- To maintain the focus of the peer review process on scientific merit, previous and current pay lines and funding policies are not discussed and are not relevant.

2. Application Receipt and Referral Process

The NCTN Program applications are received and processed initially by the NIH Center for Scientific Review (CSR) and are assigned to NCI. The NCI referral office subsequently assigns the application to the Cancer Therapy Evaluation Program in NCI/DCTD. Finally, Division of Extramural Activities review staff group the NCTN Program applications for review based on the 6 key component categories of the NCTN Program (i.e., Network Group Operation Centers, Network Group Statistics and Data Management Centers, Integrated Translational Science Centers, Network Lead Academic Participating Sites, Network Radiotherapy and Imaging Core Services Centers, and the Canadian Collaborating Clinical Trials Networks) and recruit appropriate reviewers for Special Emphasis Panel(s) or SEP(s) as needed to review the different categories of key components of the NCTN Program depending on the expertise needed. **In general, the reviewers will need to assess the value of the applications from the perspective of how the application contributes to the clinical research of the NCTN Program as a whole.**

3. Application Administrative Review

Upon receipt, the SRO reviews the application for conformance to applicable NIH and PHS policies and Program Staff accepts the application based upon responsiveness to the NCTN Program Guidelines. If there are extensive deficiencies in the structure, organization or format of the application, or the application fails to address required NIH policies in ways that cannot be resolved quickly, the application will be returned to the applicant without further consideration.

4. Review Format

All review panels are constituted as SEPs. The SEP reviewers evaluate and score general and relevant specific review criteria as appropriate for applications for each key component of the NCTN and then assign an overall impact/priority score to the entire application.

The SEP membership will include (a) senior investigators, many of whom have experience with clinical treatment and advanced imaging trials (especially late phase clinical trials) as well as clinical trial networks and organizations in oncology and who can view the proposed science from an overall perspective, and (b) specialists for specific scientific areas (e.g., statistics, data management, translational science, radiotherapy, imaging). In organizing the review panel membership, conflicts of interest, either real or apparent, will be managed according to NIH policy.

The SEP review will be based on the written applications submitted only.

The SEP will convene in a face-to-face meeting (F2F) of reviewers in the Washington, DC, metropolitan area or elsewhere at the convenience of the reviewers. **Senior NCI/DCTD staff will be available to provide clarification upon SRO's request during orientation for reviewers of the NCTN Program.**

The SRO will provide an introductory orientation on NIH and NCI review policies and procedures and administrative and logistic matters relating to the review. Then, each application will be evaluated by the reviewers. The reviewers will evaluate and rate the general and relevant specific review criteria as appropriate for applications for each key component of the NCTN Program. **The reviewers will need to assess the value of each application as to how it contributes to the clinical research of the NCTN Program as a whole. The review panel will then assign the final overall impact/priority score to the each application.**

NCI SROs prepare the summary statement using the minimally edited reviewers' comments as well as summaries of the discussion.

5. Selection of Reviewers

The size and composition of the SEP will be determined by the particular details of the applications to be reviewed. It is the responsibility of the SRO to make these determinations based upon thorough understanding of the work proposed in the applications and consultation with NCI/DCTD staff and other NCI review staff, as appropriate. The review panel members are recruited based on the scientific areas, approaches, and administrative expertise needed to evaluate the applications. It is anticipated that the SEP convened for NCTN reviews in the future will therefore change every review cycle.

Since clinical trials are based on outcome endpoints for human subjects, the SEP will also include one or more patient/consumer advocates in the review group. These individuals, who have full reviewers' rights, often address clinical or population-based study issues related to protection, recruitment and retention of human subjects in the proposed research that is essential for the success of the NCTN Program.

In identifying prospective qualified reviewers, the SRO takes full advantage of many available resources, including existing databases of experienced reviewers, lists of grantees and contractors, and consultation with recognized authorities in the scientific community. The SEP roster will be available on the NIH Web site approximately 30 days before the review meeting, but is subject to change. All review-related communications with actual or potential reviewers are through the SRO.

The Chairperson of the review panel will generally be a senior investigator experienced in the review of complex multidisciplinary multi-institutional clinical trials, especially late phase clinical trials, and generally knowledgeable about clinical trial networks/organizations as well as the scientific areas to be reviewed.

B. Review Criteria

1. General Information on Review Criteria and Evaluation for All Key Components of the NCTN

The five core review criteria for an application for any of the key components of the NCTN Program are Significance, Investigators, Innovation, Approach, and Environment (see NIH Guide Notice **NOT-OD-09-025** at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-024.html). The sections below give more detail about how these review criteria are applied for each key component of the NCTN Program. In addition, some of the key components of the NCTN Program may have additional specific review criteria that may or may not be scored separately.

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. For the NCTN Program, as previously stated, the specific goal is to promote excellence in the conduct of clinical treatment and advanced imaging studies that may lead to a reduction in the incidence of morbidity and mortality attributable to cancer and the focus of the review is on the ability of each key component of the NCTN Program to help develop, implement, and conduct meritorious clinical trials. In their written critiques, reviewers will be asked to comment on each of the criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of the review criteria will be addressed and considered in assigning the overall impact/priority score, and weighted as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high impact/priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative, but is essential to move a field forward.

The emphasis of the review criteria for all the 6 key components of the NCTN Program is on the capabilities and experience of the applicant team to successfully address the specific roles of the key component in the development, organization, coordination, conduct, and/or support for future NCTN trials, especially large scale definitive clinical trials. As all applications submitted in response to the initial Funding Opportunity Announcements (FOAs) for the NCTN program will be "new" applications, those aspects will be largely evaluated based on the prior performance and productivity of the applicants. These capabilities and commensurate performance/productivity must be appropriate and consistent with specific requirements stated in the FOAs with reference to these Guidelines.

The required capabilities and experience are expected to reflect the properly documented successful performance of the applicant team under the former NCI National Clinical Trials Cooperative Group Program or equivalent large-scale NIH or other non-profit clinical trials networks or programs for the specific key component. Reviewers will be using this information as benchmarks in evaluating all aspects of an application. In order to provide information on prior performance and productivity, applicants should provide information related to performance/productivity in the 5 1/2 calendar years prior to the application receipt date (i.e., January 2007 through June 2012).

The complete review criteria for each of the 6 key components of the NCTN Program are presented in the next sections.

2. Specific Review Criteria for Each of the Key Components of the NCTN

2.1 Criteria for Network Group Operations Center

Only the review criteria described below (and the Additional Review Criteria – Overall listed in Part 2 – Section III.B.3.) will be considered in the review process for an application for a Network Group Operations Center. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

2.1.1 Overall Impact - Overall

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the proposed Network Group Operations Center to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the proposed Network Group Operations Center).

2.1.2 Scored Review Criteria – Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a proposed Network Group Operations Center that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed Network Group Operations Center address an important problem or a critical barrier to progress in the field? If the aims of the proposed Network Group Operations Center are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed Network Group Operations Center and its research strategy? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? Given that the NCTN Operations Centers will be involved in collaborative (and irrespective of whether the applicants choose to use the multi-PD/PI option), do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the proposed Network Group Operations Center?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the proposed Network Group Operations Center? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the clinical research conducted by the Network Group Operations Center benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Scored Review Criteria

In addition to the above review criteria, the following criteria will be applied to applications in the determination of scientific merit and the impact/priority score. Reviewers will consider each of the additional review criteria below in the determination of scientific merit, and give a separate score for each.

A. Clinical Trials Development Program
B. Member Site Accrual Program
C. Operational Management
D. Program for Collaborations & Participation in Collective Management of NCTN

2.1.3 Scored Review Criteria – Criterion A. Clinical Trial Development Program

(Note: The entire Criterion A will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Significance

Overall Research Strategy: How well does the applicant's research strategy reflect an integrated scientific approach within oncology disease areas as well as across disease areas? Does the research strategy address important unmet clinical needs? Is the research strategy sufficiently practical and feasible? Are the disease areas included in the applicant's overall research strategy appropriate and beneficial to the NCTN? How well would the applicant team contribute to the development of clinical trials for patients with rare cancers and how well would the applicant address underserved patient populations through trials that it leads or participates in across the NCTN?

Quality of Clinical Trials: Based on the clinical trials currently being conducted as well as those proposed, what is the likelihood that the applicant's team can contribute meaningfully to developing and implementing multi-disciplinary, multi-institutional trials in a broad range of cancer types and special populations with specific scientific strategy and goals? Do the trials contain important integral and integrated translational science research questions that are appropriate and well justified? To what degree do their results reflect qualitatively new knowledge that advances the field and may inspire future clinical trials? Will (or have) the results lead (led) to meaningful practice changes for cancer care or other meaningful results (e.g., Phase 2 trials leading to Phase 3 trials

conducted by government or private sector, provision of important toxicity or dosing information)? Does the applicant team have effective mechanisms for promoting timely presentation and publications of the results of clinical trials and associated studies?

Investigator(s)

Senior Group Leadership for Clinical Trials Development: How well can the PD(s)/PI(s) and the entire team of investigators assembled by the applicant provide scientific leadership for state-of-the-art early and late phase clinical trials in adults and/or children with cancer? Will these investigators be able to work as a cohesive research team to efficiently and expeditiously develop and conduct NCTN clinical trials? Does the applicant have appropriate and clearly defined succession and transition plans for the senior leadership of the proposed Network Group Operations Center? Does the applicant have reasonable and appropriate limitations on terms for senior leadership that encourage rotation of leadership responsibilities?

Scientific Research Committee Leadership: Do the research experience and qualifications of the leadership of the applicant's Scientific Research Committees provide multi-disciplinary representation (e.g., medical oncology, radiation oncology, imaging, surgery, pathology, translational science, patient advocacy) across a broad range of oncology diseases appropriate to the stated research goals? Does the leadership of the scientific committees have a track record of successful multi-institutional early phase and especially late phase clinical trials research as evidenced by publications? Do the Scientific Research Committees provide leadership opportunities for a broad range of investigators and are there reasonable and appropriate limits on terms for senior leadership of the Scientific Research Committees that encourage rotation of leadership responsibilities and provide continuity and stability in the Committees?

Administrative Committee Leadership: Are the experience and qualifications of the leadership of the applicant's Administrative Committees appropriate for development and oversight of the administrative management categories needed for conducting both early phase and especially late phase, multi-institutional, clinical trials (e.g., support functions for trials including involvement of patient advocates, support programs for enrollment of members of underserved patient populations, financial management)?

Innovation

Innovation in Early and Late Phase Clinical Trials: Within the confines of the ethical constraints applicable to early and late phase clinical trials for oncology patients, does the applicant propose novel or improved ways and/or methods to enhance or better serve its overall research strategy and the goals of developing and implementing multi-disciplinary, multi-institutional trails in a range of cancer types and special populations with specific scientific strategy and goals?

Approach

Approach to Clinical Trial Development: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific clinical aims of the applicant? Are potential problems, alternative strategies, and benchmarks for success presented for specific clinical trials?

Environment

Leveraging Resources to Support Research: How successful are the members of the applicant team in obtaining other funding (from NCI, other governmental agencies,

industry, charitable foundations, etc.) for the conduct of integral and integrated translational research and other ancillary studies related to their clinical trials?

New & Junior Investigator Leadership Mentoring/Training: Does the applicant team have in place an adequate mentorship/training program for new and junior investigators that provides opportunities for leadership of clinical trials (e.g., developing concepts for trial proposals, serving as study chairs for trials, participating in scientific committees in support or leadership roles, participating in other clinical trial activities) at appropriate levels as well as the potential to provide opportunities to these investigators to participate in the future in NCTN activities or initiatives?

2.1.4 Scored Review Criteria – Criterion B. Member Site Accrual Program

(Note: The entire Criterion B will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Accrual Potential: Given its past record of accrual, does the applicant have the potential to provide substantial accrual to clinical trials conducted across the NCTN as a whole, especially in the applicant's stated areas/diseases of research interest? Does the applicant team have the potential to contribute to accrual of minority and underserved patient populations to trials at an appropriate level? Does the applicant's member institutions/sites have the potential to contribute to accrual of patients to NCTN clinical trials in rare tumors as needed for the NCTN goals? Does the applicant's membership appear able to accrue to trials for rare subset populations of more common cancers? Does the applicant demonstrate the ability to meet protocol-specified accrual goals in a timely manner for trials it conducts? Are the PD(s)/PI(s), collaborators, and other researchers who comprise the scientific and technical leadership team for this application well suited to help drive accrual for NCTN trials?

Accrual Monitoring: Has the applicant and its member institutions/sites developed novel means to assess accrual potential to clinical trials? How good are the applicant's systems/procedures to rapidly assess and monitor accrual and implement appropriate corrective action plans if accrual is lagging at a specific site or across all sites? Do the applicant's member institutions/sites demonstrate high levels of biospecimen collection in conjunction with clinical trials indicating the potential to contribute to biospecimen collection in NCTN trials?

Member Institution/Site Support for Accrual: How will the scientific and administrative environment of the applicant's member institutions/sites contribute to the probability of accrual success? Are the institutional support, equipment and other physical resources available at member institutions/sites adequate for the level of accrual proposed? How will accrual to NCTN trials benefit from unique features of the scientific environment, patient populations, and/or collaborative arrangements with other organizations provided by applicant's member institutions/sites?

2.1.5 Scored Review Criteria – Criterion C. Operational Management

(Note: The entire Criterion C will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Operational Structure, Policies, and Procedures: Are the organizational structure and management policies of the proposed Network Group Operations Center clear and appropriate? Does the applicant incorporate procedures and tools that enhance

coordination and productivity of operational activities including protocol development? Does the staffing plan for the proposed Network Group Operations Center provide appropriate and clearly defined position descriptions and qualifications and is it adequate for required activities? Does the applicant propose sound financial management policies and procedures for grant administration, subcontracting with collaborating organizations, purchase service agreements for member institutions/sites, and other related activities (e.g., laboratory testing needed for specific clinical trials)?

Governance: Does the applicant team define a clear governance structure for the proposed Network Group Operations Center? If the application includes multiple PD(s)/PI(s), is it clear how activities and responsibilities will be carried out among the multiple PD(s)/PI(s) and is the delineation of responsibilities appropriate? Are the scope and authority of the senior leadership, Director of Operations position, and Executive/Advisory Committee for the proposed Network Group Operations Center clearly and appropriately addressed? How comprehensive are the expertise and experience of the applicant's senior administrative management team? Are the background and expertise of the proposed Director of Operations appropriate to oversee the operational management of the Group? Are the policies and procedures for institution/site membership clear and appropriate for the NCTN Program? Are the proposed operating procedures for interactions with member institutions/sites appropriate?

If the applicant proposes to include international institutions/sites as full members of the Network Group Operations Center, does the applicant have appropriate monitoring plans for these sites as well as performance assessment monitoring to ensure that the NCTN-supported activities meet the same requirements regarding conduct of clinical trials expected of a full U.S. member institution/site? If the applicant plans to enroll patients on trials that are led by non-NCTN international clinical trials organizations, does the applicant propose appropriate policies and procedures to comply with applicable regulations and requirements defined in the Terms and Conditions of the Award for a Network Group Operations Center?

Clinical Trial Operations - Development: Are the structure and composition of trial proposal and protocol development teams proposed by the applicant appropriate? How well does the applicant's proposed trial proposal and protocol development process mesh with NCI standard tools and services, including use of Common Data Elements and standard Case Report Form modules? How appropriate are the proposed Network Group Operations Center's policies and standardized procedures for development and monitoring of trial proposals and protocols (including its tracking and project management systems) for ensuring that the applicant would meet NCI-mandated trial activation timelines for operational efficiency (i.e., Operational Efficiency Working Group [OEWG] timelines)?

Clinical Trial Operations – Conduct: How appropriate are the proposed Network Group Operations Center's policies for timely and efficient development and processing of protocol amendments, including timely communication of new safety information and amendments to member institutions/sites? Are appropriate communications policies proposed to support the work of the scientific research and administrative committees, coordinate activities with the associated proposed Network Group Statistics and Data Management Centers as well as member institutions/sites and the NCI Cancer Trials Support Unit (CTSU) related to trial conduct? Does the applicant propose appropriate training programs for protocol chairs, institutional site PD(s)/PI(s), and CRAs? Does the proposed Network Group Operations Center have appropriate key standard operating

procedures related to a Data and Safety Monitoring Board Policy for Phase 3 trials and randomized Phase 2 trials, Data and Safety Monitoring Plans for phase 1 and Phase 2 trials, Conflict of Interest Policies, and a standard template for the Informed Consent Document for clinical trials that are in compliance with NCI/CTEP, NIH, and federal regulations?

Compliance/Quality Assurance/Auditing: How well do the applicant's proposed policies and procedures for clinical trial conduct comply with good clinical practice, including all Federal/HHS/NIH/NCI requirements related to clinical trial research with human subjects, as well as with NCI/DCTD requirements related to NCI/DCTD Intellectual Property policy, NCI/DCTD Cooperative Research and Development Agreements for clinical trials conducted under an NCI Investigational New Drug (IND) or Device Exemption (IDE) or other NCI binding collaborative agreement? How appropriate are the applicant's plans to ensure the quality assurance of clinical trial data and collection of biospecimens? How appropriate are the applicant's proposed policies and procedures in meeting the onsite audit requirements of the NCI Clinical Trials Monitoring Branch Guidelines (CTMB) for its member institutions/sites? How appropriate are the applicant's plans to appropriately address issues with member institutions/sites noted at the time of audit, including non-compliance, data quality, data reporting requirement, and timeliness of audits and re-audits? Does the applicant propose a quality assurance program with its associated Statistics and Data Management Center that is adequately proactive in terms of ensuring ongoing quality control of data during trial conduct?

2.1.6 Scored Review Criteria – Criterion D. Program for Collaboration & Participation in Collective Management

(Note: The entire Criterion D will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Collaborations with NCTN Network Groups, NCTN Programs/Initiatives, and other NCI-sponsored Programs/Investigators: Does the applicant have a track record for collaborations with other trial organizations and other NCI-sponsored programs and investigators (e.g., SPORE awardees, NCI Cancer Centers, R01/P01 investigators) on clinical trials and translational science studies that demonstrates its potential for collaboration within the NCTN Program? Has the applicant demonstrated that it has the capacity to conduct clinical trials that come from investigators outside its own organization?

Collective Management Activities: Does the applicant have a track record that demonstrates that the members of it scientific leadership teams (i.e., scientific research committee members) actively participate in or can actively contribute to NCI-supported clinical trial activities (e.g., disease-specific Scientific Steering Committees and related task forces or working groups, Clinical Trials Planning Committees for meetings supported by the NCI disease-specific Steering Committees, membership on the NCI Central IRB, participation in other NCI programs and initiatives related to clinical research)? Do Group members participate as members of the NCI Central IRBs? Do Group members participate in the onsite auditing program for the Network Group Operations Center?

2.2 Network Group Statistics and Data Management Center Review Criteria

Only the review criteria described below (and the Additional Review Criteria – Overall listed in Part 2 – Section III.B.3.) will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

2.2.1 Overall Impact - Overall

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the proposed Network Group Statistics and Data Management Center to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the proposed Network Group Statistics and Data Management Center).

