Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

National Cancer Institute at the National Institutes of Health

NATIONAL CANCER INSTITUTE EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK (ETCTN) PROGRAM GUIDELINES

DIVISION OF CANCER TREATMENT AND DIAGNOSIS
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH

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Part 1: Overview of the ETCTN

1.I. Introduction

1.I.1. Purpose and Content of Guidelines

Guidelines for the National Cancer Institute (NCI) Experimental Therapeutics Clinical Trials Network (ETCTN) have been developed by NCI staff of the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), in consultation with staff of the NCI Office of Grants Administration (OGA) and the NCI Division of Extramural Activities (DEA),as well as with the advice of qualified members of the extramural scientific community. The 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 an innovative, state-of-the-art experimental therapeutics clinical trials program executed by an integrated network of investigators and participating institutions who are experienced in conducting early phase clinical trials with emphasis on molecular characterization, biomarker assays, pharmacogenomics, integral and integrated assay development, pharmacodynamics (PD), pharmacokinetics (PK), and advanced imaging technology. For more information on the PK laboratories, please see The Experimental Therapeutics Clinical Trials Network (ETCTN) Pharmacokinetic Resource Laboratories Guidelines at https://ctep.cancer.gov/initiativesPrograms/etctn.htm.

The ETCTN includes the NCI CTEP Phase 1 and Phase 2 clinical trials programs and complements the National Clinical Trials Network (NCTN), which focuses on late phase development with an emphasis on phase 3, disease-specific studies. The ultimate purpose of the ETCTN is to develop new approaches to cancer treatment based on molecular characterization and biomarker assay development used for patient selection in early phase experimental therapeutic clinical trials. Participants collaborate with NCI staff to achieve ETCTN objectives. The NCI provides centralized support for such activities as data management, clinical trial registration, regulatory support, and Central Institutional Review Board (CIRB) review.

This Guidelines document is divided into three parts:

A. **Part 1 – Overview of the ETCTN Program**
   This part describes the ETCTN and its policies and procedures, including the Terms and Conditions of Award.
B. **Part 2 – Guidelines for Submission of Continuing Applications**
   This part describes the progress report (Research Performance Progress Report (RPPR)) and budgetary issues for non-competing continuation applications.
C. **Part 3 – Appendices**
   This part contains appendices relevant to the policies and procedures associated with the ETCTN and with the application and review processes.

A variety of rules and regulations affect the ETCTN (NIH Grants Policy, policies of the Office of Human Research Protections [OHRP], the Code of Federal Regulations, etc.). These Guidelines are intended to cover NCI/DCTD's general and special requirements for the ETCTN and to supplement NIH and Department of Health and Human Services (DHHS) policies. These Guidelines, as well as the policies applicable to all awardees under the ETCTN, must adhere to NCI, NIH, and DHHS policies. Applicants should contact the responsible NCI ETCTN Science Officer and the NCI ETCTN Administration and Grants Manager to resolve any apparent discrepancies in the interpretation of these Guidelines and/or if they

believe these Guidelines conflict with other applicable federal policies. A list of contacts for the ETCTN Program is provided at https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Contacts.pdf.

1.I.2. Background, Overview, and Purpose of the ETCTN

The NCI supports a program to facilitate the early stages of development of cancer therapeutic agents in partnership with industry and academia. The Experimental Therapeutics Development Program funds and oversees clinical development of new agents for the Cancer Therapy Evaluation Program (CTEP) (http://ctep.cancer.gov/). The program has contributed to the clinical development of many anticancer agents. The Experimental Therapeutics Development Program has rapidly taken advantage of new scientific opportunities to promote therapeutic innovation that is generally not addressed by the private sector. The program has:

1. Utilized new discoveries regarding signaling pathways that promote tumor growth and metastases, as well as those that are multiple, redundant, and induced when a "dominant pathway" is inhibited to develop novel therapies.
2. Sponsored over 500 investigational agent combination clinical trials (200 since 2001). These combinations include over 100 new molecular entity (NME)/NME combinations.
3. Used new technologies to allow rapid, deep assessment of DNA mutations, methylation patterns, gene expression profiles, and RNA expression arrays in human tumor samples.
4. Conducted studies with genetically defined tumor subtypes to optimize potential benefit to patients and to facilitate characterization of drug effect on the putative target.
5. Defined dosing and dose modification licensing recommendations for patients with hepatic and renal dysfunction.
6. Evaluated drug/drug interactions in patients with HIV-associated malignancies receiving Highly Active Antiretroviral Therapy (HAART).
7. Identified and developed a drug combination with promising anti-tumor activity that has been independently verified resulting in a phase 3 licensing trial being conducted by the NCTN with support by the pharmaceutical collaborator.

The NCI's experimental therapeutics program melds NCI partnerships between pharmaceutical companies that are developing novel agents and the specialized clinical trial expertise of NCI-supported investigators in academic medical centers to develop new agents or novel agent combinations for new clinical indications. Through this program, over 900 INDs for investigational agents have been filed since 1972. CTEP currently holds approximately 175 INDs for investigational oncology agents (including 23 INDs for novel combinations of investigational agents), involving 60 pharmaceutical/biotechnology collaborators.

NCI accepts new agents into its portfolio through the NCI Experimental Therapeutics Program (NExT; https://next.cancer.gov/) and negotiates Cooperative Research and Development Agreements (CRADAs) with pharmaceutical companies to develop these agents within the ETCTN. As the Investigational New Drug Application (IND) sponsor, NCI/CTEP assumes responsibility for ensuring that all regulatory requirements are met for CTEP clinical trial protocols using these agents. CTEP prepares and submits approximately 19-24 IND applications to the Food and Drug Administration (FDA) each year. Agents under evaluation include small molecules, antibodies, vaccines, targeted toxins, oligonucleotides, and gene transfer agents. Most CTEP-IND agents are from pharmaceutical and bio-pharmaceutical collaborators, but some may come from academia.

To develop these agents, -NCI provides funding for a network of specialized expertise of academic centers with expertise in oncology drug development to conduct early phase clinical trials. CTEP administers the grant award and its funding. This network, the Experimental Therapeutics Clinical Trials Network (ETCTN), -is overseen and administered by CTEP to create collaborations with experts across the country who can conduct these complex studies of CTEP-IND agents. Combination studies with molecularly targeted agents have become an increasingly high priority for NCI, based on the clinical relevance of these agents and lack of single-agent, long-term effectiveness. Because of its extensive collaborations with industry (through CRADAs) and with the research community (through the ETCTN), NCI is uniquely positioned to facilitate important studies that address unmet medical needs, involve difficult-to-accrue patient populations, involve combining agents from different pharmaceutical companies, and are otherwise challenging to accomplish in the private sector.

The Goals of the ETCTN include:

1. Early clinical development of CTEP-IND agents; including determination of tolerable dose schedules of these agents alone and in combination; early determination of efficacy in defined patient populations; and development of biomarkers of biological effects and clinical response.
2. Effective integration of scientific rigor into biomarker development and clinical trials.
3. Promotion of collaborations with cancer biology experts to investigate critical pathways and processes in the treatment of oncology patients with investigational drugs.
4. Acquiring high quality human specimens for ETCTN correlative laboratory studies.
5. Efficient and timely activation and conduct of clinical trials that meet regulatory requirements and Good Clinical Practice (GCP) standards and principles.
6. Providing clinical study leadership opportunities for early career clinical investigations.
7. Commitment to enrolling racial/ethnic and rural populations to reduce cancer disparities.

The ETCTN often accomplishes its objectives by forming multi-institutional, multi-disciplinary Drug Project Teams for drugs accepted into NCI's drug development program. These teams prioritize the initial clinical trials of these agents, either in novel indications or in novel combinations with other agents. All ETCTN awardees will be expected to participate on Project Teams to define the development plans for specific novel agents/combinations relevant to their expertise and capabilities. Representatives of other NCI-supported programs will also participate on those teams. The NCI will coordinate and support logistically the formation and operation of the Project Teams. As novel agents progress from Phase 1 to Phase 2 clinical trials, investigators representing various relevant NCI-supported programs will collaborate with NCI's Investigational Drug Steering Committee (IDSC) and its disease-specific steering committees. These Drug Project Teams develop novel treatments requiring molecularly guided patient selection and pathway-driven investigational combination therapies in a wide variety of malignancies.

NCI created two programs to expand the number of cancer centers that can participate in ETCTN trials. The Early Drug Development Opportunity Program (EDDOP) includes an accrual program that allows selected NCI-designated cancer centers (NCI-CCs) to participate in ETCTN trials. These centers are funded through administrative supplements to their Cancer Center Support Grants (CCSG, P30). Recently additional cancer centers were added to the ETCTN to focus on recruitment of minority and underserved patients to ETCTN trials, Create Access to Targeted Cancer Therapy- for Underserved Populations (CATCH-UP), also funded through CCSG administrative supplements.

To provide clinical research leadership opportunities in the ETCTN to the wider clinical research community, the EDDOP includes the opportunity for any member of an NCI-CC that is not affiliated with

an ETCTN UM1 cooperative agreement to lead innovative early phase studies of anti-cancer agents held under a CTEP IND. Currently, approximately half of all NCI-CCs are included in the ETCTN, either by holding a UM1 award or as an affiliate of a UM1 awardee. Upon approval of proposals submitted by a non-ETCTN NCI-CC for innovative clinical studies, they will be provided with the necessary ETCTN resources to be able to conduct their study. These resources include access to NCI-IND agents for the clinical trial, access to ETCTN clinical trial sites for patient accrual, complete centralized clinical trial support of the ETCTN, a Central Institutional Review Board (CIRB), centralized patient registration, centralized data collection and data management, laboratories for translational analyses (*e.g.,* National Clinical Laboratories Network [NCLN], U24 Pharmacokinetic Resource Laboratories), and CTEP regulatory support.

1.II. Process and Organizational Structure for the NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

1.II.1. Initial Clinical Development Process

Overview of the Initial Development of CTEP IND Agents

To address the new opportunities and challenges in the development of novel targeted cancer therapeutics, the NCI has established a systematic approach with several interacting functional components. NCI brings investigational agents into DCTD/CTEP for development through the NExT program. After a new agent is chosen for development, if there is substantial preclinical and/or clinical evidence to support various clinical studies, the Investigational Drug Branch (IDB) Project Team Leader forms an internal NCI Project Team from the various clinical, translational, and basic biology programs at NCI to begin the process of identifying the highest priority studies for initial CTEP development. Members of the NCI Project Team draft a preliminary drug and biomarker assay development plan. Once this plan is approved by the NCI Senior Advisory Committee (SAC), NCI sends out a Request for Project Team Member Applications (PTMAs) to ETCTN members, NCTN awardees, and other appropriate investigators identified by the NCI Project Team to initiate establishing an extramural Drug Project Team.