2.2.2 Scored Review Criteria – Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a proposed Network Group Statistics and Data Management Center that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed Network Group Statistics and Data Management Center help address an important problem or a critical barrier to progress in the field? If the aims of the proposed Network Group Statistics and Data Management Center are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed Network Group Statistics and Data Management Center's Statistics Program and Data Management Program as well as its plans for collaborations and collective management? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? Given that all NCTN Program research projects/trials are collaborative, and regardless of whether the applicants choose to use the multi-PD/PI option, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the clinical research that the proposed Network Group Statistics and Data Management Center helps conduct and manage?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the proposed Network Group Statistics and Data Management Center? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Since the proposed Statistics and Data Management Center will help conduct clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of statistical analysis plans for minorities and members of both sexes/genders, as well as the inclusion of children, if applicable, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the clinical research analyzed and the clinical data managed by the proposed Network Group Statistics and Data Management Center benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Scored Review Criteria

In addition to the above review criteria, the following criteria will be applied to applications in the determination of scientific merit and the impact/priority score. Reviewers will consider each of the additional review criteria below in the determination of scientific merit, and give a separate score for each.

A. Statistical Analysis Program & Collaborative Research/Collective Management-
B. Data Management Program

2.2.3 Scored Review Criteria – Criterion A. Statistical Analysis Program & Collaborative Research and Collective Management

(Note: The entire Criterion A will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Statistical Analysis Program: How comprehensive is the expertise of the applicant's investigators overall and the Senior Leadership of the applicant's proposed Network Group Statistics and Data Management Center? How well can the PD(s)/PI(s) and the entire team of investigators assembled by the applicant provide statistical leadership for state-of-the-art early and late phase clinical trials in adults and/or adolescents and young adults and children with cancer? Do the research experience and qualifications of the leadership team demonstrate understanding of design and analysis of multi-institutional clinical trials and relevant laboratory studies? Will these investigators be able to work as a cohesive research team to efficiently and expeditiously develop the statistical analysis plans for NCTN clinical trials as well as analyze results from completed trials? Does the Network Group Statistics and Data Management Center have a well-defined organizational structure and clearly defined roles and responsibilities for its staff? Does the applicant have appropriate and clearly defined succession and transition plans for the senior leadership of the proposed Network Group Statistics and Data Management Center?

If the application includes multiple PD(s)/PI(s) (which is encouraged), are the proposed leadership governance, organizational structure, and decision-making processes and interactions among the members of the leadership team for providing statistical expertise for effective scientific design and conduct of multi-disciplinary, multi-institutions in a range of cancer types and special populations with specific scientific strategy and goals?

How well has the proposed Network Group Statistical and Data Management Center (SDMC) demonstrated its ability and track record to provide appropriately designed, robust, statistical analysis plans for early phase and especially late phase, definitive, multi-institutional clinical trials in oncology, including integral and integrated biomarker/correlative science studies? Does it appear that the applicant has the necessary expertise and experience to incorporate new molecular and imaging biomarkers into the overall evaluation of NCTN trials appropriately? Are the procedures for sample size estimation, end point selection and 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 by the SDMC demonstrate thorough and state-of-the-art methodology, awareness of problems of multiple analyses, and sufficient independence and lack of bias of statistical collaborators? Does the sample of trial reports from the Report of Studies indicate appropriate and timely data and study analyses?

Collaborative Research: Does the applicant have a track record for collaborations with other clinical trial organizations and other NCI-sponsored programs and investigators (e.g., SPOREs, NCI Cancer Centers, R01/P01 investigators) on statistical design and analysis on clinical trials and translational science studies that demonstrates its potential for collaboration within the NCTN Program? Has the applicant demonstrated that it has the capacity to provide statistical design and analysis (as well as data management) for clinical trials that come from investigators outside its associated Network Group Operations Center? Does the applicant demonstrate the ability to perform independent statistical research?

Collective Management Activities: Does the applicant have a track record that demonstrates that the members of its scientific and technical staff can participate in or can actively contribute to NCI clinical trial activities (e.g., disease-specific and modality-specific Scientific Steering Committees and related task forces or working Groups, Clinical Trials Planning Committees for meetings supported by the NCI disease-specific Steering Committees, participation in other NCI programs and initiatives related to clinical research)? Do SDMC members demonstrate the potential to participate as members of the NCI Central IRBs? Does the applicant have a robust plan to ensure that clinical data is provided in a timely and user-friendly format for public access to data from clinical trials and for studies approved for use of biospecimens and data as an indication of the applicant's potential to provide these services efficiently for the NCTN Program? How well does the applicant demonstrate its potential to implement new initiatives and new standards for clinical trial conduct and data management in a timely fashion?

2.2.4 Scored Review Criteria – Criterion B. Data Management Program

(Note: The entire Criterion B will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Data Management Program: Does the applicant describe well defined policies and procedures for data management of NCTN trials led by the applicant's associated Network Group Operations Center (including approved, multi-center phase 2 and phase 3 trials that originated from investigators outside the Network Group Operations Center)?

How appropriate and robust are the data management and study monitoring practices of the proposed SDMC, including the flow and review of data following submission from individual institutions/sites and investigators? How appropriate is SDMC training for investigators, Clinical Research Associates, and study chairs related to data management and study monitoring for clinical trials? How well do the data management systems employed by the proposed SDMC use standard NCTN tools including the NCTN Common Data Management System (CDMS) and use of NCTN-approved Common Data Element (CDEs) from the ca-DSR, the NCTN Regulatory Support System (RSS), the NCTN Oncology Patient Enrollment Network (OPEN), the NCI/DCTD Clinical Data Update Systems (CDUS/CDS), the NCI Expedited Adverse Event Reporting System (AdEERs), the NCI Common Terminology Criteria for Adverse Events (CTCAE) for data management for NCTN trials, and trial registration in the NCI Clinical Trials Reporting Program (CTRP) and in the U.S. National Library of Medicine (NLM) (www.clinicaltrials.gov) along with results reporting, as applicable? How able is the applicant to coordinate with the associated Network Group Operations Center to ensure that data and biospecimens can be made available to the public for future research?

How robust are the applicant's policies and procedures for study monitoring as well as for data quality control and accuracy verification, including how the proposed SDMC would work with its associated Network Group Operations Center on auditing activities as well as other quality assurance programs? How comprehensive and appropriate are the applicant's methods for active trial monitoring, including procedures for accrual and biospecimen collection tracking, assessing case, eligibility and evaluability, ensuring timely medical review and assessment of patient data, monitoring of data timeliness, and facilitating SDMC staff interactions with study chairs?

Does the proposed SDMC have appropriate procedures in place to ensure compliance with federal/DHHS/NIH/NCI regulations for clinical research involving human subjects as well as with NCI/NIH administrative requirements for conduct of clinical trials with respect to NCI/DCTD's IP Option and NCI/DCTD's collaborative binding agreements for NCI/DCTD IND studies?

Does the SMDC have clear guidelines for institutions/sites related to data timeliness and metrics for data quality for the clinical trial data and timely reporting to the institutions/sites of this information that indicate its potential to operative efficiently within the NCTN Program?

Do the facilities and equipment (including computer hardware and software) available as well as the information technology (IT) support for central storage, security, analysis and retrieval of clinical data for the proposed SDMC appear adequate for clinical trial research? Does the proposed SDMC have policies and procedures in place that are in compliance with federal regulations related to confidentiality of patient data, including the Health Insurance Portability and Accountability Act (HIPAA) regulations?

2.3 Network Group Integrated Translational Science Support Center Review Criteria

Only the review criteria described below (and the Additional Review Criteria – Overall listed in Part 2 – Section III.B.3.) will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

2.3.1 Overall Impact - Overall

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the proposed Network Group Integrated Translational Science Center to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the proposed Network Group Integrated Translational Science Center).

2.3.2 Scored Review Criteria – Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a proposed Network Group Integrated Translational Science Center that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed Network Group Integrated Translational Science Center help address an important problem or a critical barrier to progress in the field? If the aims of the proposed Network Group Integrated Translational Science Center are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed Network Group Integrated Translational Science research plans as well as its plans for collaborations? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? Since NCTN Program research projects/trials are collaborative, and regardless of whether the applicants choose to use the multi-PD/PI option, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the translational science research studies and pilot studies that the proposed Network Group Integrated Translational Science Center plans to perform?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the proposed Network Group Integrated Translational Science Center? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Since the proposed Network Group Integrated Translational Science Center will help support clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders (as well as the inclusion of children, if applicable as not all applications will involve translational studies for clinical trials involving children) justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the translational research studies and pilot studies designed and performed by the Network Group Integrated Translational Science Center benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria

As applicable for the research that the Network Group Integrated Translational Science Center has proposed, reviewers will evaluate the following additional items A-B while determining scientific and technical merit, and in providing an overall impact/priority score, **but will not give separate scores for these items**.

2.3.3 Additional Review Item A – Integrated Translational Science Program

A. Integrated Translational Science Program

How complete and comprehensive are the expertise of the PD(s)/PI(s) and the entire team of investigators assembled by the applicant in terms of their ability to provide scientific and technical expertise for state-of-the-art translational science for early and late phase clinical trials in adults and/or adolescents and young adults and children with cancer? Have the PD(s)/PI(s) had a successful track record of developing integral and integrated translational science studies, including molecular and/or imaging biomarker assessment, for large-scale, multi-institutional clinical trials conducted by a non-profit clinical trials network? Do the experience and qualifications of the PD(s)/PI(s) provide complementary scientific, technical, and administrative expertise for the research team?

Will the investigators involved be able to work as a coherent research team with the Network Group Operations Center(s) and Network Group Statistics and Data Management Center(s) supporting the application to provide these services efficiently and expeditiously for NCTN clinical trials? Does the application describe a clear governance structure for how the investigators and their institutions will interact and coordinate activities with the supporting Network Group components? In particular, how will activities be coordinated across various disciplines and departments at different institutions? Are the time and effort that the PD(s)/PI(s) are devoting to the Center appropriate and sufficient to

achieve the goals of the application? Does the application clearly show substantial commitment of the institution(s) and investigators in terms of leveraging institutional and investigator resources, especially laboratory resources, to enhance development of translational science studies as well as pilot studies, including validation of assay performance?

If the application includes multiple PD(s)/PI(s), are the proposed leadership governance, organizational structure, and decision-making processes and interactions among the members of the leadership team for the application optimal for achieving the goals of the application?

Does the application describe a well-defined plan for how the PD(s)/PI(s) will actively participate in the scientific meetings of the Group Operations Center(s) and Network Group Statistics and Data Management Center(s) supporting the application as well as other activities of the NCTN Program (e.g., NCI disease-specific Steering Committees and associated task forces and working groups, Clinical Trials Planning Committees for meetings, and other NIH/NCI initiatives related to translational science research)?

Do the applicants have procedures in place to verify that they can comply with all applicable federal/DHHS/NIH/NCI policies and regulations regarding the use of data from clinical trials involving human subjects, including data security and protected medical information safeguards?

2.3.4 Additional Review Item B – Pilot Studies and Collaborative Projects

B. Pilot Studies and Collaborative Projects

Does the research plan adequately address the how pilot studies will be selected and how they will be performed to enable acquisition of preliminary data for further research that will be conducted related to the overall translational science research strategy? Is the relationship between these pilot studies and the overall research strategy clearly explained and appropriate for the overall goals of the application?

Do the applicants have the appropriate facilities and expertise to perform the non-clinical aspects of any pilot studies proposed (e.g., molecular biomarker assays)? Can the investigators leverage independently funded laboratory resources with clinical data and biospecimens from the clinical trials conducted by the supporting Group Operations Center(s) and Network Group Statistics and Data Management Center(s) to benefit the research aims of the application?

Are there an adequate plan and potential for collaborating with other NIH/NCI programs and organizations (e.g., SPOREs, NCI Cancer Centers, etc.) to facilitate hand-offs of results from early phase clinical trials and/or translational science research discoveries?

2.4 Lead Academic Participating Site Review Criteria

Only the review criteria described below (and the Additional Review Criteria – Overall listed in Part 2 – Section III.B.3.) will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

2.4.1 Overall Impact - Overall

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the proposed Network Lead Academic Participating Site to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the proposed Network Lead Academic Participating Site).

2.4.2 Scored Review Criteria – Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a proposed Network Lead Academic Participating Site that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed Network Lead Academic Participating Site help address an important problem or a critical barrier to progress in the field? If the aims of the proposed Network Lead Academic Participating Site are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed Network Lead Academic Participating Site as well as its plans for collaborations and collective management? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? Given that NCTN research projects/trials are collaborative, and regardless of whether the applicants choose to use the multi-PD/PI option, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the clinical research that the proposed Network Lead Academic Participating Site is expected to help conduct and manage?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the proposed Network Lead Academic Participating Site? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Since the proposed Network Lead Academic Participating Site will help conduct clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, if applicable, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the clinical research analyzed and the clinical data managed by the Network Lead Academic Participating Site benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Scored Review Criteria

In addition to the above review criteria, the following criteria will be applied to applications in the determination of scientific merit and the impact/priority score. Reviewers will consider each of the additional review criteria below in the determination of scientific merit, and give a separate score for each.

A. Clinical Trial Program
B. Site Accrual Program

2.4.3 Scored Review Criteria – Criterion A. Clinical Trial Program

(Note: The entire Criterion A will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

How complete and comprehensive are the expertise of the PD(s)/PI(s) and the entire team of investigators assembled by the applicants in terms of their ability to provide scientific leadership for state-of-the-art early and late phase clinical trials in adults with cancer? Will these investigators be able to work as a cohesive research team at the institution and with their associated adult Network Groups to efficiently and expeditiously complete NCTN clinical trials? Are the proposed governance structure, decision-making processes, and interactions among the leadership at the site optimal for participating in multi-disciplinary, multi-institutional trials in a range of cancer types and special populations with diverse scientific strategies?

Do the research experience and qualifications of the Program Director(s)/Principal Investigator(s) provide multi-disciplinary representation in several relevant fields (e.g., in medical oncology, radiation oncology, imaging, surgery) and across a broad range of cancers? Have the PD(s)/PI(s) and other investigators involved in NCTN research at the site have a track record of successful multi-institutional early phase and, especially, late phase clinical trials research as evidenced by publications?

Do the PD(s)/PI(s) have sustained, high-level participation in the scientific leadership of at least one adult Network Group that is applying under the NCTN Program FOA (e.g., serving as scientific committee or protocol/trial study chairs, contributing new trial ideas to adult Network Group(s) including participating in concept development, co-authoring publications on clinical trials research)?

Do the PD(s)/PI(s) contribute in a meaningful way to the development of trials in rare cancers? Is there evidence that the PD(s)/PI(s) are capable of providing important contributions to translational science/correlative science associated with adult Network Group trials, particularly translational research that is integral to or integrated into the clinical trial? Do the PD(s)/PI(s) demonstrate the ability to facilitate collaborations between NCTN investigators and other clinical/translational science investigators at the academic center? Does the academic center have an effective plan to mentor junior faculty in NCTN clinical research activities?

Do the PD(s)/PI(s) demonstrate the potential to participate actively in the scientific meetings and other activities of 1 or more adult Network Groups? Do the PD(s)/PI(s) demonstrate the potential to participate actively as members in any of the NCI disease-specific Steering Committees for the NCTN, as well as in the task forces or working groups of the NCI disease-specific Steering Committees, and Clinical Trials Planning Committees for meetings sponsored by the NCI disease-specific Steering Committees?

Do the PD(s)/PI(s) have adequate and appropriate administrative experience in clinical trial research, including organization and management of the infrastructure required for patient recruitment/accrual, data collection, data reporting and safety monitoring for patients enrolled on clinical trials?

Does the academic center have a well-defined plan and an appropriate governance structure to coordinate activities related to the NCTN across the various disciplines and departments at the academic center? If the academic center application includes multiple PD(s)/PI(s), is it clear how activities and responsibilities will be carried out among the multiple PD(s)/PI(s)?

In particular, does the academic center's application clearly describe how funding associated with patient enrollment and clinical data collection and management will be distributed to the various disciplines and clinical departments involved in the trials at the academic center according to workload as determined principally by accrual to trials to ensure/enhance participation by various disciplines at the academic center in NCTN trials?

Is the staffing plan to conduct the activities for the award appropriate with clearly defined position descriptions and qualifications as well as adequate numbers to cover required activities?

2.4.4 Scored Review Criteria – Criterion B. Site Accrual Program

(Note: The entire Criterion B will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Does the academic center demonstrate the potential to overcome critical barriers for robust accrual to advance progress in the field? Does the academic center (without affiliates) demonstrate the potential for robust accrual (e.g., 55 to 70 patients per year or more) to multi-institutional early and late phase clinical treatment trials and

advanced imaging trials based on previous accrual history as demonstrated in the former NCI National Clinical Trials Cooperative Group Program or an equivalent program? Does the academic center have timely activation of clinical treatment and advanced imaging trials? Are robust institutional infrastructure and policies in place to support accrual to NCTN trials? Does the academic center have active programs to recruit minorities and underserved patient populations to NCTN trials?

Does the accrual to clinical trials by the academic center demonstrate the clinical focus of clinical practice and research at the institution and of the PD(s)/PI(s)? Do clinical trials conducted at the academic center appear to be conducted in accordance with good clinical practice as evidenced by audit results?

Has the academic center developed processes and tools to expedite protocol approval in their center that would benefit accrual to NCTN trials? Has the institution demonstrated evidence of targeted information dissemination regarding availability of Network trials? Does the institution have IT tools or other processes to facilitate information dissemination? Does the institution use Patient Navigators or other approaches to encourage accrual of minorities?

Does the academic center provide complete management services and oversight for any affiliate sites and if so, are the divisions of responsibilities between affiliates and the academic center clearly and appropriately defined?

Do the investigators at the academic center demonstrate the potential to participate as members on the NCI CIRB? Does the academic center demonstrate the ability to have timely review of studies by its local IRB if a phase 1 or phase 2 study is not under the NCI CIRB?

Does the academic center have appropriate processes in place to provide timely, accurate, and complete reporting of protocol-specified data, including reporting of adverse events and submission of required and optional biospecimens, for patients enrolled on clinical trials? Does the academic center have procedures in place to verify that it can comply with all applicable Federal/DHHS/NIH/NCI policies and regulations regarding the use of investigational agents in oncology trials?

2.5 Network Radiotherapy and Imaging Core Services Centers Review Criteria

Only the review criteria described below (and the Additional Review Criteria – Overall listed in Part 2 – Section III.B.3.) will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

2.5.1 Overall Impact - Overall

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the proposed Network Radiotherapy and Imaging Core Services Centers to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the proposed Network Radiotherapy and Imaging Core Services Centers).

2.5.2 Scored Review Criteria – Overall (Including Program for Collaborations & Participation in Collective Management)

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a proposed Network Radiotherapy and Imaging Core Services Centers that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed Network Radiotherapy and Imaging Core Services Centers' organization help address an important problem or a critical barrier to progress in the field? If the aims of the proposed Network Radiotherapy and Imaging Core Services Centers are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed Network Radiotherapy and Imaging Core Services Centers' plans for support of NCTN trials as well as the Centers' plans for collaborations? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? Given that NCTN Program research projects/trials are collaborative (and irrespective of whether the applicant chooses to use the multi-PD/PI option), do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the support services that the proposed Network Radiotherapy and Imaging Core Services Centers plan to provide?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad

sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the proposed Network Radiotherapy and Imaging Core Services Centers? How able do the proposed Network Radiotherapy and Imaging Core Services Centers appear to be with respect to providing basic interoperability between the radiotherapy and imaging core service components as well as with other key components of the NCTN, including electronic exchange of digital planning data and images and web-based software tools to facilitate trial-specific digital data review by study chairs for NCTN trials?