The Request for PTMAs includes publicly available information about the drug being developed and the types and focus of the clinical trials being considered in the preliminary drug and biomarker assay development plan. Recipients are invited to apply to participate in the Project Team as a Clinician Scientist, Translational Scientist, and/or Basic Scientist. Other specialized roles may be defined by CTEP in the Request letter, depending on the agent and the Project Team's needs. Individuals are free to apply to one or more of these roles based upon both their interests and qualifications, as documented in the PTMA. Junior investigators (clinicians with less than 7 years of training post-oncology fellowship) with mentors are especially encouraged to apply for Career Development Applications (CrDAs). Applications from clinical scientists must be approved by the Program Director(s) / Principal Investigator(s) (PDs/PIs) of the Lead Academic Organizations (LAOs).

Once the PTMAs have been reviewed and prioritized by the NCI, the IDB Project Team Leader selects the Drug Project Team members consisting of clinical, translational, and basic scientists. In addition, extramural Team Leaders are chosen. This Drug Project Team meets via regularly scheduled teleconference/web-based meetings (participation is mandatory) over a period of 8-12 weeks to develop and refine the drug and biomarker assay development plan for a team presentation to the Investigational Drug Steering Committee (IDSC). The Drug Project Team's goals are to arrive at a well-supported preclinical/translational plan which addresses critical questions that will inform drug

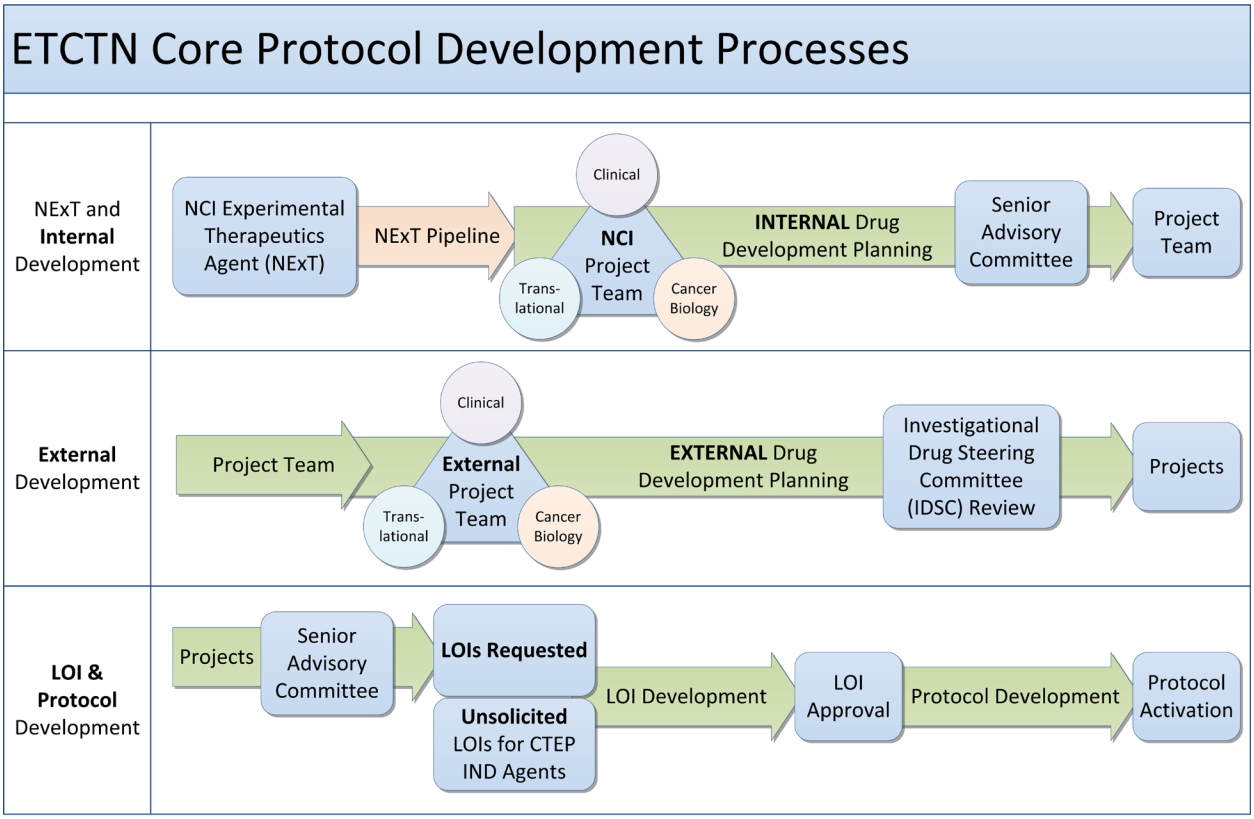
development, and to propose innovative disease-based or biomarker-based clinical trials incorporating appropriate safety, PK, PD, and efficacy endpoints. Following IDSC presentation and subsequent approval by the SAC, Letters of Intent (LOIs) are requested from the extramural Clinician Scientists of the Project Team, who are encouraged to collaborate as needed with the Translational and Basic Scientists to submit an LOI that incorporates the clinical and biomarker plans that were agreed upon. After review and approval of the LOIs by CTEP/DCTD and the pharmaceutical collaborator, the protocols are developed and submitted to DCTD/CTEP for review and approval prior to activation. The Drug Project Team may determine that additional preclinical data are needed to recommend prioritization of a clinical study, and supplemental funds may be awarded through the UM1 LAO to project team members to support these studies.

There are three caveats concerning the Drug Project Teams: (1) Project Team participation is not a guarantee that team members will lead a trial or lead a laboratory correlative study; (2) participation is not a guarantee of any supplemental funds; and (3) if team members participate, but then drop out and submit an unsolicited LOI that was included in the Drug Project Team discussions, their LOI will not be considered for review and approval.

A schematic overview of the development cycle for experimental therapeutics via the ETCTN is outlined on the next page. An expanded view of the NCI Project Team and the IDSC Project Team evolution through the stage of protocol development is available in the Appendices.

Clinician Scientists at ETCTN participating institutions may respond to Requests for PTMAs by submitting PTMAs and, subsequently, a Letter of Intent (LOI) for a clinical trial developed by the Project Team. Unsolicited LOIs will be considered after the conclusion of Project Team activities and the issuance of an Announcement of Availability to Investigators of [Agent Name] for Clinical and Nonclinical Study Proposals. Information regarding the submission of LOIs may be found at: https://ctep.cancer.gov/protocolDevelopment/letter_of_intent.htm.

Process for Initial Development Cycle of NCI IND Agents via the ETCTN



Parallel processes not shown include: Biomarker and assay development and review
Regulatory agreement development and sign-off (e.g. CRADA)
Additional levels of internal review

1.II.2. Subsequent Clinical Development Process

After the Project Team has finished with the development process, these Project Team investigators may submit a solicited LOI for NCI IND agents for CTEP review

1.II.2.A. Ancillary Studies

The database of patient information accumulated during ETCTN 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 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's total scientific program and are encouraged. A variety of funding mechanisms may be applicable for supporting ancillary studies.

1.II.2.B. Collaborations Among Network Partners and External Investigators

ETCTN participating institutions 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 early

phase 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 ETCTN LAOs/Lead Protocol Organizations (LPOs) are encouraged, as is the collaboration with investigators outside the ETCTN.

1.II.2.C. Conduct of ETCTN 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. Participating institutions in the ETCTN should comply with this standard as 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: https://www.fda.gov/science-research/science-and-research-special-topics/clinical-trials-and-human-subject-protection.

The integrity of clinical data is a function of the entire process of data recording, data collection, reporting, and analysis. ETCTN participating institutions must follow detailed Quality Control (QC) and Quality Assurance (QA) plans and systems to ensure compliance with regulatory requirements, and 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.

Scope of Scientific Activities

Consistent with the objectives and priorities of the ETCTN, each proposed ETCTN site and its investigators need to be capable of clinical research involving the following main scientific activities:

1. Conducting early phase experimental therapeutic clinical trials (pilot, phase 0, phase 1, phase 1/2, phase 2 and randomized phase 2 clinical trials) using single or combinations of novel agents from the NCI CTEP IND portfolio. The emphasis will be on novel agents that target relevant cancer cell signaling pathways and essential cellular machinery involved in the regulation of angiogenesis, cell survival, apoptosis, proliferation, and differentiation.
2. Participating in investigational agent-specific Project Teams to define the drug development plan.
3. Establishing relationships between PK and PD of the studied agents and the dose, schedule, exposure, and effect will be performed by the assigned U24 awardee.
4. Developing statistically appropriate clinical trial designs, including integral and integrated biomarker trials, accelerated titrations, Bayesian designs, and other advanced design schemes.
5. Studying special populations, including investigations involving patients with organ dysfunction(s), human immunodeficiency virus (HIV) infection, autoimmune disorders, *etc*.
6. Establishing safe and biologically active treatment schedules for patients with cancer.
7. Obtaining mechanistic proof-of-principle data for new agents directed at novel molecular cancer targets.
8. Collecting, processing, and, when appropriate, shipping biospecimens for biomarker analysis.
9. Evaluating data from clinical trials that involve combinations of CTEP IND agents.
10. Evaluating data from related laboratory studies that assess the nature of drug-drug interactions (DDIs) (additive/synergistic/antagonistic).

11. Evaluating translational endpoints in clinical trials of investigational agents (*e.g.*, the levels of expression and/or activity of molecular targets and/or downstream effectors pertinent to a given agent).

1.II.2.D. Structure of the ETCTN

The ETCTN consists of extramural LAOs and one intramural component, the Developmental Therapeutics Clinic (DTC), DCTD, NCI. Each LAO possesses an integrated organizational structure with scientific leadership and a site organization that facilitates team science, PK, PD, biomarkers, clinical trials support, statistics, protocol development, data management and administration, and regulatory and research pharmacy management. The clinical trials of the ETCTN must be conducted in accordance with the instructions as outlined in the "Investigator's Handbook, A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI" (http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf). An ETCTN organization chart is presented in the Appendices of this document.

The following definitions related to organization structure will be utilized:

1. Grant Administrator: The individual, named by the applicant organization, is responsible for the administrative coordination, communications, and all operational aspects of the clinical research project for the ETCTN LAO. The Grant Administrator will be the Cancer Trials Support Unit (CTSU) LAO contact for roster building and maintenance activities at the LAO. This person is not required to be the contact for scientific or financial matters. This individual will be granted rights to make changes to the organization's person roster and role information within the CTSU's Regulatory Support System (with appropriate training). This individual is typically a non-physician.
2. Institution Business Office Official: The individual, named by the applicant organization, authorized to act for the applicant and to assume the obligations imposed by the Federal laws, regulations, requirements, and conditions that apply to grant applications or grant awards. This individual is equivalent to the Signing Official in the eRA Commons, i.e., holds the Signing Official (SO) Role or is the Authorized Organization Representative (AOR).
3. Lead Academic Organization (LAO): The institution receiving the award under this Cooperative Agreement. In the case of a Multiple PDs/PIs application, the LAO will be the institution of the designated contact PDs/PIs on the application.
4. Integrated Component: A component of the awardee institution that may be at a different location but is under a shared financial system and governance structure.
5. Affiliated Organization (AO): An institution or academic site collaborating with the LAO. For multiple PDs/PIs applications, an AO is defined as an academic site(s) led by the designated multiple PIs on the Cooperative Agreement, other than the LAO institution.
6. ETCTN sites: the LAO, integrated components, and AOs.
7. Lead Protocol Organization (LPO): The organization (LAO) of the protocol PI.