Do the proposed Network Radiotherapy and Imaging Core Services Centers have adequate and appropriate plans for future participation in the development of NEMA DICOM-RT standards (http://medical.nema.org/) and in the support of trials which merge imaging from different platforms such as FDG PET, CT, MRI, and other platforms? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Since the proposed Network Radiotherapy and Imaging Core Services Centers will help support clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Do the proposed Network Radiotherapy and Imaging Core Services Centers have procedures in place to verify that they can comply with all applicable federal/DHHS/NIH/NCI policies and regulations regarding the use of data from clinical trials involving human subjects, including data security and protected medical information safeguards?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the support services that the proposed Network Radiotherapy and Imaging Core Services Centers plan to provide benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Does the applicant adequately demonstrate the capacity for interoperability with the common data management system (CDMS) of the NCTN Program to collect clinical trial data and link information to clinical data collected by other key components of the NCTN Program such as Network Group Operations Centers and associated Network Group Statistics and Data Management Centers? How well does it appear that the proposed Network Radiotherapy and Imaging Core Services Centers will be able to work with the NCTN Program tools and services employed for regulatory support and patient enrollment (i.e., the Regulatory Support System (RSS) and the Oncology Patient Enrollment Network (OPEN) for all NCTN clinical trials?

Do the proposed Network Radiotherapy and Imaging Core Services Centers have a track record for collaborations with other clinical trial organizations and/or other NCI-sponsored programs and investigators (e.g., SPOREs, NCI Cancer Centers, R01/P01 investigators), especially with respect to development of standards and harmonization of processes and data collection that indicates the Centers have the potential to be provide additional benefits to the NCTN Program? Do the proposed Network Radiotherapy and Imaging Core Services Centers demonstrate the potential to enhance services and provide best practices and/or standards for selected assessments of radiotherapy and advanced imaging techniques?

Do the proposed Network Radiotherapy and Imaging Core Services Centers have a track record that demonstrates that the members of its senior leadership team and staff can actively participate in and contribute productively to NCI and NCTN clinical trial activities (e.g., disease-specific and modality-specific Scientific Steering Committees and related task forces or working Groups, Clinical Trials Planning Committees for meetings supported by the NCI disease-specific Steering Committees, participation in other NCI programs and initiatives related to clinical research)? Does the applicant demonstrate the capacity to implement new initiatives and standards in a timely fashion?

Do the proposed Network Radiotherapy and Imaging Core Services Centers provide adequate real-time user support in the form of a "Help Desk" which can also collect feedback for continual improvement of functionality of the core services?

Additional Scored Review Criteria

In addition to the above review criteria, the following additional criteria A-B will be applied to applications in the determination of scientific merit and the impact/priority score. Reviewers will consider each of the additional review criteria below in the determination of scientific merit, and give a separate score for each.

A. Radiotherapy Core Services Center Program
B. Imaging Core Services Center Program

2.5.3 Scored Review Criteria – Criterion A. Radiotherapy Core Services Center Program

(Note: The entire Criterion A will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Does the plan for providing support services for radiotherapy in clinical trials adequately address the key functional needs for a Radiotherapy Core Services Center, including collection, distribution, analysis, and storage/archiving of all primary and adjunct radiotherapy treatment delivery data for applicable NCTN trials?

Does the plan for providing support services for radiotherapy in clinical trials include an adequate approach, with appropriate policies and procedures, for how information and services will be coordinated with the Imaging Core Services Center?

Does the proposed Radiotherapy Core Services Center provide continued maintenance of robust physical hardware and information technology (IT) networks which ensure the operational integrity and security of the core services? How well does it appear the proposed Radiotherapy Core Services Center could incorporate data from legacy trials of potential Network Group Operations Centers and their associated Network Group Statistics and Data Management Centers (SDMCs)?

Do implementation plans for the functional services provided by the Radiotherapy Core Services Center appear that they are or will be implemented efficiently and in a cost-effective manner? Do the standard operating procedures (SOPs) as well as tool generation and evaluation by the proposed Radiotherapy Core Services Center appear to be effective and efficient?

How well would the proposed Radiotherapy Core Services Center be able to provide core services support for NCTN collaborative trials with other NCI-sponsored investigators and programs (e.g., NCI/DCTD early phase clinical trials programs)?

Does the proposed Radiotherapy Core Services Center have the appropriate infrastructure to provide appropriate uniform quality assurance (QA) procedures and review for advanced radiotherapy trials, including dosimetry, that are developed by the NCTN, including digital data capture, rapid analysis of volumetric treatment planning data, and physical dose assurance capabilities?

Does the proposed Radiotherapy Core Services Center have the infrastructure and ability to provide appropriate quality assurance support for the following elements associated with multi-institutional clinical trials: radiation dose delivery by photons, electron and protons for external beam radiotherapy and brachytherapy, use of anthropomorphic phantoms for complex treatment delivery, archiving and remote review of digital data including 3D and 4D images and RT objects?

Does the proposed Radiotherapy Core Services Center have the ability to provide uniform credentialing of institutions that might participate in applicable NCTN trials including those which use advanced radiotherapy treatment and assist Network Group Operations Centers and their associated SDMCs in the development of applicable trials with advanced radiotherapy, especially related to the need for specialized quality assurance, target volume definitions, and data submission requirements?

2.5.4 Scored Review Criteria – Criterion B. Imaging Core Services Center Program

(Note: The entire Criterion B will receive one individual score; the subcategories and aspects listed will be assessed but not scored separately).

Does the plan for providing support services for imaging in clinical trials adequately address the key functional needs for an Imaging Core Services Center, including collection, distribution, analysis, and storage/archiving of all primary and adjunct imaging delivery data for applicable NCTN trials?

Does the plan for providing support services for imaging in clinical trials include an adequate approach, with appropriate policies and procedures, for how information and services will be coordinated with the Radiotherapy Core Services Center?

Does the proposed Imaging Core Services Center provide continued maintenance of robust physical hardware and information technology (IT) networks which ensure the operational integrity and security of the core services? How well does it appear the proposed Imaging Core Services Center could incorporate data from legacy trials of potential Network Group Operations Centers and their associated Network Group Statistics and Data Management Centers (SDMCs)?

Do implementation plans for the functional services provided by the proposed Imaging Core Services Center appear that they are or will be implemented efficiently and in a cost-effective manner? Do the standard operating procedures (SOPs) as well as tool generation and evaluation by the proposed Imaging Core Services Center appear to be effective and efficient?

Does the proposed Imaging Core Services Center have the capacity to provide appropriate core services support for NCTN collaborative trials with other NCI-sponsored investigators and programs (e.g., NCI/DCTD early phase clinical trials programs)?

How well does it appear the proposed Imaging Core Services Center would provide quality assurance for imaging-related activities in applicable NCTN trials, including site and scanner qualification/calibration, review of imaging data for acceptability and protocol compliance, and central analysis and evaluation of images?

Does the proposed Imaging Core Services Center provide appropriate standardized and harmonized imaging processes and procedures that could be used by investigators participating in applicable NCTN trials using the Center's core services?

How well would the proposed Imaging Core Services Center be able to provide assistance with development of trials that have imaging as either a research objective or use imaging in support of other research goals for applicable NCTN trials?

How well does it appear that the proposed Imaging Core Services Center would be able to evaluate and assimilate evolving imaging technologies into future trials as well as to incorporate new commercial tools used for image processing and analysis as they become available? How well would the proposed Imaging Core Services Center be able to develop and maintain processes and procedures to conduct remote central imaging reads with the required scientific expertise? Would the proposed Imaging Core Services Center be able to provide appropriate procedures by which the priority and needs of imaging support could be adjusted for specific trials, including providing both "real-time" and "post-review" of images and providing expertise as to the best approach for a particular trial?

Does the proposed Imaging Core Services Center have an appropriate plan to incorporate a technical capacity to segregate access-limited collection for ongoing clinical trials from open-access collection when they are conducted by the NCTN?

2.6 Canadian Collaborating Clinical Trials Network Review Criteria

Only the review criteria described below (and the Additional Review Criteria – Overall listed in Part 2 – Section III.B.3.) will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

2.6.1 Overall Impact - Overall

Reviewers will provide an overall impact/priority score to reflect their assessment of the likelihood for the proposed Canadian Collaborating Clinical Trials Network to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the proposed Canadian Collaborating Clinical Trials Network).

2.6.2 Scored Review Criteria – Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a proposed Clinical Trials Network that by its nature may not be innovative but it may be essential to advance a field.

Significance

Does the proposed Canadian Collaborating Clinical Trials Network address an important problem or a critical barrier to progress in the field? If the aims of the proposed Canadian Collaborating Clinical Trials Network are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed Canadian Collaborating Clinical Trials Network? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? Given that the NCTN Program research projects/trials are collaborative and the proposed Canadian Collaborating Clinical Trials Network will be involved in collaborative activities (and irrespective of whether the applicants choose to use the multi-PD/PI option), do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the clinical research conducted by the proposed Canadian Collaborating Clinical Trials Network?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the proposed Canadian Collaborating Clinical Trials Network? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

Since the proposed Canadian Collaborating Clinical Trials Network will conduct clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, if applicable, justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the clinical research conducted by the proposed Canadian Collaborating Clinical Trials Network benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria - Overall

As applicable for the research that the Canadian Collaborating Clinical Trials Network applicant has proposed, reviewers will evaluate the following additional items A-C listed below while determining scientific and technical merit, and in providing an overall impact/priority score, **but will not give separate scores for these items**.

2.6.3 Additional Review Item A - Clinical Trial Development & Member Site Accrual Program

Overall Research Strategy: Does the applicant articulate a clear, well-developed, overall research strategy to achieve the stated clinical research goals with respect to complementing the research of the U.S. Network Groups of the NCTN Program? Is the research strategy for complementing research activities of the NCTN Program practical and feasible? Are the disease areas included in the applicant's overall research strategy appropriate and beneficial to the NCTN? How well would the applicant contribute to the development of and/or accrual to clinical trials in rare cancers?

Clinical Trial Quality: Do the clinical trials currently being conducted as well as those proposed by the applicant address important clinical treatment questions based on strong hypotheses and preliminary data and indicate that the applicant can contribute meaningfully in the NCTN? Do the trials use scientifically rigorous approaches to trial design with use of innovative approaches as appropriate and with sound justification? Do the trials contain integral and integrated translational science research questions that are appropriate and well-justified to answer specific research questions? Is the past record of results from the trials completed by the applicant scientifically important? Do these results provide new information that advances the field and provide guidance for future trials? Will (or have) the results lead (led) to meaningful practice changes for cancer care, supported FDA approvals of oncologic drugs or devices, changes in practice guidelines, or other meaningful impacts (e.g., phase 2 trials leading to phase 3 trials conducted by government or private sector, provision of important toxicity or dosing information)? Does the applicant's record of past results

indicate it will present and publish results from clinical trials it leads in a timely manner?

Senior Group Leadership for Clinical Trials Development: How complete and comprehensive is the expertise of the applicant's investigators overall and the Senior Leadership of the applicant's organization (operations, statistics, and data management)? How well can the PD(s)/PI(s) and the entire team of investigators assembled by the applicant provide scientific leadership for state-of-the-art early and late phase clinical trials? Will these investigators be able to work as a cohesive research team to efficiently and expeditiously develop and conduct NCTN clinical trials? Does the applicant have appropriate and clearly defined succession and transition plans for the senior leadership of the proposed Canadian Collaborating Clinical Trials Network?

Are the scope and authority of the senior leadership, Director of Operations position, and Executive/Advisory Committee for the organization clearly and appropriately addressed? Are the background and expertise of the proposed Director of Operations appropriate to oversee the operational management of the Group? Is the Director of Operations identified as key personnel in the application? Are the policies and procedures for institution/site membership (included in the Constitution and By-laws of the proposed Canadian Collaborating Clinical Trials Network) clear and appropriate for the NCTN Program?

If the application includes multiple PD(s)/PI(s), are the proposed leadership governance, organizational structure, and decision-making processes and interactions among the members of the leadership team for the application optimal for achieving the goals of the application and the overall NCTN Program?

Do the research experience and qualifications of the leadership of the applicant's Scientific Research Committees provide multi-disciplinary representation (e.g., medical oncology, radiation oncology, imaging, surgery, pathology, translational science, patient advocacy) across a broad range of diseases appropriate to the stated research goals? Are the experience and qualifications of the leadership of the applicant's Administrative Committees appropriate for development and oversight of the administrative management categories needed for conducting both early phase and especially late phase, multi-institutional clinical trials (e.g., support functions for trials including involvement of patient advocates, support programs for enrollment of underserved patient populations, financial management)?

Training and Investigator Leadership Mentoring/Training: Does the applicant have appropriate training programs for study chairs and Clinical Research Associates? Does the applicant have a mentorship/training program for new and junior investigators that provides opportunities for leadership of clinical trials (e.g., developing concepts for trial proposals, serving as study chairs for trials, participating in scientific committees in support or leadership roles, participating in other clinical trial activities) at appropriate levels as well as the potential to provide opportunities to these investigators to participate in the future in NCTN activities or initiatives?

Accrual Potential: Given its past track record of accrual, does the applicant have the potential to provide accrual to clinical trials conducted across the NCTN as a whole, especially in the applicant's stated areas/diseases of research interest, given the patient population of Canada? Does the applicant have the potential to contribute to accrual of Canadian minority and underserved patient populations to trials? Do the

applicant's member institutions/sites have the potential to help contribute to accrual of patients to NCTN clinical trials in rare tumors? Does the applicant demonstrate the ability to meet protocol-specified accrual goals in a timely manner for trials it conducts?

2.6.4 Additional Review Item B – Operational Management

Operational Structure, Policies, and Procedures: Are the organizational structure and management policies of the proposed Canadian Collaborating Clinical Trials Network clear and appropriate, including appropriate sound financial management policies and procedures for grant administration, subcontracting with collaborating organizations, purchase service agreements for member institutions/sites, and other related activities (e.g., laboratory testing needed for specific clinical trials)? Does the applicant incorporate procedures and tools that enhance coordination and productivity of operational activities including protocol development?

If the applicant proposes to include international institutions/sites as full members of the Canadian Collaborating Clinical Trials Network participating in NCTN trials, does the applicant propose appropriate monitoring plans for these sites as well as performance assessment monitoring to ensure that the NCTN-supported activities meet the same requirements regarding conduct of clinical trials expected of full U.S. member institutions/sites? If the applicant plans to enroll patients on clinical trials that are led by non-NCTN international clinical trials organizations, does the applicant propose appropriate policies and procedures to comply with the applicable regulations and requirements defined in the Terms and Conditions of Award for a Canadian Collaborating Clinical Trials Network?

Clinical Trial Operations - Development & Conduct: Are the structure and composition of trial proposal and protocol development teams proposed by the applicant appropriate? How well does the applicant's proposed trial proposal and protocol development process mesh with NCI standard tools and services, including use of Common Data Elements and standard Case Report Form modules? How appropriate are the proposed Canadian Collaborating Clinical Trials Network policies and standardized procedures for development and monitoring of trial proposals and protocols (including its tracking and project management systems) for ensuring that the applicant would meet NCI-mandated trial activation timelines for operational efficiency (i.e., Operational Efficiency Working Group or OEWG timelines)?

Does the proposed Canadian Collaborating Clinical Trials Network have appropriate key standard operating procedures related to a Data and Safety Monitoring Board Policy for Phase 3 trials and randomized Phase 2 trials, Data and Safety Monitoring Plans for Phase 1 and Phase 2 trials, Conflict of Interest Policies, and a Model Informed Consent Document for clinical trials that address how it will assure compliance with NCI, NIH, and HHS policies and all U.S. federal regulations regarding the protection of human subjects in clinical research as well as how it will address study monitoring and reporting (e.g., explain how these aspects are covered by the applicant's policies on Data and Safety and Monitoring, Data Sharing, Biospecimen Sharing, and Onsite Auditing)?

Does the applicant demonstrate that it can adhere to regulations regarding trial registration in the NCI Clinical Trials Reporting Program (CTRP) and in the U.S. National Library of Medicine (NLM) (www.clinicaltrials.gov) along with results reporting, as applicable? Does the applicant demonstrate that it can publish results in

peer-reviewed manuscripts in a timely manner consistent with NCTN Program requirements?

Compliance/Quality Assurance/Auditing: How well do the applicant's policies and procedures proposed for the conduct of NCTN-supported clinical trials comply with good clinical practice, including all applicable NCI, NIH, and HHS policies and U.S. federal regulations related to clinical trial research with human subjects, as well as with NCI/DCTD requirements related to the NCI/DCTD IP policy, NCI/DCTD CRADAs, CTAs, and CSA for clinical trials conducted under an NCI IND, NCI IDE, or NCI binding collaborative agreements? How appropriate are the applicant's proposed policies and procedures in meeting the onsite audit requirements of the NCI National Clinical Trials Monitoring Branch Guidelines (CTMB) for its member institutions/sites? How appropriate are the applicant's plans to appropriately address issues with member institutions/sites noted at the time of audit, including non-compliance, data quality, data reporting requirement, and timeliness of audits and re-audits? Does the applicant propose a quality assurance program that is adequately proactive in terms of ensuring ongoing quality control of data during trial conduct?

2.6.5 Additional Review Item C - Statistics Analysis and Data Management Program

Statistics Analysis: How well has the proposed Canadian Collaborating Clinical Trials Network demonstrated its ability and track record to provide appropriately designed, robust, statistical analysis plans for early phase and especially late phase, definitive, multi-institutional clinical trials in oncology, including integral and integrated biomarker/correlative science studies? Does it appear that the applicant has the necessary expertise and experience to incorporate new molecular and imaging biomarkers into the overall evaluation of NCTN trials appropriately? Are the procedures for sample size estimation, end point selection, and monitoring plans adequately described and justified? Are analytical techniques, procedures, and policies adequate, appropriate, and consistent with accepted standards? Does the sample of trial reports from the Report of Studies indicated appropriate and timely data and study analyses?

Data Management: Does the applicant describe well defined policies and procedures for data management of NCTN trials? How appropriate and robust are the data management and study monitoring practices of the organization? How well do the data management systems employed by the proposed SDMC use standard NCTN tools including the NCTN Common Data Management System (CDMS) and use of NCTN-approved Common Data Element (CDEs) from the caDSR, the NCTN Regulatory Support System (RSS), the NCTN Oncology Patient Enrollment Network (OPEN), the NCI/DCTD Clinical Data Update Systems (CDUS/CDS), the NCI Expedited Adverse Event Reporting System (AdEERs), the NCI Common Terminology Criteria for Adverse Events (CTCAE) for data management for NCTN trials, and trial registration in the NCI Clinical Trials Reporting Program (CTRP) and in the U.S. National Library of Medicine (NLM) (www.clinicaltrials.gov) along with results reporting, as applicable?

Does the proposed Canadian Collaborating Clinical Trials Network have appropriate procedures in place to ensure that the NCTN-supported activities are in compliance for the conduct of clinical trials with respect to NCI/DCTD's IP Option and NCI/DCTD's collaborative binding agreements for NCI/DCTD IND studies?

Does the Canadian Collaborating Clinical Trials Network have clear guidelines for institutions/sites related to data timeliness and metrics for data quality for the clinical

trial data and timely reporting to the institutions/sites of this information that indicate its potential to operative efficiently within the NCTN Program?

Do the facilities and equipment (including computer hardware and software) available as well as the information technology (IT) support for central storage, security, analysis and retrieval of clinical data for the proposed Canadian Collaborating Clinical Trials Network appear adequate for clinical trial research? Does the proposed Canadian Collaborating Clinical Trials Network have policies and procedures in place that are in compliance with federal regulations related to confidentiality of patient data, including Health Insurance Portability and Accountability Act (HIPAA) regulations for NCTN-related activities?