The functions of specific required organizational components and key components for each ETCTN site are outlined below.

1.II.2.E. Key Components

Each awarded LAO has the following primary responsibilities:

1. **Scientific Leadership and Site Organizational Structure**
   The purpose of this component is to provide scientific leadership for the ETCTN LAO and AO sites, plans for ETCTN participation, and organization of the sites. It is essential that ETCTN awardees have considerable expertise and well documented experience and accomplishments (past performance) in the conduct of cancer clinical trials and clinical development of experimental therapeutics.

   A. Scientific Leadership:
      i. PDs/PIs at the academic participating sites are expected to be leaders in the areas of science and administration. PDs/PIs should have documented administrative leadership experience.
      ii. PDs/PIs at the ETCTN sites are expected to be national and international leaders in cancer related clinical trials of novel therapeutic agents, related clinical areas, and translational research relevant to such studies.
      iii. PDs/PIs are expected to accomplish cooperative and productive collaborations between participating ETCTN sites and other clinical and translational research investigators using a team science approach.
      iv. Scientific Leadership will oversee all clinical trials operations. Each ETCTN site is required to establish a specific structure to oversee the conduct of early phase therapeutic clinical trials, ensure data safety monitoring, compliance with the required policies and regulations, and facilitate interactions with other ETCTN and NCI staff.
      v. Scientific Leadership will assure timely preparation, presentation, and publication of clinical trial results and research findings at global meetings.

   B. Site Organizational Structure:
      i. Establish a clinical trials operations office to oversee the conduct of early phase therapeutic trials. This office is expected to have the requisite statistical expertise for trial design, coordinate patient enrollment, and have the requisite statistical expertise for monitoring and data analysis on all clinical trials open in the ETCTN.
      ii. Ensure data safety and monitoring oversight for patients on all active trials.
      iii. Establish an internal committee to monitor and oversee patient safety, protocol compliance, and outcome and response review.
      iv. Ensure collaboration between ETCTN members and NCI staff to achieve ETCTN goals and objectives.

2. **Team Science for Project Development**
   Each ETCTN site is expected to lead and/or participate in multi-disciplinary scientific Project Teams formed during the development and implementation of ETCTN drug development plans. This objective requires that ETCTN investigators are highly capable of inter- and trans-disciplinary team-based research efforts, including potential for interactions with investigators from other ETCTN sites, other NCI-sponsored programs, and NCI staff members. This is carried out by:

   A. Focusing on early drug development using inter- and trans-disciplinary team-based scientific research project approaches, nationally or internationally.
   B. Cooperating with investigators across disciplines.
   C. Promoting team efforts answering complex research challenges.

D. Enhancing existing capabilities and adapting new approaches to reach collaborative team goals.
E. Having procedures for addressing failure by participating investigators or institutions to meet study timelines and objectives.

3. PK/PD, Biomarker Assay, and Molecular Characterization of Patients

Each ETCTN site must have the capability to support clinical trials by conducting various laboratory testing of clinical specimens as needed. This component will support laboratory testing by:

A. Using validated molecular imaging capabilities, as appropriate.
B. Coordinating the acquisition, handling, preparation, evaluation, and shipment of specimens to ETCTN sites or tumor banks/repositories. This includes the requisite expertise in acquiring fresh specimens from a high percentage of patients on trials.
C. Analyzing tumors and other specimens to define response and resistance mechanisms and inform follow-on therapy and investigational combination treatment regimens.
D. Analyzing data from genomic and expression arrays or other biomarker-based studies.
E. Supporting and overseeing processes for requesting and reviewing proposals to perform correlative laboratory studies including PK/PD analyses with the assigned U24 laboratory group.
F. Participating in the molecular characterization of all patients enrolled on early phase therapeutics trials.
G. Correlating appropriate molecular, biological, and pharmacological endpoints with clinical outcomes which may be done in collaboration with the NCLN or other appropriate parties.

4. Coordination of Clinical Trials and Associated Activities

The Administrative Component is responsible for the organization and coordination of all aspects of clinical trials operations, implementation, and safe conduct. The administrative component collaborates with NCI support infrastructure to coordinate ETCTN activities. The coordination component is responsible for:

A. Facilitating member interactions and communications for single institution or multi-institution sites.
B. Supporting clinical trials performed by the research project team maintaining a team of qualified personnel necessary for the conduct of clinical trials.
C. Collecting and analyzing data by appropriate medical, statistical, and Clinical Research Associate (CRA) staff members.
D. Providing high-quality data management using an effective QA/QC program, including internal review and oversight of data submission.
E. Monitoring activities to guarantee data integrity and ample auditing.
F. Performing statistical evaluations essential for the appropriate design, conduct, and analysis of all clinical trials.
G. Participating in the NCI-sponsored CIRB, with all US sites required to use the NCI CIRB as the IRB of record for ETCTN trials. A Canadian LPO that leads an ETCTN trial must submit it for NCI CIRB review so that it can be reviewed and approved for US participation, but non-US sites cannot use the NCI CIRB as the IRB of record for their site; instead, Canadian sites use their appropriate country-specific, local IRB as the IRB of record.
H. Reporting program performance.

I. Distributing funding and reimbursing participating institutions and laboratories for work performed.
J. Reporting and monitoring safety on all trials enrolling patients at their site.