2.6.6 Additional Review Item D - Program for Collaborations & Participation in Collective Management

Collaborations with NCTN Network Groups, NCTN Programs/Initiatives, and other NCI-sponsored Programs/Investigators: Does the applicant have a track record for collaborations with other trial organizations and NCI-sponsored programs and investigators on clinical trials and translational science studies that demonstrates its potential for collaboration within the NCTN Program?

Collective Management Activities: Does that applicant have a track record that demonstrates that the members of its scientific leadership teams (i.e., scientific research committee members) actively participate in or can actively contribute to NCI clinical trial activities (e.g., disease-specific and modality-specific Scientific Steering Committees and related task forces or working Groups, Clinical Trials Planning Committees for meetings supported by the NCI disease-specific Steering Committees, participation in other NCI programs and initiatives related to clinical research)?

3. Additional Review Criteria – Overall – for All Key Components of the NCTN Program

As applicable for the clinical research that the applicant for a key component under the NCTN program has proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact/priority score, but will not give separate scores for these items.

3.1 Protections of Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Human Subjects Protection and Inclusion Guidelines.

3.2 Inclusion of Women, Minorities, and Children

When the proposed key component of the NCTN Program involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the Human Subjects Protection and Inclusion Guidelines.

3.3 Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

3.4 Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

3.5 Resubmissions, Renewals, and Revisions

Resubmissions, renewals, and revisions are not applicable at the current time for NCTN Program.

4. Additional Review Considerations – Overall – for All Key Components of the NCTN Program

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact/priority score.

4.1 Applications from Foreign Organizations

Applications from foreign organizations are not permitted for the following key components of the NCTN Program:

- Network Group Operations Centers
- Network Group Statistics and Data Management Centers
- Network Group Integrated Translational Science Support Center
- Network Lead Academic Participating Sites
- Network Radiotherapy and Imaging Core Services Centers

4.2 Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

4.3 Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms, if applicable, and 3) Genome Wide Association Studies (GWAS).

Applicants should review the information in the associated Funding Opportunity Announcement for the key component of the NCTN Program as to what needs to be submitted with respect to Resource Sharing Plans. However, final approval of all Resource Sharing Plans is determined by NCI/DCTD staff prior to the start date of the award:.

4.4 Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

C. Review Scoring

All scored components of the applications under the NCTN Program (i.e., the General Core Review Criteria Category and the Scored Additional Specific Review Criteria Categories) are scored numerically using the 9-point scale (1 =exceptional; 9=poor) scoring scale. Any of these components can be rated Not Recommended for Further Consideration (NRFC) if the component lacks significant and substantial merit.

For each discussed application, a final numerical impact/priority score from 1 (exceptional) to 9 (poor) will be given by each eligible SEP member (those without conflicts of interest). Each reviewer's overall impact/priority score will reflect his/her evaluation of the likelihood that the overall application will have a sustained powerful impact clinical research conducted by the NCTN.

Reviewers will focus on the scored categories, excluding any components not recommended for further consideration, in assigning the final overall impact/priority score. However, inclusion of components of poor quality will be considered evidence of poor judgment by the Principal Investigator(s) for the application. Reviewers do not have the option to select only the better components of an application to improve the overall impact/priority score.

If an application has many major weaknesses and therefore is likely to have low impact relative to all other applications normally received by the NCI, the review panel may choose to expedite the discussion/ or to not discuss the application. An entire application can be not recommended for further consideration if it lacks significant and substantial merit or presents serious ethical problems

in the protection of human subjects from research risks, use of vertebrate animals, biohazards, and/or select agents.

D. Review Summary Statement

The summary statement is the official record of the review of the application. The summary statement includes administrative information about the application, the final overall impact/priority score if the application was discussed, codes for the committee's determination of the adequacy of protections for human subjects and animal welfare (if applicable) and several narrative sections conveying the opinions and recommendations of the reviewers assigned to the application. The summary statement for applications discussed during the review meeting will include a Resume and Summary of Discussion, an Overall Critique section summarizing the strengths and weaknesses of the Overall Program, summary paragraphs listing the strengths and weaknesses and the final impact score/rating of each scored review criteria category, and resumes for human subjects, vertebrate animals (if applicable) and other additional review criteria, which are prepared by the SRO.

The summary statement will also contain individual reviewers' criteria category scores along with the essentially unedited critiques and other components of the application. Applicants should note that some reviewers may not have updated their critiques after the review meeting to reflect their final opinions after the discussion. However, the overall Resume and Summary of Discussion, the Overall Critique section, and the summary paragraphs prepared by the SRO will reflect the final opinions of the review committee.

For applications that are not discussed during the meeting, the summary statement may not include an Overall Critique section, but it will include the individual criteria category scores along with the essentially unedited critiques and other components of the application.

The SRO prepares the summary statements as soon as possible after each review meeting. Each summary statement is released as soon as it is completed. Depending on the number of applications that were reviewed in each SEP, summary statements are usually completed within 6 weeks after the review meeting. The Principal Investigator(s) can access the summary statement through the NIH eRA Commons (http://commons.era.nih.gov) after it has been finalized and released by the SRO. The summary statement will be transmitted to the National Cancer Advisory Board (NCAB) for second level peer review, to the NCI official file and to the appropriate NCI/DCTD staff.

E. Awards

The award and administration of key components of the NCTN Program are subject to the same policies and procedures as other research grants. These policies and cost principles are set forth in the current PHS Grants Policy Statement, other NIH and NCI issuances and Federal legislation and regulations.

Following review by the NCAB, scored applications are considered for funding by the NCI. NCI/DCTD program staff may administratively delete funding or reduce the duration of support for components of the key component that are judged by peer review to be less meritorious and/or nonessential to the conduct of the component.

F. Questions on Review Process

Questions related to the review of all NCTN Program key components review may be directed to:

Referral Officer
Division of Extramural Activities (DEA)
National Cancer Institute (NCI)
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892 (for U.S. Postal Service express or regular mail)

Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-3428
FAX: (301) 402- 0275
Email: ncirefof@dea.nci.nih.gov

Part 3: Guidelines for Submission of Continuing Applications (Annual Progress Reports)

I. Pre-Application Consultation and Application Submission Instructions

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 each of the 6 key components of the NCTN Program, i.e., the Annual Progress Reports. Applicants should consult the PHS 2590 at: http://grants.nih.gov/grants/funding/2590/2590.htm 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) may be submitted in the future under the Program.

The Progress Report should contain the basic information needed to allow the responsible Lead NCTN Program Director and Co-Program Directors/Project Scientists to monitor the progress and performance of all the key components.

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

SENDING A NON-COMPETING APPLICATION TO THE NIH:
Two (2) months before the start of the budget period, submit the original application, signed by the Principal Investigator(s) 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 U.S. 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 all key components of the NCTN Program are the same. 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 and should follow the requirements of the PHS2590 available at: http://grants.nih.gov/grants/funding/2590/2590.htm.

Providing the information in a standard format will allow both the key component of the NCTN Program and the responsible the responsible Lead NCTN Program Director and Co-Program Directors/Project Scientists to evaluate the progress of the key component more easily and to identify areas that need attention. The format may be varied somewhat, depending on the key component submitting the application; however, it should be similar to what is presented here. The instructions on the following pages cover application formats for all key components of the NCTN Program. 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.

It is anticipated that additional instructions/modification as to what information should be included in the annual progress report may be given to awardees of all the key components of the NCTN Program by the Lead NCTN Program Director prior to submission of the first annual progress report, especially with respect to streamlining the report.

A. Applications for all Key Components of the NCTN Program

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

The Research Plan for each Type 5 application should follow the requirements of the PHS2590. In all cases, brief and concise descriptions in the research plan of annual progress are encouraged. **Sections 1.1 and 1.2 on accrual and clinical trial performance described below apply only to the annual progress reports for the Network Group Operations Centers, the Canadian Collaborating Clinical Trials Network, and the Network Lead Academic Participating Sites. Section 1.3 on clinical trial development applies only to the annual progress reports for the Network Group Operations Centers and the Canadian Collaborating Clinical Trials Network.**

1.1 Accrual Performance & Accrual by Gender and Ethnicity/Race

Network Group Operations Centers, Network Academic Participating Sites, and the Canadian Collaborating Clinical Trials Network 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. Accrual for all studies (treatment and advanced imaging) and per patient biospecimen collection on trials that were open during the annual project period should be reported summarized by major disease category and trial phase. A similar report summing accrual across all disease areas should also be provided. Total accrual provided by the Network Group Operation Center's or the Canadian Collaborating Clinical Trials Network for all its member institutions/sites (or by the Network Lead Academic Participating Site for its sites and affiliate(s) for which it provides complete management serviced) broken down by sex/gender and ethnicity/race for all accrual across all NCTN trials should also be presented using the standard Inclusion Enrollment Report format provided in the PHS2590. This table should be modified to show sex/gender and ethnicity/race breakdown in accrual for the previous 3 years (if applicable) in addition to the current funding period summarized by major disease category only. A summary table for accrual across all diseases should also be provided. Distribution of subjects should NOT be provided by individual study or trial phase.

Summary Accrual Table for ALL Studies by a Network Group Operations Center or Canadian Collaborating Clinical Trials Network by Annual Funding Period - (Annual Grant Year)

Disease Area: _____ (AND PROVIDE REPORT SUMMARIZING ACCRUAL ACROSS ALL DISEASE AREAS)

Time Period (Calendar Dates) for Actual Accrual: _____

Time Period (Calendar Dates) for Projected Accrual: _____

TYPE OF STUDY	PILOT Treatment or Advanced Imaging Studies (% Screened Pts)	PHASE 1 Treatment or Advanced Imaging Studies (% Screened Pts)	PHASE 2 Treatment or Advanced Imaging Studies (% Screened Pts)	PHASE 3 Treatment or Advanced Imaging Studies (% Screened Pts)	Other Per Patient Special or Biospecimen Collection (% Biospecimen Pts)	ALL Treatment or Advanced Imaging Studies
Patients Enrolled in Current Period on All NCTN Studies Led by Network Group: **Actual (projected) Accrual - Credited to Group** **Actual (projected) Accrual - Credited to Other Groups** ========== **Patients Enrolled in Current Period on All NCTN Studies NOT Led by Network Group:** **Actual (projected) Accrual - Credited to Group**						
Total Patients in Follow-Up on All NCTN Studies Led by Network Group **Actual (projected) – Credited to Any Group**						

- 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 and any other trials that do not fit into the other categories listed.
- 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 applicant 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 an applicant does not make projections by certain categories (e.g., the applicant projects data only by "all studies" not by specific categories of studies, the applicant 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 applicant 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

Summary Accrual Table for ALL Studies by a Lead Academic Participating Site (LAPS) by Annual Funding Period - (Annual Grant Year)

Disease Area: _____ (AND PROVIDE REPORT SUMMARIZING ACCRUAL ACROSS ALL DISEASE AREAS)

Time Period (Calendar Dates) for Actual Accrual: _____

Time Period (Calendar Dates) for Projected Accrual: _____

TYPE OF STUDY	PILOT Treatment or Advanced Imaging Studies (% Screened Pts)	PHASE 1 Treatment or Advanced Imaging Studies (% Screened Pts)	PHASE 2 Treatment or Advanced Imaging Studies (% Screened Pts)	PHASE 3 Treatment or Advanced Imaging Studies (% Screened Pts)	Other Per Patient Special or Biospecimen Collection (% Biospecimen Pts)	ALL Treatment or Advanced Imaging Studies
Patients Enrolled in Current Period on All NCTN Studies by LAPS & Affiliates: **Actual (projected) Accrual - Lead Center/Components** **Actual (projected) Accrual - Affiliates (Affiliates are those completely managed by LAPS and included in the LAPS award**						

- 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 and any other trials that do not fit into the other categories listed.
- 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 applicant 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 an applicant does not make projections by certain categories (e.g., the applicant projects data only by "all studies" not by specific categories of studies, the applicant 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 applicant 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

1.2 Clinical Trial Performance

Network Group Operations Centers (or Network Lead Academic Participating Sites) should also summarize the timeliness of AdEERS reports submission, the date of the last audit for institutional members (or Lead Academic Participating Site), compliance with specimen submission, etc. in the annual report.

The NCI-Guidelines for Onsite 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 Network Group Operations Center's compliance with this requirement, each Network Group Operations Center should conduct an annual review of all audits performed and provide in the non-competing continuation application an accounting similar to the table provided for new applications. Any significant audit problems, as defined in the Clinical Trials Monitoring Branch Guidelines for Onsite Auditing, encountered during the preceding year should be fully described and the corrective action(s) taken explained for any Network Group Operations Center's institutional/site members (including and Network Lead Academic Participating Site).

The Network Lead Academic Participating Sites should also provide a similar report for any audits conducted during the reporting period for the main academic site and any individual components that are audited as well as any affiliate(s) for which the main academic site provides complete management services.

1.3 Timelines for Protocol Development, Trial Activation, and Trial Completion

The annual progress report should list protocol development activities during the current funding period for the Network Group Operations Centers and the Canadian Collaborating Clinical Trials Network, in terms of submitted and approved Letters of Intent (LOIs) and Concepts, submitted and approved protocols, activated and completed trials with associated OEWG timelines. This table should be organized by major disease category and then by trial phase.

1.4 Progress & Summary of Research Accomplishments of Key Components of NCTN Program

The annual progress report for each key component of the NCTN Program should report on the component's progress regarding the goals and activities outlined in the research plan of the corresponding Type 1 application (or Type 2 application, if applicable in the future). This should include information on how the key component has contributed to the goals of the NCTN Program with emphasis on what the key component has accomplished in the current funding period.

The application should provide a brief, narrative description of the contributions of the key component to NCTN clinical trials and research goals and other NCTN Program activities and initiatives, including important collaborations, during the current funding period. This summary narrative should be adequate to convey the important facets of the activity and any significant findings (e.g., patients accrued, open dose level, important toxicities observed, pharmacokinetic findings, anti-tumor activity observed, scientific leadership on new trials, translational science advances, etc.).

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. Only those publications resulting directly from activities of the key component of the NCTN Program funded by the Cooperative Agreement should be reported.

1.5 Key Personnel and Training on Human Subjects Protection for New Key Personnel

Each key component of the NCTN Program should submit a list of key personnel, highlighting any changes. In addition, the key component should indicate the type of training course/program on human subjects protection completed by each new key personnel member.

2. Budget (Annual Progress Report – Type 5 Application)

2.1 General Budget Information

The budget included in the non-competing application should be similar to that provided in the new application, except it is limited to the upcoming 12-month funding period. A Common Budget Outline, similar to that required for a new application may also be requested by the NCI/DCTD on an ad hoc basis with the Annual Progress Report, but this is not expected to be provided annually.

2.2 Non-Competing Budget Adjustments

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 a change in the funds available to the government for distribution.

Requests for the adjustments are initiated by the key component, and are based on such factors as increased or decreased level of activity at an institution. The effect of any such adjustment 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 Lead NCTN Program Director. Funding adjustments are facilitated by the NCI/DCTD Senior Program Specialist.

Process: Informal administrative discussions about a contemplated adjustments or carryover may take place between the NCI/DCTD Senior Program Specialist and administrator for the key component of the NCTN Program, and may be initiated by either party. The NCI/DCTD Senior Program Specialist is responsible for providing an estimate of available budget for the Program as a whole and for the various key components for the Program, based on discussions with the Lead NCTN Program Director. Similarly, the Lead NCTN Program Director and Co-Program Directors/Project Scientists are typically in ongoing discussions with the key components of the NCTN Program on their budgetary needs and scientific priorities.

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 any request for redistribution or carryover. 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 NCI/DCTD for Key Components of the NCTN Program

Adjustments may be made by NCI/DCTD in the funding of the key component of the NCTN Program at the time of a non-competing continuation award. Such adjustments provide the NCI with the ability to ensure that available funds are put to their best use. Authority to effect adjustments in funding rests with the Lead NCTN Program Director, who works in conjunction with the NCI/DCTD Senior Program Specialist.

Budget commitments for the non-competing years are based upon the funding level for the competing year. Increases or decreases in funding for any key component of the NCTN Program 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 awardee, particularly with respect to funding restricted for use to cover data collection/management and biospecimen collection related to enrollment of patients on clinical trials and their follow-up and/or a change in the funds available to the government for distribution.

In particular, the Network Lead Academic Participating Sites will undergo assessment with possible decrement in funding after 3-years of performance based on the awardee's accrual to NCTN trials.

B. Notification of International Involvement in Key Components of NCTN Program

The key component of the NCTN Program must alert the NCI/DCTD Senior Program Specialist for the NCTN Program and to the Office of Grants Administration (OGA) when a non-competing application involves any new international (non- U.S.) component, regardless of whether the component receives federal funding under the awardee's grant. In such cases, advance clearance from the U.S. Department of State is required for each non- U.S. component prior to the start date of the award. The information required by U.S. Department of State is listed below (this information should also include all non- U.S. subcontracts).

- Estimated annual Total Cost dollar award for the non- U.S. component
- Name, organization, city, and country of the International (non- U.S.) 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

In addition, for international sites collaborating with a U.S. Network Group or Canadian Collaborating Clinical Trials Network on trials sponsored under the NCTN Program (regardless of whether the U.S. or Canadian organization or the international organization is leading the trial and regardless of whether any funding is being provided), U.S. Department of State clearance is required for the non-U.S. country as clinical data is being passed between the U.S./Canadian organization supported under the NCTN Program and the other country.

Part 4: Appendices

I. NCI/DCTD Policies for the NCTN Program (URLs to Websites)

A. NCI National Clinical Trials Network Program (NCTN) Guidelines
http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

B. Investigator's Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI)
http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

C. NCI-CTMB Guidelines for Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU)
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm

D. IP Option Policy:
http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations
http://ctep.cancer.gov/industryCollaborations2/default.htm

E. Operational Efficiency Working Group (OEWG) Policy and Timelines:
http://ctep.cancer.gov/SpotlightOn/OEWG.htm

F. Policy on Contract Review
http://ctep.cancer.gov/industryCollaborations2/guidelines.htm
(Under NCI Standard Protocol Language for Collaborative Agreements)

G. Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies
http://ctep.cancer.gov/protocolDevelopment/default.htm#cde_data_pol_cdus
(Under CDE / Data policies / CDUS – Slow Accrual Guidelines for Phase 3 Trials)

H. Adverse Event Expedited Reporting System (AdEERS)
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

I. Information on Common Data Elements (CDE) Approved for Use in CTEP-sponsored Clinical Trials
https://cabig.nci.nih.gov/community/concepts/caDSR/

J. NCI's Common Terminology Criteria for Adverse Events (CTCAE)
http://ctep.cancer.gov/reporting/ctc.html

K. NCI Clinical Trials Cooperative Group Program Guidelines for the Development, Conduct and Analysis of Clinical Trials with International Collaborating Institutions (Under Guidelines & Policies**)**
http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

L. CTEP Conflict of Interest Policy for Cooperative Group Phase 3 Clinical Trials (Under Guidelines and Policies**)** http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

M. NCI Templates for Simplified Model Informed Consent Documents for NCTN Trials
http://cancer.gov/clinicaltrials/patientsafety/simplification-of-informed-consent-docs/page3

II. Suggested Formats - Tables for New & Non-Competing Applications

Current and/or relevant information in the past 5-6 years should be used in the tables unless otherwise indicated.