5. Research Pharmacy Management

It is essential that all ETCTN sites have a dedicated component to conduct investigational drug pharmacy operations required to adequately fulfill obligations related to investigational agents. This component should have:

A. Secured access to storage space and storage unit(s) necessary to meet storage conditions of agents.
B. Ability to properly order, receive, store, and maintain investigational agents.
C. Safe and secure handling, preparation, and disposal of dangerous goods, and hazardous and infectious substances.
D. Written standard operating procedures (SOPs) related to investigational agent management.
E. Existing procedures for reconciling deviations.
F. Research pharmacy personnel experienced in the preparation, storage, and dispensing of investigational agents.

6. Career Development and Mentored Training of Junior Investigators

Each ETCTN site is expected to organize appropriate career development and mentored training. The program should provide an adequate mentorship and/or training for new and junior investigators, including opportunities for trainees to lead clinical trials and participate in future ETCTN activities and/or initiatives. The development of junior faculty through mentorship, initiatives, and activities is demonstrated by:

A. Conducting experimental therapeutics education and training for junior investigators (less than 10 years post oncology fellowship training) who have not successfully competed as PDs/PIs for a substantial independent NIH research award.
B. Mentoring and/or training programs for new and junior investigators.
C. Providing opportunities for young investigators to lead clinical trials, as well as participate in experimental therapeutic development activities and/or initiatives.
D. Providing opportunities to enhance skill in and teach principles of experimental therapeutics.
E. Integrating translational science (bench-to-bedside and bedside-to-bench) into the training/mentoring program.

1.II.2.F. ETCTN Sites

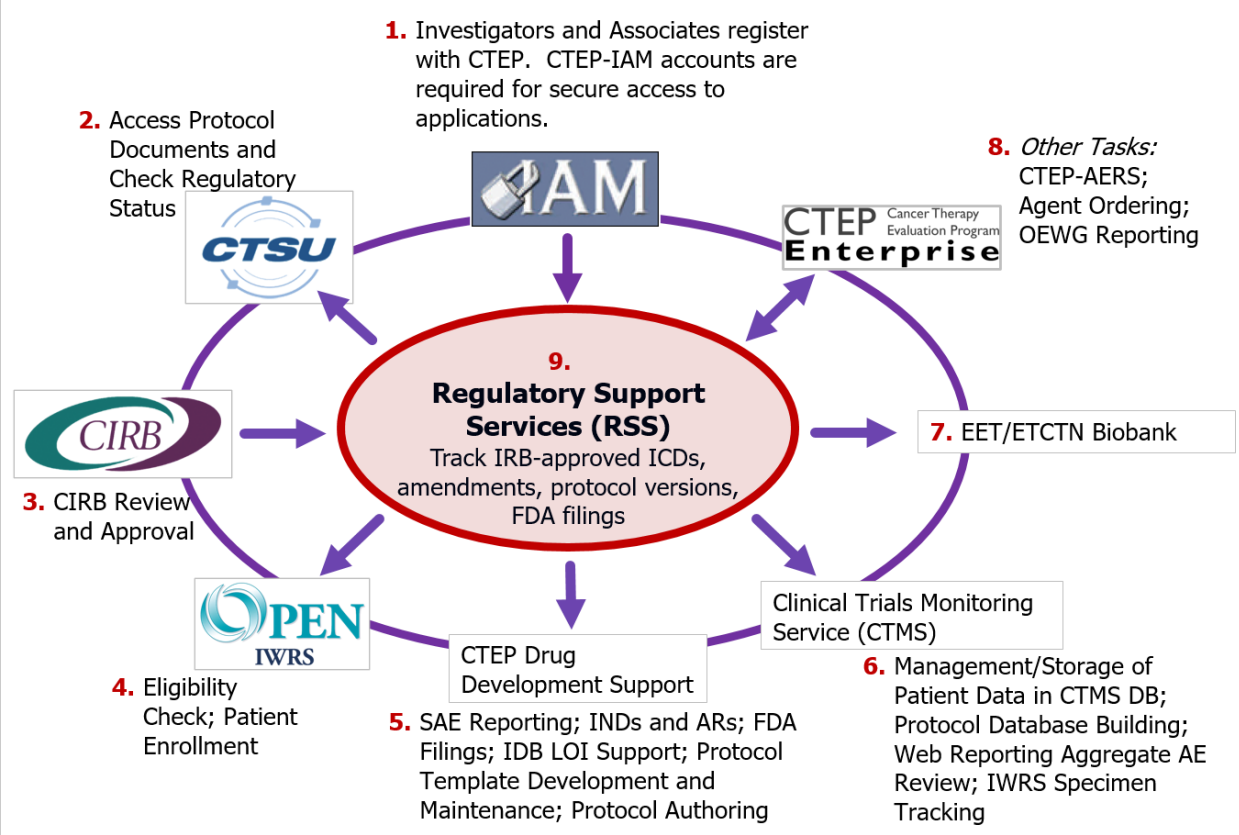
The Principal Investigator(s) [PI(s)] at the LAOs are expected to accomplish collaboration between all participating ETCTN sites and other clinical and translational research investigators as identified. Unless otherwise specified in the protocol document, Network members, sites, or others will be able to enroll patients on all trials conducted by the ETCTN, irrespective of the LPO leading the trial. All ETCTN sites will be responsible for screening, enrolling, and treating patients; collecting required biospecimens; and monitoring and reporting safety information throughout the conduct of their clinical trials.

1.II.2.G. Interactions with Other NCI-supported Programs

The ETCTN awardees are expected to interact as appropriate with entities/programs such as the NCLN Genomics Laboratory, NCLN PD Laboratory, EET Biobank, the NCI Cancer Trials Support Unit (CTSU), the Clinical Trials Monitoring Service (CTMS), the NCI CIRB, and NCI Advisory and Scientific Committees including the IDSC.

A schematic of the entities/programs with which ETCTN awardees interact is outlined below and followed by a reference table to facilitate finding help on ETCTN centralized services topics:

NCI-Sponsored Infrastructure for ETCTN Trials



A more detailed workflow for ETCTN centralized service applications is available in the Appendices.

1. **CTEP-Identity and Access Management (IAM)**
   IAM streamlines and provides access to CTEP Enterprise and CTSU Applications utilizing unique usernames and passwords. A CTEP-IAM user account is required to access the members' area of the CTSU web site as well as the Oncology Patient Enrollment Network (OPEN) and -the common data management system. Accounts can be used for certain Cooperative Group and CTEP functions. A CTEP-IAM Information Sheet is available. CTEP-IAM registration requests can be placed at: https://ctepcore.nci.nih.gov/iam/index.jsp.

2. **The Cancer Trials Support Unit (CTSU)**

The CTSU is a service of NCI's CTEP developed to provide administrative support for the clinical trials conducted by the ETCTN as well as other NCI-supported clinical trial programs. Key areas in which the CTSU supports the ETCTN include the following:

A. Providing centralized regulatory support via the CTSU Central Regulatory Office and the Regulatory Support System (RSS), including the database that maintains all regulatory documentation for ETCTN trials (*e.g.*, IRB approvals, other protocol-specific requirements).
B. Centralized communication and document posting via the CTSU members' website (https://www.ctsu.org).
C. Providing 24/7 centralized, web-based, patient enrollment for all ETCTN trials via the Open Patient Enrollment Network (OPEN) supported by ETCTN site rosters and site-level regulatory approvals provided via RSS; and
D. Providing support for the Common Data Management System (CDMS), including remote data entry, used for all ETCTN sites and ETCTN trials, and helping to harmonize procedures and policies related to operational aspects of trial conduct across the ETCTN.

The CTSU will also be overseeing the ETCTN Centralized Protocol Writing Service (CPWS) starting in 2022. A brief description of the CPWS is provided below.

Centralized Protocol Writing Support (CPWS)
The CPWS program was developed to streamline the development of ETCTN protocols from LOI approval to protocol activation. ETCTN protocols will be authored by the CPWS unless otherwise specified by the Contracting Officer's Representative (COR) and/or CTEP leadership. The exceptions include but are not limited to studies being conducted at the Clinical Cancer Center or DTC. The CPWS will be involved in the drafting of revisions, changes, and amendments unless otherwise specified by the COR and/or CTEP leadership. Initial drafts are created from the source LOI and any supplementary agent, disease-, or protocol-specific materials and are sent to the study investigators for review, editing, and approval before submission to CTEP.

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

3. **NCI Central Institutional Review Boards (CIRBs)**
The NCI Central Institutional Review Board (CIRB) Initiative includes four CIRBs that conduct IRB review of select Adult and Pediatric trials. All studies developed in the ETCTN will be reviewed by the NCI Adult CIRB-Early Phase Emphasis (EPE), or on occasion, by the NCI Adult CIRB – Late Phase Emphasis (LPE) or the NCI Pediatric CIRB (Peds). The membership of the EPE includes physicians, patient advocates, nurses, pharmacists, and statisticians who are knowledgeable about the design and conduct of early phase oncology trials, in general. Participating ETCTN institutional investigators and other staff are encouraged to participate as members of the EPE.

The CIRB conducts the IRB review of a study before it receives final CTEP approval. The Protocol PI is responsible for addressing any concerns the CIRB may have during the IRB review process. After completion of the IRB review, CTEP grants final approval of the study, and the study is made available to the network. PIs at institutions that are enrolled in the CIRB Initiative

complete a study-specific electronic form for approval by the CIRB. Once CIRB approval is obtained, the study can open.

To enroll in the CIRB Initiative, the CIRB requires institutions to complete an application, an Authorization Agreement, and electronic worksheets describing institutional practices, state and local laws governing research, and institutional PIs.

For more information, contact the CIRB Helpdesk from 8am-4pm Eastern Standard Time at:
1-888-657-3711
NCICIRBContact@emmes.com

Or visit the CIRB website at: www.ncicirb.org

4. **OPEN/Interactive Web Response System (IWRS)**
ETCTN sites will be rostered in RSS and use OPEN for patient registration. Within OPEN, a link to IWRS will be provided to support the LPO with functions relating to slot reservations and cohort management. Clinical trial database study builds and data management for all ETCTN protocols are managed by NCI DCTD/CTEP contractors. More information on OPEN and IWRS is located on the OPEN tab on the CTSU members' website: https://www.ctsu.org/OPEN_SYSTEM/ (password-protected website). You can also refer to the ETCTN Patient Enrollment Information Sheet in the appendix.

5. **Drug Development Support Service**
The Drug Development Support Service provides a variety of early drug development support services to ETCTN studies, including regulatory filings (including INDs and IND annual reports); LOI and PTMA review support; safety and pharmacovigilance support including serious adverse event (SAE) report triage, reporting, and narrative review/submission; and development and maintenance of protocol templates.