A. Network Group Operations Centers & Canadian Collaborating Clinical Trials Network List of Tables with Suggested Formats

Table 1. Key Leadership Staffing As of Date of Application Preparation: MM/DD/YYYY

Staffing Category for Network Group Operations Center	Member Status	Member Name	Title	Institution	Length of Service in Position
Executive or Oversight Committee (All members should be listed)	Chair				
	Vice-Chair				
	Member				
	Member etc.				
Data and Safety Monitoring Board or Data Monitoring Committee (All members should be listed)	Chair				
	Vice-Chair				
	Member				
	Member etc.				
Scientific Committee #1 (List Chair and Vice-Chair(s) only)	Chair				
	Vice-Chair				
Scientific Committee #2 (List Chair and Vice-Chair(s) only)	Chair				
	Vice-Chair				
Administrative Committee #1 (List Chair and Vice-Chair(s) only)	Chair				
	Vice-Chair				
Administrative Committee #2 (List Chair and Vice-Chair(s) only)	Chair				
	Vice-Chair				

etc.

Table 2. Primary Scientific Achievements for Trials by Disease Area, Trial Phase, & Trial # from MM/DD/YYYY to MM/DD/YYYY (Include primary scientific achievements that were reported only in the past 5-6 years)

Cancer Site	Trial Phase	Year (Publication or FDA Indication or Other)	Trial Number & Brief Title	Experimental Agent or Regimen	Primary Endpoint Result - Indication	Manuscript or Abstract Reference	Incorporated into Practice Guidelines (Type Guidelines, Year)?	FDA-Approved Labeling Indication or Other Important Impact (Describe)?	Date Trial Activation	Date Trial Closure	Total Accrual

etc.

Table 3. Other Important Achievements for Trials by Disease Area, Trial Phase, & Trial # from MM/DD/YYYY to MM/DD/YYYY

(Include important achievements that were reported only in the past 5-6 years. QOL funded by DCP CCOP Research Base grant should not be included in this table, but can be referenced/described in the collaborations section of the Research Plan)

Cancer Site	Trial Phase	Year (Publication)	Trial Number & Brief Title	Experimental Agent or Regimen	Secondary Endpoint or Sub-study Result	Manuscript or Abstract Reference	Description of Importance from Secondary Endpoint or Sub-study	Date Trial Activation	Date Trial Closure	Total Accrual
etc.										

Table 4. List of Approved Applications for Use of "Banked" Biospecimens from Applicant Clinical Trials from MM/DD/YYYY to MM/DD/YYYY (Include approved applications only over the past 5-6 years)

Cancer Site	Year of Request	Trial Phase	Trial Number & Brief Title	Brief Description of Request	# and Type Samples Provided	Date Samples Provided	Reference to Publication Resulting from Approved Request or Other Result (or Pending Publication)
etc.							

Table 5. Summary Accrual for All Clinical Trials (All Cancers) by Trial Phase by Members of the Applicant Network Group (Include accrual only over the past 5-6 years)

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Treatment Studies	PHASE 1 Tx Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies		
			Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total
Accrual by **Applicant Members to Trials Led** by Applicant Network Group Operations Center											
Accrual **by Applicant Members to Trials NOT Led** by Applicant Network Group Operations Center											

TOTALS:

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Treatment Studies	PHASE 1 Tx Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies		
			Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total
Per Patient Biospecimen Collection by **Applicant Members to Trials Led** by Applicant Network Group Operations Center	**Note:** This is # Pts with ≥1 specimen(s) (NOT # of specimens)										

Accrual figures should include eligible & ineligible patients. Screened patients refer to patients who are screened only for studies that have screening as a distinct part of the protocol - patients are consented and screened as part of the trial but may not undergo randomization/intervention because the screening excludes them from that part of the study (i.e., patient's tumor did not have the required characteristic for treatments if the tumor is tested as part of the study). Pilot studies refer to studies testing the feasibility of administration of the therapeutic intervention/approach and/or are explicitly determined to be "pilot studies" at the time of NCI/DCTD approval.

Table 6. Summary Accrual By Major Cancer Category and Trial Phase by Members of the Applicant Network Group Operations Center to All Trials
(Include accrual only over the past 5-6 years)

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Treatment Studies	PHASE 1 Treatment Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies		
			Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients
Cancer Type #1											
Accrual by **Applicant Members to Trials Led** by Applicant Network Group Operations Center											
Accrual by **Applicant Members to Trials NOT Led** by Applicant Network Group Operations Center											
Total for Cancer Type # 1											
Cancer Type #2											
Accrual by **Applicant Members to Trials Led** by Applicant Network Group Operations Center											
Accrual by **Applicant Members to Trials Led** by Applicant Network Group Operations Center											
Total for Cancer Type # 2											
etc.											
Grand TOTAL (All Diseases)											

Table 7. Summary Accrual By Major Cancer Category and Trial Phase to All Trials Led by Applicant Network Group by Members of the Applicant Network Group & Other Groups
(Include accrual only over the past 5-6 years)

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Tx Studies	PHASE 1 Treatment Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies (includes Phase 1/2 Studies)		
			Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients
Accrual by **Applicant Members to Trials Led** by Applicant Network Group Operations Center											
Accrual by **Members of Other Groups to Trials Led** by Applicant Network Group Operations Center											
Total for Cancer Type # 1											
Cancer Type #2											
Accrual by **Applicant Members to Trials Led** by Applicant Network Group Operations Center											
Accrual by **Members of Other Groups to Trials Led** by Applicant Network Group Operations Center											
Total for Cancer Type # 2											
etc.											
Grand TOTAL (All Diseases)											

Table 8. Operational Timelines for Development of Clinical Trial Proposals (LOIs and Concepts) Submitted after 4/1/2010 to Date of Application Preparation (4/1/2010 to MM/DD/YYYY) Sorted by Major Cancer Category, Start Date, and Trial #

(4/1/2010 is used as start date as prior to that date, NCI/DCTD did not have standard definitions for milestones in the study development process)

IND Studies –
Pilot and Phase 1

Cancer Site	Trial Phase	LOI or Concept	Trial Number & Brief Title	Operational Efficiency Start Date for LOI/Concept	Date of LOI/Concept Approval	Date 1st Protocol Submission	# Protocol Revisions	Date NCI/DCTD Approval	Date Study Open for Patient Accrual	# Days in Development	Comments
etc.											

Median Days in Development for IND Studies – All Pilot & Phase 1: _____

IND Studies - Phase 2

Cancer Site	Trial Phase	LOI or Concept	Trial Number & Brief Title	Operational Efficiency Start Date for LOI/Concept	Date of LOI/Concept Approval	Date 1st Protocol Submission	# Protocol Revisions	Date NCI/DCTD Approval	Date Study Open for Patient Accrual	# Days in Development	Comments
etc.											

Median Days in Development for IND Studies - Phase 2: _____

IND Studies - Phase 3

Cancer Site	Trial Phase	LOI or Concept	Trial Number & Brief Title	Operational Efficiency Start Date for LOI/Concept	Date of LOI/Concept Approval	Date 1st Protocol Submission	# Protocol Revisions	Date NCI/DCTD Approval	Date Study Open for Patient Accrual	# Days in Development	Comments
etc.											

Median Days in Development for IND Studies - Phase 3:_____

Median Days in Development for All IND Studies:_____

Create the Same Tables for NON-IND Studies……..

Median Days in Development for ALL Studies: _____

Table 9. Operational Timelines for Trial Conduct by Major Cancer Category & Trial Phase/#
Sorted by Major Cancer Category, Start Date, and Trial # from MM/DD/YYYY to MM/DD/YYYY
(Include only trials open during the past 5-6 year period that are still accruing patients or that are temporarily closed to accrual and/or treatment)

Cancer Site	Trial Phase	LOI or Concept	Trial Number & Brief Title	Date Study Open for Patient Accrual*	Trial Status (Open or Temporarily Closed to Accrual and/or Tx)	Sample Size	Accrual to Date	% Projected Monthly Accrual Rate	Estimated Study Closure Date (i.e., Closed to Accrual)	Anticipated Primary Completion Date **
etc.										

*For studies with the initial LOI/Concept submitted prior to 4/1/2010, use the date of activation of the trial for the "Date Study Open for Patient Accrual" column in the table. For studies with the initial LOI/Concept submitted after 4/1/2010, the NCI/DCTD OEWG definition used to define the date the study was open for patient enrollment should be used for this column in the table.

** Anticipated primary completion date follows the definition used for the NCI Clinical Trials Reporting Program (CTRP) and www.clinicaltrials.gov.

Table 10. Operational Timelines for Trial Completion by Major Cancer Category & Trial Phase/#
Sorted by Major Cancer Category, Start Date, and Trial # from MM/DD/YYYY to MM/DD/YYYY
(Include only trials closed to accrual during the past 5-6 year period)

Cancer Site	Trial Phase	Trial Number & Brief Title	Date Study Open for Patient Accrual	Date Study Closed	Sample Size	Total Accrual	Anticipated Primary Completion Date **	Results Reporting Date for CTRP/FDAAA	Publication Submission Date	Publication Date	Publication Reference	Comments
etc.												

*For studies with the initial LOI/Concept submitted prior to 4/1/2010, use the date of activation of the trial for the "Date Study Open for Patient Accrual" column in the table. For studies with the initial LOI/Concept submitted after 4/1/2010, the NCI/DCTD OEWG definition used to define the date the study was open for patient enrollment should be used for this column in the table.

** Anticipated primary completion date follows the definition used for the NCI Clinical Trials Reporting Program (CTRP) and www.clinicaltrials.gov.

Table 11. Summary of Onsite Auditing Activity for Clinical Trials

The NCI-CTMB Guidelines for 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 (Institutional NCI Code)	Site Type	Membership Date	Current Site Status	Status Date	Accrual _____*	Accrual _____ *	Accrual _____ *	Accrual Projected for upcoming year _____ *	Date Last Audit	Date Next Proposed Audit
Name	Main Member		Active	2008						
Name	Affiliate		Active	2009						
Name	Affiliate		Terminated	2009						
Name	NIA		Active	2010						
Name	CCOP		Active	2011						
Name	CCOP component		Withdrawn	2008						
Name	CCOP component		Active	2009						
Name	Main Member		Active	2010						

* Fill in accrual blank with year (this should cover the preceding 36 months, e.g. 2009, 2010, 2011). Please Note: The actual "Date of Last Audit" for any Participating Site listed as "Active" on the Group roster should be provided, even if site has not been audited in the past 3 years.

B. Network Group Statistics & Data Management Centers & Canadian Collaborating Clinical Trials Network – List of Tables with Suggest Formats

Current and/or relevant information in the past 5-6 years should be used in the tables unless otherwise indicated.

Table 1. Key Leadership Staffing for the SDMC – Use the same format and reporting date as in the table for the Network Group Operations Center Application

Table 2. Summary of General Data Timeliness* for Open Studies from MM/DD/YYYY to MM/DD/YYYY for Open Studies Led by the Applicant Network Group (Include only for studies open over the past 5-6 years)

Phase Trials	Year	Accrual	%Eligible Patients	Eligibility CRF Reporting % Timeliness	Eligibility CRF Reporting % Accuracy	Treatment Cycle # (or Equivalent) % Timeliness	Treatment Cycle # (or Equivalent) % Accuracy	Off-Study CRF Reporting % Timeliness	Off-Study CRF Reporting % Accuracy
Phase 1	1								
	2								
	3								
	4								
	5								
	6								
Phase 2	1								
	2								
	3								
	4								
	5								
	6								
Phase 3	1								
	2								
	3								
	4								
	5								
	6								

*Applicant team can select major CRF categories that it believes represent a measure of the submission of general data timeliness to its trials (the columns above are examples only). Also, table may report general data timeliness by members of applicant Network Group as well as by non-members of the applicant Network Group to trials led by the applicant.

Table 3. Summary of Data Quality and Data Timeliness – Serious AE Reporting for All Member Sites for Trials Led by the Applicant Network Group from MM/DD/YYYY to MM/DD/YYYY

Institution Name: _____ (NCI Site ID #: _____; – TABLE FOR EACH MEMBER INSTITUTION/SITE

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 (include sub-columns for IRB/ICC, Pharmacy, Patient Case Review)
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%	1/6/2007	Unacceptable
4	13	2.0%	98.2%	99.0%	99.0%	1/23/2008	Acceptable
5	40	3.0%	90.2%	95.0%	92.0%	1/23/2011	Acceptable
6	N/A	N/A	N/A	N/A	N/A	N/A	

Summary Statistics for All Member Institutions/Sites for Applicant Network Group

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.

C. Network Lead Academic Participating Sites - List of Tables with Suggested Formats

Current and/or relevant information in the past 5-6 years should be used in the tables unless otherwise indicated. Academic Site applicants should include accrual information from participation in the former NCI Clinical Trials Cooperative Group Program. Only if the Academic Site applicant did not participate in the former NCI Clinical Trials Cooperative Group Program should the applicant provide accrual information from cancer clinical treatment trials supported by an equivalent non-profit clinical trials network organization.

Table 1. Key Leadership Staffing for Network Group(s) As of Date of Application Preparation: MM/DD/YYYY

Network Group	Network Group Activity	Academic Member Status	Academic Member Name	Academic Member Title & Discipline	Length of Service in Position
Network Group #1	Breast Scientific Committee	Chair			
Network Group #1	GI Scientific Committee	Vice-Chair			
Network Group #2	Executive Committee	Member			
Network Group #3	Data and Safety Monitoring Board	Member			
etc.					

Table 2. Primary Scientific Achievements for Trials by Major Cancer Category, Trial Phase, & Trial # from MM/DD/YYYY to MM/DD/YYYY

(Include primary scientific achievements that were reported only in the past 5-6 years)

Cancer Site	Trial Phase	Year (Publication or FDA Indication or Other Impact)	Network Group, Trial Number & Brief Title	Manuscript or Abstract Reference	Important Impact of Primary Scientific Achievement? (Brief Description)	Contribution by Academic Site Member
etc.						

Table 3. Other Important Achievements for Trials by Major Cancer Category, Trial Phase, & Trial # from MM/DD/YYYY to MM/DD/YYYY

(Include other important achievements that were reported only in the past 5-6 years. QOL funded by DCP CCOP Research Base grant should not be included in this table, but can be referenced/described in the collaborations section of the Research Plan)

Cancer Site	Trial Phase	Year (Publication or FDA Indication or Other Impact)	Network Group, Trial Number & Brief Title	Manuscript or Abstract Reference	Important Impact of Other Important Achievement? (Brief Description)	Contribution by Academic Site Member
etc.						

Table 4. List of Approved Applications from Academic Site Applicant for Use of "Banked" Biospecimens from Phase 2 and Phase 3 Clinical Trials from MM/DD/YYYY to MM/DD/YYYY

(Include approved applications only over the past 5-6 years)

Cancer Site	Year of Request	Trial Phase	Trial Number & Brief Title	Brief Description of Approved Request	# and Type Samples Provided	Date Samples Provided	Reference to Publication Resulting from Approved Request or Other Result (or Pending Publication)
etc.							

Table 5. Summary Accrual by Lead Academic Participating Site Applicant for All Clinical Trials for All Cancers by Trial Phase (Include accrual only over the past 5-6 years)

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Treatment Studies	PHASE 1 Tx Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies		
			Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total
Accrual by Main Lead Academic Center											
Accrual by Lead Academic Component #1											
Accrual by Affiliate(s) if part of application											

TOTALS:

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Treatment Studies	PHASE 1 Tx Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies		
			Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total	Screened Only	Screened & Intervention	Total
Per Patient Biospecimen Collection Accrual by Main Lead Academic Center	**Note:** This is # Pts with ≥1 specimen(s) (NOT # of specimens)										
Per Patient Biospecimen Collection by Lead Academic Component #1	**Note:** This is # Pts with ≥1 specimen(s) (NOT # of specimens)										
Per Patient Biospecimen Collection by Affiliate(s) if part of application											

Accrual figures should include eligible & ineligible patients. Screened patients refer to patients who are screened only for studies that have screening as a distinct part of the protocol - patients are consented and screened as part of the trial but may not undergo randomization/intervention because the screening excludes them from that part of the study (i.e., patient's tumor did not have the required characteristic for treatments if the tumor is tested as part of the study). Pilot studies refer to studies testing the feasibility of administration of the therapeutic intervention/approach and/or are explicitly determined to be "pilot studies" at the time of NCI/DCTD approval.

Table 6. Summary Accrual by Lead Academic Participating Site Applicant Components by Major Cancer Category and Trial Phase
(Include accrual only over the past 5-6 years)

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Treatment Studies	PHASE 1 Treatment Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies		
			Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients
Cancer Type #1											
Accrual by Main Lead Academic Center											
Accrual by Lead Academic Component #1											
Accrual by Affiliate(s) if part of application											
Total for Cancer Type # 1											
Cancer Type #2											
Accrual by Main Lead Academic Center											
Accrual by Lead Academic Component #1											
Accrual by Affiliate(s) if part of application											
Total for Cancer Type # 2											
etc.											
Grand TOTAL (All Diseases)											

Table 7. Summary Accrual by Major Cancer Category and Trial Phase to All Trials
(Note: This table is a condensed summary of Table 6 and is optional)

Type Study Accrual Accrual Period (MM/DD/YYYY to MM/DD/YYYY)	PILOT Tx Studies	PHASE 1 Treatment Studies	PHASE 2 Treatment Studies (includes Phase 1/2 Studies)			PHASE 3 Treatment Studies (includes Phase 2/3 Studies)			All Treatment Studies (includes Phase 1/2 Studies)		
			Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients	Screened Only	Screened & Intervention	Total Patients
Total for Cancer Type # 1											
Total for Cancer Type # 2											
etc.											
Grand TOTAL (All Diseases)											

Table 8. Operational Timelines for Activation of Clinical Trial Proposals at Academic Participating Site Applicant (at Academic Center Components & Affiliates)

Academic Site or Affiliate	Cancer Site	Trial Phase	Trial Number & Brief Title	Date Study Open for Patient Accrual	Date Study Submitted for Evaluation at Academic Center	Date Study Opened at Academic Center	# Days to Activation at Academic Center	Accrual to Date	Comments
	etc.								

D. Network RT & Imaging Core Services Centers – List of Tables with Suggested Formats

Table 1. Summary of Clinical Trials Using RT Core Services by Major Cancer Category, Trial Phase, & Trial

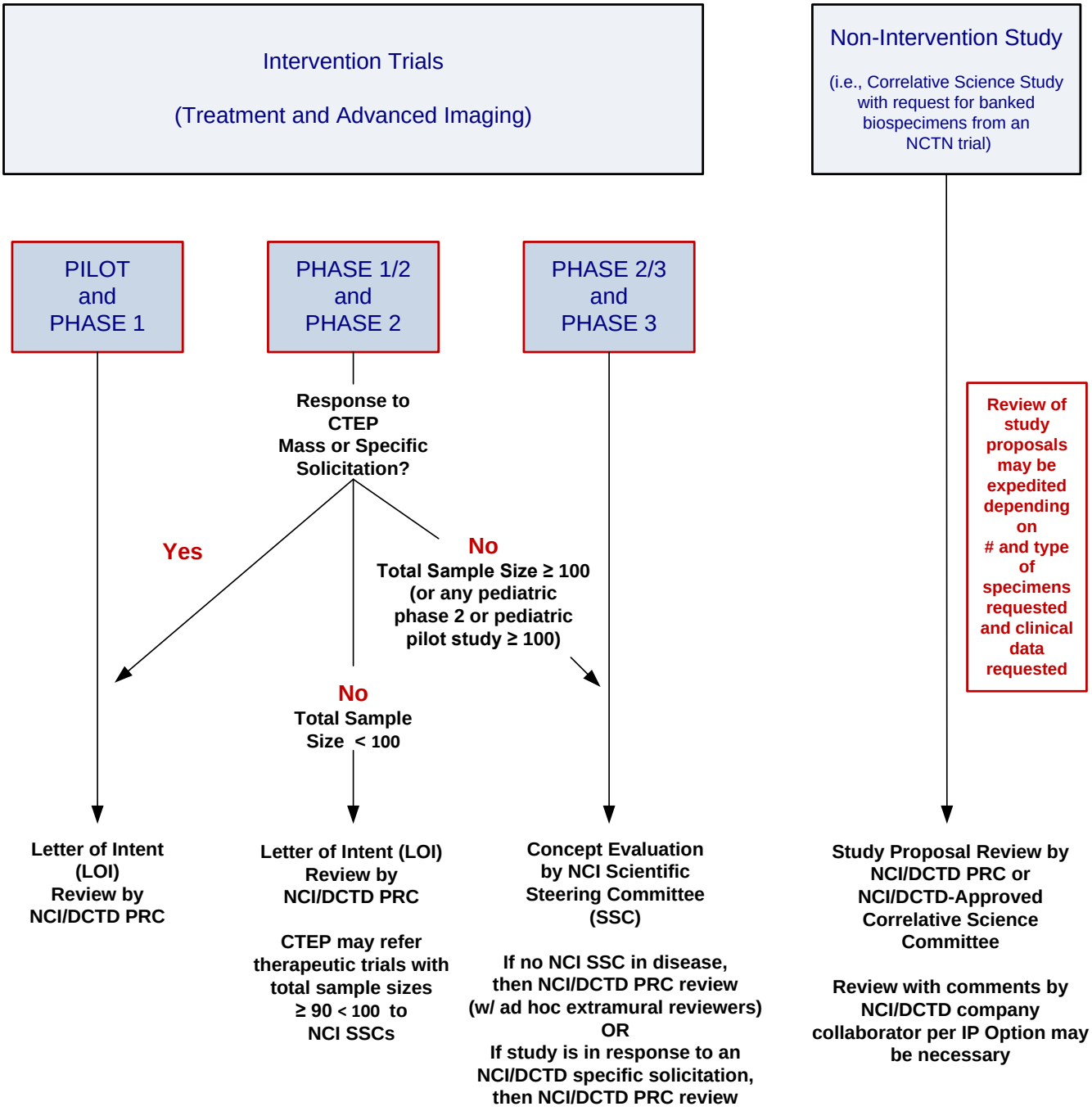
Cancer Site	Trial Phase	Trial Number & Brief Title	Date Study Open for Patient Accrual	Sample Size	Total Accrual to Date	Description of Support Provided by Radiotherapy Core Center
etc.						

Table 2. Summary of Clinical Trials Using Imaging Core Services by Major Cancer Category, Trial Phase, & Trial

Cancer Site	Trial Phase	Trial Number & Brief Title	Date Study Open for Patient Accrual	Sample Size	Total Accrual to Date	Description of Support Provided by Imaging Core Center
etc.						

III. Schema of NCI/DCTD Study Proposal Review/Evaluation

NCI/DCTD Review/Evaluation Process for NCTN Study Proposals



IV. Cost Components for Budget Preparation for Network Group Operations Centers and SDMCs, Network Lead Academic Participating Sites, and Canadian Collaboration Clinical Trials Network New Applications

A. Guidelines for General Budget Inputs for Estimating Total Cost Budget Requests – Type 1 Application

TOTAL COST Credit Value for Type 1 Applications: $500

"Per Case Management" Funding Category	Credit Multiplier	Total Cost Value (Total Cost Credit Value of $500 x Credit Multiplier)	Intervention or Non-Intervention Category
High Performance Intervention - Therapeutic	8	$4,000	Intervention
Basic Intervention (Including Therapeutic Pilot Studies) – Therapeutic	4.5	$2,250	Intervention
Basic Intervention - Advanced Imaging	2	$1,000	Intervention
Screening	1	$500	Non-Intervention
Biospecimen	1	$500	Non-Intervention
Special	N/A	Determined on trial-specific basis by NCI/DCTD	N/A

Total Cost for Financial Management Oversight Based on % of Total Cost of "Per Case Management" Funding for Intervention and Non-Intervention Categories (Suggested Range for %)	Intervention Per Case Category	Non-Intervention Per Case Category
Adult Network Groups	10% to 20%	5% to 10%
Pediatric Network Groups	10% to 20%	5% to 10%
Lead Academic Participating Sites - Network	10% to 20%	5% to 10%

Total Cost for Operations Center and SDMC Infrastructure Based on $ Multiplier for Accrual to Network Group Trials Per Patient Enrolled for Intervention and Non-Intervention Categories (Suggested Range for $ Multiplier)	Intervention Accrual Category (Per Enrolled Patient)	Non-Intervention Accrual Category (Per Enrolled Patient)
Operations & SDMCs for Network Groups & Canadian Network	$2,500 to $3,300	$250 to $500

Total Cost for Scientific Leadership/Coordination at Lead Academic Participating Sites & Pediatric High-Performance Sites Based on % of Total Cost for "Per Case Mgt" Funding for Intervention and Non-Intervention Categories (Suggested Range for %)	Intervention Per Case Category	Non-Intervention Per Case Category
Network Lead Academic Participating Sites	10% to 20%	5% to 10%
Pediatric Network Groups	10% to 20%	5% to 10%

Suggested Range for Pediatric Threshold for "High-Performance Intervention Per Case Mgt" Funding as % of Total Intervention Accrual (Therapeutic Enrollments + 50% Advanced Imaging Enrollments)	Range
Pediatric Network Group	55% to 75%

B. Guidelines for Estimating Type 1 Application Total Cost Budget Request for Adult Network Group Operations Center and SDMC & Canadian Collaborating Clinical Trials Network

Total Cost Credit Value for Type 1 Application	$500	$500	$500	$500	$500
TOTAL COST FOR PATIENT ENROLLMENT DATA/BIOSPECIMEN COLLECTION/MGT COSTS FOR ADULT NETWORK "Per Case Management" Funding Category	**Screening Only (Pts screened on study who did not go on to intervention)**	**Biospecimens**	**Basic Therapeutic Intervention (Including Any Pilot Studies)**	**Advanced Imaging Intervention**	**High-Performance Intervention**
Credit Multiplier for Category	1	1	4.5	2	8.0
Value of "Per Case Mgt" Funding Category (Credit Value x Credit Multiplier)	$500	$500	$2,250	$1,000	$4,000
# of Patients Enrolled to NCTN Trials Led by Network Group (& Enrollment Credited to Network Group)	408	2000	2000	40	N/A
Total Cost "Per Case Mgt" Funding (# Patients x Value of "Per Case Mgt" Funding)	$204,000	$1,000,000	$4,500,000	$40,000	N/A
# of Patients Enrolled to Other NCTN Trials NOT Led by Network Group (& Enrollment Credited to Network Group)	66	320	320	8	N/A
Total Cost "Per Case Mgt" Funding (# Patients x Value of "Per Case Mgt" Funding)	$32,800	$160,000	$720,000	$8,000	N/A
Total Cost "Per Case Mgt" Funding - All Member Sites by Category	$236,800	$1,160,000	$5,220,000	$48,000	N/A
Total Cost "Per Case Mgt" Funding - All Member Sites - All Categories	$6,664,800				
Total Cost Financial Management of All Member Sites 20% Used (Total Cost "Per Case Mgt" Funding for Intervention x 0.20)	$1,053,600				
Total Cost Financial Management of All Member Sites 10% Used (Total Cost "Per Case Mgt" Funding Non-Intervention x 0.10)	$139,680				
Total Cost "Per Case Mgt" Funding & Financial Mgt of All Member Sites	$7,858,080				

TOTAL COST BUDGET FOR INFRASTRUCTURE FOR ADULT NETWORK GROUP (OPERATIONS CENTER & SDMC)		
# Pts on NCTN Trials Led by/Credited to Network Group-High-Performance	N/A	
#Pts on NCTN Trials Led by/Credited to Network Group-Advanced Imaging	40	
# Pts on NCTN Trials Led by/Credited to Network Group-Basic Intervention	2,000	
#Pts on NCTN Trials Led by/Credited to Network Group-All Interventions	2,040	
# Pts on NCTN Trials Led by/Credited to Network Group-with Biospecimens	2,000	
# Pts on NCTN Trials Led by/Credited to Network Group-Screening Only	408	
# Pts on NCTN Trials Led by/Credited to Network Group- All Non-Interventions	2,408	
# Pts on NCTN Trials Led by/but **NOT** Credited to Network Group-All Interventions	2000	
# Pts NCTN Trials Led by/but **NOT** Credited to Network Group-All Non-Interventions	2400	
Total All Patients on NCTN Trials Led by Network Group-Intervention Trials	4,040	
Total All Patients on NCTN Trials Led by Network Group-Non-Intervention Studies	4,808	
	$2500 Per Pt	**$3300 Per Pt**
Total Cost for Infrastructure - Intervention ($2500 to $3300 per patient)	$10,100,000	$13,332,000
Total Cost for Infrastructure Non-Intervention ($250 to $500 per patient)	$1,202,000	$2,404,000
Total Cost for Infrastructure	$11,302,000	$15,736,000
Total Cost for Network Group Operations Center & Associated SDMC Applications	$19,160,080	$23,594,080

C. Guidelines for Estimating Type 1 Application Total Cost Budget Request for Pediatric Network Group Operations Center and SDMC

TOTAL COST FOR PATIENT ENROLLMENT DATA/BIOSPECIMEN COLLECTION/MGT COSTS FOR PEDIATRIC NETWORK GROUP

Total Cost Credit Value for Type 1 Application	$500	$500	$500	$500	$500
"Per Case Management" Funding Category	**Screening Only (Pts screened on study but did not go on to intervention)**	**Biospecimens**	**Basic Therapeutic Intervention (Including Any Pilot/Hx Studies)**	**Advanced Imaging Intervention**	**High-Performance Intervention**
Credit Multiplier for Category	1	1	4.5	2	8.0
Value of "Per Case Mgt" Funding Category (Credit Value x Credit Multiplier)	$500	$500	$2,250	$1,000	$4,000
# of Patients Enrolled by Pediatric Sites - High Performance Sites	574	2800	N/A	71	2800
Total Cost "Per Case Mgt" Funding (# Patients x Value of "Per Case Mgt" Funding)	$287,100	$1,400,000	N/A	$71,000	$ 11,200,000
# of Patients Enrolled by Pediatric Sites - Other Sites	267	1300	1300	33	N/A
Total Cost "Per Case Mgt" Funding (# Patients x Value of "Per Case Mgt" Funding)	$133,300	$650,000	$2,925,000	$33,000	N/A
Total Cost to Cover "Per Case Mgt" Funding for All Pediatric Sites By Category	$420,400	$2,050,000	$2,925,000	$104,000	$ 11,200,000

Total Cost for "Per Case Mgt" Funding for All Pediatric Sites for All Categories	$16,699,400
# Patients on Intervention (High-Performance, Adv Imaging, & Basic Therapeutic)	4204
# Patients on Non-Intervention (Biospecimens & Screening)	4941
Total Cost for Financial Mgt of All Pediatric Sites for Intervention Studies 20% Used (Total Cost "Per Case Mgt" Funding for Intervention Studies x 0.20)	$2,845,800
Total Cost for Financial Mgt of All Pediatric Sites for Non-Intervention Studies 10% Used (Total Cost "Per Case Mgt" Funding-Non-Intervention Studies x 0.10)	$247,040
Total Cost for Scientific Leadership/Coordination at High-Performance Sites 20% Used (Total Cost "Per Case Mgt" Funding-Intervention Studies x 0.20)	$2,254,200
Total Cost for Scientific Leadership/Coordination at High-Performance Sites 10% Used (Total Cost "Per Case Mgt" Funding-Non-Intervention Studies x 0.10)	$168,710
Total Cost for "Per Case Mgt" Funding, Financial Mgt of All Pediatric Sites, and Scientific Leadership/Coordination at High-Performance Sites	$22,215,150
% Accrual Threshold for Pediatric High Performance Sites % Intervention Accrual from High-Performance Sites (Therapeutic+50% Advanced Imaging)/ All Intervention Accrual from All Sites (Therapeutic+50% Advanced Imaging)	**68.3%**

Budget continued on next page

TOTAL COST BUDGET FOR INFRASTRUCTURE FOR PEDIATRIC NETWORK GROUP (OPERATIONS CENTER & SDMC)		
# Patients Enrolled on Network Group Trials - High-Performance Intervention Trials	2,800	
# Patients Enrolled on Network Group Trials - Advanced Imaging Interventions	104	
# Patients Enrolled on Network Group Trials - Basic Intervention (including Pilot and Hx)	1,300	
# Patients Enrolled on Network Group Trials - All Intervention Studies	4,204	
# Patients Enrolled with Biospecimen Collection	4,100	
# Patients Enrolled for Screening Only	841	
# Patients Enrolled on All Non-Intervention Studies (Biospecimens & Screening)	4,941	
	$2500 Per Pt	**$3300 Per Pt**
Total Cost for Infrastructure for Intervention ($2500 to $3300 per patient)	$10,510,000	$13,873,200
Total Cost for Infrastructure for Non-Intervention ($250 to $500 per patient)	$1,235,200	$2,470,400
Total Cost for Infrastructure	$11,745,200	$16,343,600
Total Cost for Pediatric Network Group Operations Center & Associated SDMC Applications	**$33,960,350**	**$36,088,350**

D. Guidelines for Estimating Type 1 Application Total Cost Budget Request for Adult Network Lead Academic Participating Sites

FOR PATIENT ENROLLMENT DATA MANAGEMENT COSTS

Credit Value for Type 1 Application:	$500	$500	$500	$500	$500
"Per Case Management" Funding Category	**Screening Only (Pts screened on study but did not go on to intervention)**	**Biospecimens**	**Basic Therapeutic Intervention (Including Any Pilot Studies)**	**Advanced Imaging Intervention**	**High-Performance Intervention**
Credit Multiplier for Category	1	1	4.5	2	8.0
Value of "Per Case Mgt" Funding Category (Credit Value x Credit Multiplier)	$500	$500	$2,250	$1,000	$4,000
# of Patients Enrolled at Academic Center/Components	18	85	0	3	85
Total Cost "Per Case Mgt" Funding (# Patients x Value of "Per Case Mgt" Funding)	$8,800	$42,500	$0	$3,000	$ 340,000
# of Patients Enrolled at Affiliates (Complete Mgt by Academic Center)	2	10	10	0	N/A
Total Cost "Per Case Mgt" Funding (# Patients x Value of "Per Case Mgt" Funding)	$1,000	$5,000	$22,500	$0	N/A
Total Cost to Cover "Per Case Mgt" Funding for All Sites By Category	$9,800	$47,500	$22,500	$3,000	$ 340,000

Total Cost for "Per Case Mgt" Funding for All Sites for All Categories	$422,800
Total Cost for Scientific Leadership/Coordination at Site 10% Used (Total Cost "Per Case Mgt" Funding for Non-Intervention Studies/Components x 0.10)	$5,730
Total Cost for Scientific Leadership/Coordination at Site 20% Used (Total Cost "Per Case Mgt" Funding for Intervention Studies x 0.20)	$73,100
Total Cost for Budget Request for Application	$501,630
# Patients Enrolled on Network Group Trials - All Intervention Studies	98
# Patients Enrolled on Network Group Trials - High-Performance Intervention Trials	85
# Patients Enrolled on Network Group Trials - Advanced Imaging Intervention Trials	3
# Patients Enrolled on Network Group Trials - Basic Intervention Studies (Including Pilots)	10
# Patients Enrolled on Non-Intervention Studies - Biospecimens & Screening	115
# Patients Enrolled for Screening Only	20
# Patients Enrolled with Biospecimen Collection	95
Accrual Threshold for Academic Center/Components (# Pts) (High-Performance + 50% Advanced Imaging Intervention at Academic Center/Components)	**87**

V. Other Important NCI/NIH URLs, Federal Citations, and List of Abbreviations

A listing of important URLs (links to websites) and abbreviations referenced in the text of these Guidelines is provided below.

A. Website URLs referenced in these Guidelines

NCI Website
http://www.cancer.gov/

NCI Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)
http://biqsfp.cancer.gov/

NCI Cancer Trials Support Unit (CTSU) Website
http://www.ctsu.org

NCI Cancer Diagnosis Program's Request for an Application (RFA) on Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-017.html

NCI Cancer Diagnosis Program's Website
http://cdp.cancer.gov/

NCI Center for Coordinating Clinical Trials
http://ccct.cancer.gov/about/overview

NCI Central IRB Website
http://www.ncicirb.org

NCI Clinical Trials and Translational Research Advisory Committee (CTAC)
http://ccct.cancer.gov/committees/ctac

NCI Clinical and Translational Research Operations Committee
http://ccct.cancer.gov/committees/ctroc

NCI CTWG Steering Committee System (Information on NCI Scientific Steering Committees)
http://transformingtrials.cancer.gov/steering/overview

NCI Clinical Trials Reporting Program (CTRP)
http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main/allpages

NCI Guide to Readers to Information on Other NCI Divisions/Branches
http://www.cancer.gov/aboutnci

Diagnostics Evaluation Branch (DRB) of the Cancer Diagnosis Program (CDP) Program for the Assessment of Clinical Cancer Tests (PACCT) – Clinical Tumor Marker Study Guidelines
http://www.cancerdiagnosis.nci.nih.gov/diagnostics/advice/guidelines.htm

Good Clinical Practice in FDA-Regulated Clinical Trials
http://www.fda.gov/oc/gcp/default.htm

Guidance Document on Inclusion of Manuscripts/Publications in Appendix Material with NIH/NCI Grant Applications
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-053.html

NIH Data Sharing Policy
http://grants.nih.gov/grants/policy/data_sharing

NIH Freedom of Information Act Office
http://www.nih.gov/icd/od/foia/index.htm

NIH Grants Policy Statement
http://grants.nih.gov/grants/policy/policy.htm

NIH Grant Policy for Program Income
http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income

NIH Guide Notice on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (Amendment October 2001).
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html

NIH Public Access Policy (and Manuscript Submission System)
http://publicaccess.nih.gov

NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (3/6/98)
http://www.nih.gov/grants/guide/notice-files/not98-024.html

NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001 (COMPLETE COPY OF UPDATED GUIDELINES)
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects – Policy Implementation
http://grants.nih.gov/grants/funding/children/children.htm

NIH Policy for Data and Safety Monitoring
http://grants.nih.gov/grants/guide/notice-files/not98-084.html

(Further) NIH Guidance on Data and Safety Monitoring for Phase 1 and Phase 2 trials
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

NIH Policies on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects – Policy Implementation
http://grants.nih.gov/grants/funding/women_min/women_min.htm

NIH Policy on Financial Conflict of Interest
http://grants.nih.gov/grants/policy/coi

PHS 398 Grant Application
http://grants.nih.gov/grants/funding/phs398/phs398.html

PHS 2590 Non-Competing Grant Progress Report
http://grants.nih.gov/grants/funding/2590/2590.htm

SF424 (R&R) Application and Electronic Submission Information
http://grants.nih.gov/grants/funding/424/index.htm

Office for Human Research Protections Website
http://www.hhs.gov/ohrp/

Required Education on the Protection of Human Subject Participants
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html

Updated Instructions Regarding Inclusion of Publications as Appendix Materials:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-077.html

B. Other Federal Citations for NIH Grants Involved in Human Subjects Research & Websites

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_2011/nihgps_ch8.htm#_Program_Income).

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 of 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 https://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/.

C. Important Abbreviations Referenced in these Guidelines

ABBREVIATION	FULL TERM
AD	Associate Director, CTEP, DCTD
AdEERS	Adverse Event Expedited Reporting System
ARA	Awaiting Receipt of Application
BIQSFP	Biomarker, Imaging, and Quality of Life Studies Funding Program
BRB	Biometric Research Branch (in DCTD)
CBO	Common Budget Outline
CCCT	Coordinating Center for Clinical Trials (in NCI OD)
CCOP	Community Clinical Oncology Program (in DCP)
CDE	Common Data Elements
CDP	Cancer Diagnosis Program (in DCTD)
CDUS	Clinical Data Update System
CFR	Code of Federal Regulations
CIB	Clinical Investigations Branch (in CTEP)
CIP	Cancer Imaging Program (in DCTD)
CIRB	Central Institutional Review Board at NCI
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
CSA	Clinical Supply Agreement
CSR	Center for Scientific Research (at NIH)
CTA	Clinical Trial Agreement
CTAC	Clinical Trials and Translational Research Advisory Committee
CTCAE	Common Toxicity Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program (in DCTD)

CTMB	Clinical Trials Monitoring Branch (in CTEP)
CTSU	Cancer Trials Support Unit
CTRP	Clinical Trials Reporting Program
CTWG	Clinical Trials Working Group
CTROC	Clinical and Translational Research Operations Committee
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 (also known as Data and Safety Monitoring Board)
DRB	Diagnostics Evaluation Branch (in CDP)
DSMB	Data and Safety Monitoring Board (also known as Data Monitoring Committee)
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
LOI	Letter of Intent
NCAB	National Cancer Advisory Board
NCI	National Cancer Institute
NCI SSC	NCI Scientific Steering Committees
NIH	National Institutes of Health
NCTN	National Clinical Trials Network

OD	Office of the Director at the NCI
OEWG	Operational Efficiency Working Group
OGA	Office of Grants Administration
OHRP	Office for Human Research Protections
OPEN	Oncology Patient Enrollment Network
ORI	Office of Research Integrity
PD	Program Director
PHS	Public Health Service
PI	Principal Investigator
PIO	Protocol and Information Office (in CTEP)
PMB	Pharmaceutical Management Branch (in CTEP)
PRC	Protocol Review Committee (in CTEP – also known as NCI/DCTD PRC)
RAB	Regulatory Affairs Branch (in CTEP)
RRP	Radiation Research Program (in DCTD)
RSS	Regulatory Support System (in CTSU)
SDMC	Statistics and Data Management Center
SOP	Standard Operating Procedure
SPORE	Specialized Programs of Research Excellence
SRO	Scientific Review Officer
URL	Uniform Resource Locator (internet address of resource)

VI. Sample Table of Contents for PHS 398 Application (Example: Network Group Operations Center)

SECTION I

Face Page
Description, Project/Performance Sites, Senior/Key Personnel, Other Significant Contributors, & Human Embryonic Stem Cells
Research Grant Table of Contents
Detailed Budget for Initial Budget Period & Budget for Entire Proposed Period of Support

- **Plus Common Budget Outline**
- **Accrual Input by Member Institution/Sites Used to Generate Part of Network Group Ops Center Budget**

Budget Pertaining to Consortium/Contractual Arrangements
Biographical Sketch
Program Director(s)/Principal Investigator(s) (*Not to exceed four pages each*)

- **Other Biographical Sketches (*Not to exceed four pages each – See instructions*)**
- **Other Support Information**

Resources

- **Include Required Tables**
- **Include Key SOPs**

SECTION II

Research Plan

Specific Aims (including Impact Statement)

Research Strategy Sections

A. **Operations Center Overview (up to 12 pages)**
B. **Clinical Trial Development Program (up to 30 pages)**
C. **Member Site Accrual Program (up to 12 pages)**
D. **Operational Management (up to 12 pages)**
E. **Program for Collaborations and Participation in Collective Management (up to 12 pages)**

Bibliography and References Cited
Protection of Human Subjects
Inclusion of Woman and Minorities
Targeted/Planned Enrollment Table
Inclusion of Children
Vertebrate Animals
Select Agent Research
Multiple Program Director/Principal Investigator (PD(S)/PI(S)) Leadership Plan
Consortium/Contractual Arrangements
Letters of Support (e.g., Consultants)
Resource Sharing Plans

Checklist
Appendix

VII. Model for NCTN Program Data Sharing Policy for Network Group Ops Centers & SDMCs

Introduction
Guidelines for Availability of Datasets
Request Procedure
Regulatory Considerations
Release Conditions & Disclaimer
Appeals Process
Fees

1. Introduction

This document describes general policies of the NCI National Clinical Trials Network (NCTN) Program for funded Network Groups (defined as Network Group Operations Center and its associated Network Group Statistics and Data Management Center) on providing individual patient data to investigators for use in research projects. Each Network Group may have a more detailed set of procedures implementing the general policy but those procedures should be consistent with all provisions of the general policy.

The Network Groups conduct clinical trials in cancer research. Each Network Group or NCTN study has a formal protocol document, which includes a statement of the objectives of the study. Patient consent and authorization are obtained to collect the individual patient data required for addressing the study objectives. These data are sent from the treating or enrolling institution to the Network Group's Statistics and Data Management Center, where the data are reviewed, processed and entered on an electronic database. The data may be submitted on paper or electronically. Not all information submitted on paper becomes part of the electronic database. The electronic database is used as the basis for the analysis of the Network Group's studies, with the analyses performed by the staff at the Network Group's Statistics and Data Management Center.

The procedures described here do not cover requests from the NCI, FDA or other federal agencies for information required by federal regulations or by the terms of the Network Group's grant awards. Such requests will be honored as expeditiously as possible.

This document only covers requests for existing data, not requests for use of biospecimens (which are covered under a different evaluation and review process) or for collection of additional data. Requests for individual-level genomic or other high-dimensional data not used in the primary publication may be subject to other NCI and NIH regulations.

The data requested by an investigator may include data generated from laboratory correlative studies. However, this document only covers requests for existing data, not requests for use of tissue or for collection of additional data.

2. Guidelines for Availability of Datasets

For phase 3 studies, it is anticipated that individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication (i.e., published manuscript) containing the primary study analysis would be available to individuals via the requesting procedure described in Section 3 generally within 6 months of publication of the manuscript. It is anticipated that datasets containing patient-level entry data of all baseline variables summarized in the publication would be available within 12 to 15 months after the publication of the primary analysis.

For non-phase 3 studies, a patient dataset containing the variables analyzed in the primary results paper would be expected to be available upon request (subject to restrictions stated in Section 4). This process could take several months. Since these studies could be quite small, the release of data may be constrained by the ability to de-identify data.

For publications that are not presenting the primary analysis of the trial, patient datasets containing the variables analyzed in the paper should be available upon request (subject to restrictions stated in Section 4). This process could take several months.

Release of data collected in a clinical trial conducted under a binding collaborative agreement between the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must be in compliance with the terms of the binding collaborative agreement and must be approved by CTEP and the company. Release of the data is also subject to the terms of any contracts between the Network Group and other entities, which cover any of the requested data. These two considerations could, in some instances, delay the release of data to requesting investigators.

3. Request Procedure

While most analyses of the Network Group's studies are performed at the Network Group Statistics and Data Management Center, the Network Group also makes research data available to other investigators, as required by the policies of the National Institutes of Health. An investigator who wishes to use individual patient data from one or more of the Network Group's studies must make a formal request to the Network Group Operations Center.

The Network Group Operations Center will typically require documentation of Institutional Review Board (IRB) approval (or exemption) from the institution of the requesting investigator which should include a brief description of the project; see Section 4 below. The Network Group Operations Center may also require IRB approval or exemption from the IRB associated with the Network Group Statistics and Data Management Center. The Network Group Operations Center will also typically require the investigator to sign a data use agreement specifying who will have access to the individual patient data and specifying that it will not be shared with others outside this specified set of individuals.

The Network Group Operations Center website should contain a list of the available collections of datasets from their clinical trials, the request procedure, and who to contact to obtain these collections.

There should be no scientific review of requests for data. If a Network Group is unable to fulfill a request, the Network Group Operations Center must inform the investigators of the reasons the request cannot be fulfilled. In most cases it is likely the investigators will be able to amend the request to comply with the procedures. If the Network Group believes the request will not be amendable, the Network Group Operations Center will inform the investigator of the appeal process outlined in Section 6 and also notify the Chief, Clinical Investigations Branch (CIB), Cancer Therapy Evaluation Program (CTEP) in the Division of Cancer Treatment and Diagnosis (DCTD) at the NCI who is also the Lead NCTN Program Director. Release of the data is subject to the disclaimer in Section 5.

4. Regulatory Considerations

All research use of data collected on human subjects from NCTN studies led by the Network Group Operations Center with its associated Network Group Statistics and Data Management Center is subject to applicable Office of Human Research Protections (OHRP) regulations and to applicable regulations of the Privacy Rule of the Health Insurance Portability and Accountability Act. Generally, patients have only consented to have their health information used for the objectives of the clinical trial in which they participated. Use of the data for other research projects is allowed only if an IRB has determined that use of the data in the project meets the minimal risk criteria for conducting the research without the patients' consent, if the use of the data in the project is exempt from consent requirements, or if the project does not constitute human subjects research. The required level of review or approval will generally depend on the degree to which the data have been rendered fully anonymous, de-identified, or coded.

Guidance on these matters can be found in the OHRP document "Guidance on Research Involving Coded Private Information or Biological Specimens" (http://www.hhs.gov/ohrp/policy/cdebiol.html) and at the NIH HIPAA Privacy Rule Information for Researchers site (http://privacyruleandresearch.nih.gov/clin_research.asp). The criteria for de-identification of data under HIPAA are given in the Code of Federal Regulations, Part 46, Section 164.514. It should be possible to conduct most projects using coded data (as described in the OHRP Guidance) that meet the criteria for a limited data set that can be released under a data use agreement (as described in Part 46 of the CFR, Section 164.512 and in the NIH HIPAA guidance documents), without obtaining additional patient consent or authorization.

(**NOTE:** Each Network Group Operations Center and/or Network Group Statistics and Data Management Center may need to add extra requirements imposed by the IRB's covering their Centers.)

5. Release Conditions & Disclaimer

A simple, formal data use agreement specifying who will have access to the individual patient data (and specifying that it will not be shared with others outside this specified set of individuals) as well as covering the release conditions described below and the regulatory considerations described in Section 4 above will usually be required.

It is anticipated that most data requests can be provided as non-complex data sets in electronic form. If possible, data sets from Network Group trials may be provided to the public via a website to facilitate access in the future.

It will sometimes be the case that the data requested for analysis will not all be coded on the Network Group's database but will be available in the paper charts at the Network Group Statistics and Data Management Center. In this case, the data will need to be abstracted from the charts. Data abstractions can only be performed if adequate funding to support the abstraction is available. Even if funding is available, the Network Group may not have staff available to perform the abstraction. In this case, the Group may be willing to have the investigators or their representatives or contractors come to the Network Group Statistics and Data Management Center to perform the abstraction. Some funding for clerical support may still be required. Likewise, in cases in which data requested require data sets not available in easily obtained electronic format, especially older trials, the Network Group may require some funding for support to create the dataset in a simplified electronic format.

In releasing the data, the Network Group makes no representations and extends no warranties of any kind, either expressed or implied. There are no expressed or implied warranties of merchantability or fitness for a particular purpose, or that the use of the data will not infringe any patent, copyright, trademark, or other proprietary rights. No indemnification for any loss, claim, damage, or liability will be intended or provided.

Copies of any manuscript arising from the project associated with the data request should be sent to the Network Group Operations Center; however, approval of the manuscript is not a condition for use of the data.

6. Appeals Process

If a request for data is denied, the applicant may appeal the decision. The appeal will be reviewed by the designated Network Group Chair, the Lead NCTN Program Director, CTEP Associate Director or his/her designee, and an outside statistician (i.e., a statistician that does not work for the Network Group). The outside statistician will be named jointly by the designated Network Group Chair and the Lead NCTN Program Director.

7. Fees

Routine costs associated with preparing standard data sets are viewed by NCI as covered by the grants for the Network Group Operations Centers and Network Group Statistics and Data Management Centers funded under the NCTN Program and fees should not be charged for release of non-complex electronic data sets. For complex data sets where substantial work is involved, fees may be charged for preparing and documenting the data set. Any fees will be limited to the actual time, effort and materials required for preparing and documenting the data set.

VIII. NCTN Program Data and Safety Monitoring Board (DSMB) Policy for Phase 3 Trials & Randomized Phase 2 Trials (also known as the Data Monitoring Committee (DMC) Policy)

Studies to be Monitored

One or more Data and Safety Monitoring Boards (DSMBs) or Data Monitoring Committees (DMCs) will be established to monitor all phase 3 and randomized phase 2 therapeutic and advanced imaging clinical trials of the NCI National Clinical Trials Network (NCTN) Program, and other selected studies (chosen at the Network Group Operations Center's and/or NCI's discretion). Whereas a single DSMB/DMC per Network Group (defined as a Network Group Operations Center and its associated Network Group Statistics and Data Management Center) within the NCTN Program, is acceptable and may provide the most feasible way of maximizing independence of the DSMB/DMC, separate DSMBs/DMCs could be approved by the Chief, Clinical Investigations Branch and Lead Program Director of the NCTN Program. This could be for single large trials, especially those that involve substantial risk/benefit oversight, or for a group of trials if the volume of trials to be monitored requires an additional DSMB/DMC because of workload issues.

For those Network Groups which are funded as Community Clinical Oncology Program (CCOP) Research Bases by the Division of Cancer Prevention (DCP), all phase 3 and randomized phase 2 cancer prevention and control clinical trials need to be monitored as well. The Network Group may choose to have the existing DSMBs/DMCs that cover the therapeutic and advanced imaging clinical trials of the NCTN Program review these trials. Alternatively, DCP may require the Research Bases to have separate DSMBs/DMCs funded by their DCP grant for prevention and control clinical trials and/or for large trials involving participants without cancer. In the latter case, DCP may wish to have a separate committee established with some expertise outside of oncology.

Responsibilities

1) The primary responsibility of the DSMB/DMC is to review interim analyses of outcome data (prepared by the study statistician) and to recommend whether the study needs to be changed or terminated based on these analyses. For phase 3, phase 2/3, and blinded randomized phase 2 trials, the committee also determines whether and to whom outcome results should be released prior to the reporting of study results at the time specified in the protocol.

2) The DSMB/DMC reviews reports of related studies performed by the Network Groups or other organizations to determine, considering information and recommendations supplied by the study committee, whether the group study needs to be changed or terminated.

3) The DSMB/DMC reviews interim toxicity data although that is primarily the responsibility of the study committee.

4) The DSMB/DMC reviews major modifications to the study proposed by the study committee prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size).

Membership

DSMB/DMC members will be appointed for a fixed term by the designated Network Group Chair for the Network Group Operations Center or his/her designee with the approval of the Chief, Clinical Investigations Branch (CIB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD) at the NCI or his/her designee. The nominees should be reviewed and approved by NCI/DCTD with

written confirmation by the Chief, CIB prior to their official appointment and participation in DSMB/DMC activities. The committee will include physicians and statisticians from within and outside the Network Group selected based on their experience, reputation for objectivity, absence of conflicts of interest (or the appearance of same), and knowledge of good clinical trial methodology. The committee must include a consumer representative and a voting statistician from outside the group. A NCI/DCTD physician and a NCI/DCTD Biometric Research Branch (BRB) statistician, as designated by the Chief, CIB will be non-voting members and must be free to attend all sessions of the DSMB/DMC including closed and executive sessions. The designated Network Group Statistician, or his or her designee, will also be a non-voting member of the DSMB/DMC.

For those Network Groups which are funded as CCOP Research Bases, a designee named by the Division of Cancer Prevention (DCP) Community Oncology and Preventive Trials Research Group (COPTRG) program director will be a non-voting member and must be free to attend all sessions.

The DSMB/DMC may be constituted fully by individuals who are not members of the Network Groups. Alternatively, the DSMB/DMC may have voting members who are also members of the Network Group; however, the majority of the voting DSMB/DMC members cannot be affiliated with the Network Group and voting quorums for a DSMB/DMC meeting require that the majority of voting members not belong to the Network Group. Network Group members who are members of the DSMB/DMC must see themselves as primarily representing patient interests and not the interests of the Network Group or designated Network Group Chair. Members of the study team or the leadership of the disease committee or scientific research committees of the Network Group (e.g., chair or vice-chair of the disease committee) conducting a study will recuse themselves from all DSMB/DMC discussions concerning that study and will not receive DSMB/DMC reports concerning that study. Additionally, the study statistician will not be a voting member of the DSMB/DMC for his/her trial. The designated Network Group Chair, Principal Investigator(s)/Program Director(s) on the Network Group Operations Center grant using the multiple Principal Investigator option, or any member of the executive leadership of the Network Group (including vice-chairs and executive officers, but not disease-committee chairs or members of Network Group executive committees, as long as they are not also vice-chairs or executive officers) cannot attend closed or executive sessions of the DSMB/DMC. In addition, the designated Network Group Chair, Principal Investigator(s)/Program Director(s) on the Network Group Operations Center grant using the multiple Principal Investigator option, or any member of the executive leadership of a Network Group, cannot be a member of the DSMB/DMC of a different Network Group.

The size of the DSMB/DMC should be limited, and it is unlikely that more than 10 people would be required to constitute a DSMB/DMC.

Meetings

DSMB/DMC meetings will be held at least once every six months. Each randomized clinical trial should have specified interim analysis times, although the DSMB/DMC should be apprised at each meeting of the status of all trials for which it is responsible, e.g., accrual, toxicity concerns, and the next formal monitoring date as specified in the protocol. DSMB/DMC meetings should be in person (rather than by telephone) generally, and especially when new members of the DSMB/DMC have been appointed. At a minimum, DSMB/DMC meetings must be held in person every 18 months, and any possible exceptions to this must be approved by NCI/DCTD.

It is recommended that a written report outlining the current status of each trial to be monitored be sent to the DSMB/DMC members by the study statistician at least three weeks prior to the DSMB/DMC meeting. The Study Chair may prepare a report addressing specific toxicity concerns or other concerns about the conduct of the study. The statistician's report may contain recommendations on whether to close the study, whether to report the results, whether to continue accrual or follow-up and whether DSMB/DMC

discussion is needed. In the event a study will be considered for closure due to slow accrual, the CTEP members of the DSMB/DMC may discuss with other CTEP staff the possibility of early closure due to slow accrual. Although no confidential information would be disclosed, this would allow the CTEP members of the DSMB/DMC to bring to the DSMB/DMC meeting any information from CTEP concerning early closure that might be useful in the DSMB/DMC deliberations.

Major modifications to the study design not motivated by confidential outcome data or patient safety/toxicity data (e.g., increasing the sample size because of more rapid than expected accrual) must be discussed with NCI/DCTD/CTEP before being presented to the DSMB/DMC for consideration. If NCI/DCTD/CTEP is willing to approve the modifications, the Network Group may then seek DSMB/DMC approval before submitting an official amendment to CTEP's Protocol and Information Office.

With respect to implementation of phase 2 decision rules in phase 2/3 designs of clinical trials, any protocol-specified phase 2 decision-rule analysis must be performed within 6 weeks from the date the required number of events are observed. If the trial follows the decision rule (i.e., continues or stops depending on whether the continuation threshold is met), then the Network Group notifies the DSMB/DMC and Chief, CIB of the status of the trial (i.e. continuing or stopping) based on the protocol-specified phase 2 decision rule. In the unlikely event that the study statistician wishes to request permission not to follow the protocol pre-specified decision rule, such a request must first be discussed with NCI/DCTD/CTEP by conference call within 2 weeks. This request (change in the design of the trial) needs to be approved by the CTEP Associate Director or his/her designee in consultation with the Chief, CIB who will notify the Network Group Operations Center in writing of NCI decision regarding the request. If NCI/DCTD/CTEP is willing to approve the request, the Network Group must then seek DSMB/DMC approval within 3 weeks before submitting an official amendment to CTEP's Protocol and Information Office to change the design of the trial regarding the phase 2 decision rule.

The review of each trial may include three parts. The first part will be an open session in which members of the study team and disease committee and NCI/DCTD staff not on the DSMB/DMC may be present at the request of the DSMB/DMC to answer questions. In this part, the focus is on accrual, compliance and toxicity issues, and no outcome results may be presented. Following the open session, there will be a closed session limited to DSMB/DMC members and possibly the study statistician in which outcome results will be presented either by a member of the DSMB/DMC, the designated Network Group Statistician, or the study statistician. It is generally recommended that outcome data be presented to the DSMB/DMC in an unblinded manner. However, if the Network Group desires to keep outcome data blinded (perhaps on some specific trials), then this is acceptable provided that any DSMB/DMC member request for unblinding for a trial will be honored. Following this closed session, there will be a fully closed, executive session in which the DSMB/DMC discusses outcome results, and then votes. At the executive session, those present are limited to DSMB/DMC members.

Recommendations

DSMB/DMC recommendations should be based upon results for the current study being monitored as well as upon data available to the DSMB/DMC from other related studies. The study committees, NCI/DCTD staff, and individual DSMB/DMC members will assure that the DSMB/DMC is advised about relevant non-confidential results from other related studies that become available. It will be the responsibility of the DSMB/DMC, with advice from the study committee, to determine the extent to which this information is relevant to decisions to continue or modify the current study.

The DSMB/DMC will provide recommendations to the designated Network Group Chair to change a study or to continue a study unchanged. In the event a change is recommended by the DSMB/DMC, the study statistician may send his/her written report that was prepared prior to the DSMB/DMC meeting to the

designated Network Group Chair, who may seek the advice, in a confidential manner, of the Study Chair, Disease Committee Chair, and/or designated Network Group Statistician.

1) In the event that the DSMB/DMC recommends a study change for patient safety reasons (including early stopping for inferior therapy), the designated Network Group Chair will act to implement the change as expeditiously as possible. For studies that are being closed based on a DSMB/DMC recommendation, although CTEP pre-approval is not required, the designated Network Group Chair (or his/her designee) must inform and discuss the closure of the study with the Chief, CIB or his/her designee before disclosing the study closure to anyone. If the DSMB/DMC recommends closure of a study, the NCI/DCTD physician member of the DSMB/DMC will provide the current 24/7 contact information for the Chief, CIB or his/her designee.

   In the unlikely situation that the designated Network Group Chair does not concur with the DSMB/DMC recommendation, the designated Network Group Chair must discuss his/her reasons for not accepting the DSMB/DMC recommendation with the Chief, CIB. The Chief, CIB will then inform the CTEP Associate Director of the recommendation of the DSMB/DMC and of the designated Network Group Chair's reasons for disagreeing with the recommendation. The CTEP Associate Director, Chief, CIB, and the designated Network Group Chair, in consultation with the DSMB/DMC Chair, will be responsible for reaching a mutually acceptable decision about the study. Confidentiality will be maintained during these discussions, but relevant data will be shared with the designated Network Group Chair, Chief, CIB, CTEP Associate Director, and other parties whom they wish to involve in reaching a decision. In the exceptional circumstance that a mutually acceptable decision cannot be reached, final responsibility for a decision will rest with the CTEP Associate Director in consultation with the Director of the Division of Cancer Treatment and Diagnosis.

2) In the event that the DSMB/DMC recommends a study be closed early due to slow accrual, then the recommendation of the DSMB/DMC would be processed as described in 1) above. Note: NCI/DCTD/CTEP may have additional closure policies that apply to studies with slow accrual that have not yet had formal interim efficacy analyses presented to the DSMB/DMC.

3) In the event that the DSMB/DMC recommends a change in a study for reasons other than either patient safety (e.g., to extend accrual because of an event rate lower than expected) or study closure due to slow accrual, the DSMB/DMC will provide to the designated Network Group Chair an adequate rationale. In the absence of disagreement, the designated Network Group Chair will be responsible for having an amendment prepared and submitted to CTEP's Protocol and Information Office reflecting the recommendations of the DSMB/DMC and providing the rationale for the changes. (This is required even if NCI/DCTD/CTEP approval has been obtained prior to the amendment being presented to the DSMB/DMC.) NCI/DCTD/CTEP approval of the amendment will be required prior to implementation of the change, although it is anticipated that a decision to override the recommendation of the DSMB/DMC will be made only in the most exceptional circumstances. In the event that the Network Group Chair disagrees with the DSMB/DMC recommendation, the recommendation would be processed as described in 1) above.

For DSMB/DMC recommendations specific to cancer prevention and control trials funded by a CCOP Research Base grant, the appropriate NCI staff to include and report to are the DCP/COPTRG Program Director (instead of the NCI/DCTD physician member of the DSMB/DMC), the Chief of COPRTRG (instead of the Chief, CIB) and the Associate Director for Clinical Research in DCP (instead of the CTEP Associate Director), and the Director of the Division of Cancer Prevention (instead of the Director of the Division of Cancer Treatment and Diagnosis).

Confidentiality Procedures

No communication of the deliberations or recommendations of the committee, either written or oral, should be made outside of the committee except as provided for in these policies and procedures. Statements of confidentiality should be signed by all DSMB/DMC members. Outcome (efficacy) results from phase 3, phase 2/3, and blinded randomized phase 2 trials are strictly confidential and must not be divulged to *any* non-member of the DSMB/DMC (excepting the designated Network Group Chair, Chief, CIB, and CTEP Associate Director as described above) without the approval of the DSMB/DMC until the recommendation to report the results are accepted and implemented.

Release of Results

For phase 3, phase 2/3, and blinded randomized phase 2 trials, ***any*** release of outcome data [either internal to the Network Group, to NCI personnel not members of the DSMB/DMC, or external (e.g., a paper presented at professional society meetings, seminars, papers, etc.)] prior to the final approval of general dissemination of results must be reviewed and recommended for approval by the DSMB/DMC to the designated Network Group Chair. In general, outcome data from phase 3, phase 2/3, and blinded randomized phase 2 trials would not be routinely made available to individuals outside of the DSMB/DMC until accrual has ceased and all patients have concluded their randomized treatment. After this time point, the DSMB/DMC may recommend the release of outcome data on a confidential basis to the Study Chair for planning the preparation of manuscripts, and/or to a small group of individuals for purposes of planning future trials. The DSMB/DMC will consider special requests for information from the disease committee chair prior to that time point. The DSMB/DMC should be made aware of any communication of analysis results from phase 3, phase 2/3, and blinded randomized phase 2 trials outside of the statistical center at any time. The designated Network Group Chair may not be able to accept the recommendation of the DSMB/DMC to release data for a specific trial if the Network Group and/or NCI/DCTD/CTEP has a binding agreement with a company collaborator (or other entity) that specifies data exclusivity for the trial without discussing the release with CTEP (for Network Group trials with a CTEP binding agreement) and/or the company or other collaborator (for Network Group studies that are under other binding agreements).

Conflict of Interest

Individuals invited to serve on the DSMB/DMC (voting and non-voting) will disclose to the designated Network Group Chair any potential, real or perceived conflicts of interest. These will include professional interest, proprietary interest and miscellaneous interest considerations as described in the NCI/DCTD/CTEP Conflict of Interest Policy for NCTN Program Phase 3 Trials (formerly known as the NCI Conflict of Interest Policy for Cooperative Group Phase 3 Trials). The designated Network Group Chair, with the advice of an ad-hoc committee, will review possible conflicts and determine whether there is sufficient basis to exclude the individual from serving on the DSMB/DMC. Potential conflicts which develop during the conduct of a trial should also be disclosed to the designated Network Group Chair.

NCI/DCTD Oversight

In order to satisfy its objectives of protecting patients, ensuring study integrity and assuring public confidence in the conduct of clinical trials, it is essential that the DSMB/DMC function in a manner that demonstrates competence, experience and independence of the Network Group, career or financial interests. If NCI/DCTD determines that a DSMB/DMC for a Network Group is not functioning in this manner, it will discuss with the designated Network Group Chair what changes are needed to the composition or structure of the DSMB/DMC.

Table of Membership of DSMB/DMC and Attendance at Sessions

If the DSMB/DMC has voting members who are also members of the Network Group, the majority of voting DSMB/DMC members cannot belong to the Network Group and voting quorums for a DSMB/DMC meeting require that the majority of voting members not belong to the Network Group.

DSMB/DMC Membership Type	Open session	Closed Session	Executive Session
Voting member of DSMB/DMC	Present	Present (except if member of the study team or leadership of the disease committee for the study under consideration)	Present (except if member of the study team or leadership of the disease committee for the study under consideration)
NCI/DCTD (non-voting) member of DSMB/DMC	Present	Present	Present
Study statistician	Present	Present	Absent
Designated Network Group Statistician (non-voting)	Present	Present	Present (except if study statistician for the study under consideration, in which case, the Designated Network Group Statistician can name another statistician from the Network Group as his/her non-voting designee for the executive session)
Designated Network Group Chair or any member of the executive leadership	Present (if he/she desires)	Absent	Absent

IX. Common Budget Outline – Suggested Format

										Consortium/ Contractual	
Heading for All Costs (except for per case reimbursement)	FTEs	Salaries & Wages	Fringe	Consultants	Equipment	Supplies	Travel	Alterations/ Renovations	Other	Indirect	TOTAL

INFRASTRUCTURE COSTS

A. Group Leadership

1. Group Chair and Vice Chairs (include all Multiple PI(s)/PD(s) on grant application) — Salary, fringe, travel and consortium/contractual indirect costs for Group Chair and any Vice or Deputy Chairs
2. Executive Medical Officers — Salary, fringe, travel and consortium/contractual indirect costs for physicians who have oversight responsibilities for scientific activities

SUBTOTAL - GROUP LEADERSHIP

B. Scientific Leadership

1. Scientific Committee Leadership — Salary, fringe, travel and consortium/contractual indirect costs for Chairs, Vice and Deputy Chairs, Subcommittee Chairs
2. Administrative Committee Leadership — Salary, fringe, travel and consortium/contractual indirect costs for Chairs, Vice and Deputy Chairs, Subcommittee Chairs
3. Protocol Chairs — Salary, fringe, travel and consortium/contractual indirect costs or fixed payments for protocol chairs

SUBTOTAL - SCIENTIFIC LEADERSHIP

C. Group Administration

1. General Administration — Salary, fringe, office costs, travel and consortium/contractual indirect costs for administrative management, Chair's Office, if applicable, and meeting support
2. Finance/Contracting — Salary, fringe and consortium/contractual indirect costs for finance and contracting staff
3. IT Support — Salary, fringe, consortium/contractual indirect costs or other costs for administration IT support
4. Rent — Rental costs paid for Group space from direct dollars

SUBTOTAL - GROUP ADMINISTRATION

D. Trial Operations

1. Protocol Development and Management	Salary, fringe, travel and consortium/contractual indirect costs for staff to develop, prepare, revise and manage protocols
2. Regulatory	Salary, fringe, travel and consortium/contractual indirect costs for staff to administer IRB and other regulatory paperwork
3. Audits **(RESTRICTED FUNDING)**	Salary, fringe, travel, consortium/contractual indirect and/or consultant costs for staff to conduct and manage audits and associated quality assurance activities
SUBTOTAL - TRIAL OPERATIONS	

E. Statistics & Data Management
(Provided by SDMC)

1. Statistical & Data Management Leadership	Salary, fringe, travel and consortium/contractual indirect costs for leadership of the entire function (where they are combined) and their support staff
2. Data Operations	Salary, fringe and consortium/contractual indirect costs for leadership, data coordinators and support personnel plus supplies and services , including restricted support for creation of public datasets for completed trials with primary results published
3. Biostatistics and Bioinformatics	Salary, fringe, travel and consortium/contractual indirect costs for leadership, statistics, bioinformatics and support personnel plus supplies and services
4. Information Systems	Salary, fringe and consortium/contractual indirect costs for leadership, applications development, database and IT support staff, equipment, software, etc.
SUBTOTAL - STATISTICS & DATA MANAGEMENT	

F. Scientific Services

1. Clinical Reviews	Salary, fringe, travel, consortium/contractual indirect, & consultant costs for pathology, surgery, and any other clinical reviews
2. Tissue Banks Coordination Only **(RESTRICTED FUNDING in Ops & SDMC Budgets)**	Salary, fringe, travel, consortium/contractual indirect, consultant and other costs for coordination with the Tissue Bank(s) for the Network Group
3. RT or Imaging Technical Innovation for Network Group w/ this Specialty Focus Only	Salary, fringe, travel, equipment, consortium/contractual indirect, consultant & other costs for services related to technical innovation only. For Group with special expertise need because of specific developmental research strategy in RT and/or Imaging outside Core Services (1 adult and 1 pediatric Group max)
4. Scientific Support Services	Salary, fringe, travel, consortium/contractual indirect and supply or other costs for outcomes, correlative studies or other scientific services
5. DSMB/DMC (Ops Center & SDMC) **(RESTRICTED FUNDING IN Ops & SDMC Budgets**	Salary, fringe, travel, consortium/contractual indirect and supply or other costs for administration/management of DSMB/DMCs for Network Group
6. Statistical Support for Creating Datasets for Data Sharing Policy (**RESTRICTED FUNDING in SDMC Budgets)**	Salary, fringe, travel, consortium/contractual indirect and supply or other costs for outcomes, correlative studies or other scientific services

G. Per Case Data Management Funding * - RESTRICTED FUNDING (Whether by PSA or Member Subcontracts)

1. Screening on Trial Per Case (No intervention)	Only for screening done as part of trial (i.e., consent required on study) for estimated # of patients in project period year
2. Therapeutic Basic Intervention Per Case	Based on estimates for # patients randomized and/or placed on study intervention on therapeutic study
3. Advanced Imaging Basic Intervention Per Case	Based on estimates for # patients randomized and/or placed on study intervention on advanced imaging study – basic data collection
4. Biospecimen Collections Per Case	Based on estimate of # of per patient for trials designated for biospecimen per case payments
5. Special Advanced Imaging Per Case for Network Group with Specialty Focus in this Area	Based on estimates for # patients randomized and/or placed on study intervention on advanced imaging study for advanced credentialing/imaging resources
6. For Pediatrics Network Group Only– Provide High-Performance Per Case payments here based on accrual thresholds (Basic Intervention Provided Above)	
7. For Pediatrics Network Group Only– Provide Institutional Infrastructure payments here based on accrual thresholds	

SUBTOTAL -PER CASE REIMBURSEMENTS

SUBTOTAL - ACCRUAL COSTs & TOTAL ALL DIRECT COSTS

* Please Note: Special Per Case Funding would be based on individual trial needs determined by NCI/DCTD and should not be included in the application budget from the Network Group.
Additional "high-performance" per case data management funding would be provided via special program administered by the CTSU, and should not be included in a Network Group Operations Center application budget except for a Pediatric Network Group

X. Accrual Input by Member Institution/Sites for Network Group Operations Center and Network Lead Academic Participating Site Budget Requests for New Applications

The Network Group Operations Center and Network Lead Academic Participating Site applicants must submit the breakdown of the accrual they anticipates from each of their member institutions/sites to all NCTN trials over the planned project period that was used as input to generate their budget requests in the budget section of their applications. A suggested format for a table to provide this information is provided below.

For the Network Group Operations Center applicant, these tables will reflect accrual from all member sites to all NCTN trials – both trials led by the Network Group Operations Center as well as accrual credited to it but for trials led by other Network Groups. The associated Network Group Statistics and Data Management Center should provide estimates for the total accrual anticipated for trials the Network Group Operations Center leads regardless of which Network Group the participating site may credit.

NCTN Key Component for Application:
Network Group Operations Center - Application #1

Institution Name	NCI Institution Code (if applicable)	Membership Type	Type Per Case Management Funding *	# Patients for Per Case Funding in Category				
				Year 1	Year 2	Year 3	Year 4	Year 5
University of XXX	YY000	Main Member	Basic Intervention – Therapeutic (includes pilot studies)	30	30	30	30	30
			Basic Intervention - Adv Imaging	5	5	5	5	5
			Screening	5	5	5	5	5
			Total for Screening & Intervention	40	40	40	40	40
			Biospecimen	20	20	20	20	20
Health Corner Unit	YY001	Affiliate	Basic Intervention – Therapeutic (includes pilot studies)	30	30	30	30	30
			Basic Intervention - Adv Imaging	5	5	5	5	5
			Screening	0	5	0	5	0
			Total for Screening & Intervention	35	40	35	40	35
			Biospecimen	20	20	20	20	20
XXXX CCOP	XX000	CCOP	Basic Intervention – Therapeutic (includes pilot studies)	30	30	30	30	30
			Basic Intervention - Adv Imaging	5	5	5	5	5
			Screening	5	5	5	5	5
			Total for Screening & Intervention	40	40	40	40	40
			Biospecimen	20	20	20	20	20
ZZZZ MB-CCOP	ZZ000	MB-CCOP	Basic Intervention – Therapeutic (includes pilot studies)	30	30	30	30	30
			Basic Intervention - Adv Imaging	5	5	5	5	5
			Screening	5	5	5	5	5
			Total for Screening & Intervention	40	40	40	40	40
			Biospecimen	20	20	20	20	20
ETC.								

*** For Pediatric Network Group applicants, a row for "High Performance Intervention" should be added for the appropriate pediatric sites as those sites do not have the option of applying for the Lead Academic Participating Site awards.**

NCTN Key Component for Application:
Lead Academic Participating Site - Application #1

Institution Name	NCI Institution Code (if applicable)	Membership Type	Type Per Case Management Funding *	# of Patients for Per Case Funding in Category				
				Year 1	Year 2	Year 3	Year 4	Year 5
University of XXX (Lead - Site 1)	YY002	Lead	High Performance Intervention	30	30	30	30	30
			Basic Intervention - Therapeutic & Pilot Studies	2	2	2	2	2
			Basic Intervention - Adv Imaging	5	5	5	5	5
			Screening	5	5	5	5	5
			Total for Screening & Intervention	42	42	42	42	42
			Biospecimen	20	20	20	20	20
University of XXX (Lead - Site 2)	YY003	Lead	High Performance Intervention	30	30	30	30	30
			Basic Intervention - Therapeutic & Pilot Studies	1	1	1	1	1
			Basic Intervention - Adv Imaging	2	2	2	2	2
			Screening	3	3	3	3	3
			Total for Screening & Intervention	36	36	36	36	36
			Biospecimen	20	20	20	20	20
Health Corner Affiliate	KK000	Affiliate of Lead	High Performance Intervention – **N/A for affiliates**	N/A	N/A	N/A	N/A	N/A
			Basic Intervention - (includes Pilot Studies)	10	10	10	10	10
			Basic Intervention - Adv Imaging	1	1	1	1	1
			Screening	0	3	0	3	0
			Total for Screening & Intervention	11	14	11	14	11
			Biospecimen	5	6	5	6	5

ETC.

*** For adult cancer treatment studies, pilot treatment studies are rarely performed, hence this row may or may not show any projected accrual. Estimates for basic intervention for advanced imaging studies and screening estimates may be variable as well depending on the applicant's past accrual history and anticipated future accrual.**