6. **Clinical Trials Monitoring Service (CTMS) and Common Data Management System (CDMS)**
To assist CTEP in fulfilling its regulatory responsibilities as an IND sponsor and to ensure protocol compliance and source data verification, resources for data management and monitoring will be provided under contract through the Clinical Trials Monitoring Service (CTMS). The benefits of centralized data management include increased efficiency by having a single entity responsible for the study, build a core set of common electronic Case Report Forms (eCRFs) to be utilized via the Common Data Management System (CDMS), data management, QA, adverse event analysis, and study reporting generation. The specific tasks in the contract pertaining to the ETCTN include:

   A. **TASK I:** To provide a resource, and patient data QC reviews for DCTD for clinical investigators conducting early phase experimental therapeutic clinical trials conducted through the ETCTN. All participating institutions must submit data to CTMS using the NCI-procured clinical data management system (CDMS) every 2 weeks. The CTMS will provide technical and administrative support for the ETCTN Data Safety Monitoring Board/Committee for randomized phase 2 studies conducted by the ETCTN.
   B. **TASK II:** To provide an onsite monitoring and auditing resource for the DCTD to ensure that contractors, awardees, and other clinical investigators conducting early phase experimental therapeutic clinical trials follow federal regulations, GCPs, and NCI policies and procedures.

This resource will be utilized to verify submitted protocol patient data, and ensure the quality of submitted data, protocol compliance, and patient safety through proper reporting.

More information regarding CTMS, including other services and new initiatives, is available at: https://www.theradex.com/clinicalTechnologies/?Clinical-Trial-Management-System-CTMS-3.

7. **NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank)**
NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank or EET Biobank was formerly known as ETCTN Biorepository and Accessioning Center.

Access to biospecimens with associated high quality clinical, treatment, recurrence, and outcome data is critical to developing and validating the tests needed for diagnosis, target identification, and prediction of response to therapy. High quality biobanks of uniformly collected biospecimens associated with validated clinical data from patients treated in early phase clinical trials are crucial for supporting cancer research and drug development. The EET Biobank will be responsible for collecting, processing, and storing a variety of human biospecimens from patients with cancer who are participating in NCI-funded ETCTN and other NCI-supported early and experimental clinical trials and distribution of biospecimens to qualified NCI-approved trial investigators and research laboratories. The ETCTN organizes and carries out NCI-sponsored phase 0, 1, 2 and phase 1/2 combination clinical trials and are uniquely positioned to collect and bank biospecimens from these trials. The EET Biobank is supported by the U24 Cooperative Agreement grant (RFA-CA-20-003)

The EET Biobank receives, stores, and distributes tissue specimens as well as blood and other biological fluids from patients participating in ETCTN and other NCI-supported early and experimental clinical trials. The biospecimens will encompass adult solid malignant tumors and hematologic malignancies. The biospecimens are collaboratively collected during the NCI-supported cancer clinical trials and sent to the EET Biobank. The biobank receives, processes, and stores the biospecimens and distributes them to the ETCTN and other non-ETCTN NCI supported early and experimental clinical trials investigators for approved studies.

Biospecimens consist of the following: formalin-fixed paraffin-embedded (FFPE) blocks and histological slides collected through diagnostic biopsies, surgical resections, and research biopsies from patients with cancer; frozen tissue; serum; plasma; whole blood; white blood cells; bone marrow; urine; skin and sputum/buccal samples; and molecular derivatives such as nucleic acids.

The EET Biobank ensures uninterrupted operation (collection, storage, distribution, etc.) regarding specimens from ongoing ETCTN and other NCI-supported early and experimental clinical trials. Biospecimens that remain in excess after clinical trial protocol requirements have been met will be annotated, catalogued, and made available to ETCTN investigators and qualified investigators at NCI-approved reference research laboratories and institutions for additional correlative scientific studies that have been reviewed and approved by the CTEP.

For additional NCI-supported tissue resources
see: https://cdp.cancer.gov/resources/human_specimen/finding_human_tissue.htm

8. **CTEP Enterprise – Other Tasks**

NCI Advisory & Scientific Committees

In addition to the key components of the ETCTN that are described above and are directly funded by the ETCTN, other NCI grant supported Programs and their awardees, as well as NCI Advisory Committees, will have important supporting roles in carrying out the research objectives of the ETCTN. Thus, the ETCTN awardees are expected to interact as appropriate with such entities/programs as the DCTD Clinical Assay Development Network, National Clinical Laboratories Network (NCLN), Cancer Immune Monitoring Analysis Center (CIMAC), Division of Cancer Biology, SPOREs, NCI-Designated Cancer Centers, Program Project Grants, Rare Diseases, and the NCTN.

The NCI Committees associated with clinical trials and translational research activities funded by the NCI are described briefly below. Information on the NCI Committees is available at: https://www.cancer.gov/about-nci/organization/ccct/steering-committees. 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.

A. NCI Clinical Trials and Translational Research Advisory Committee (CTAC):
The NCI CTAC is an external oversight committee, governed by the provisions of the Federal Advisory Committee Act, which 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 ETCTN evaluates the clinical trial portfolio across the entire ETCTN 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.

B. NCI Investigational Drug Steering Committee (IDSC):
The NCI IDSC is a body convened by the NCI Coordinating Center for Clinical Trials (CCCT). The characteristics and activities of the IDSC are:

i. The IDSC is constituted by the CCCT to include the following membership: two elected chairs, all cooperative agreement contact PDs/PIs and other multiple PDs/PIs, ETCTN coordinators who liaise with the NCTN Groups, subject matter experts in the areas of biomarkers, molecular characterization, statisticians, pharmacologists, radiation oncologists, interventional radiologists, research pathologists, and others added *ad hoc* based on need and expertise. Leadership of the trans-ETCTN Biospecimen Working Group (EBWG) will become members of the IDSC.

ii. The IDSC has a coordination team (CT) consisting of two leaders elected from the membership of the IDSC, the NCI Program Official of the ETCTN, the Branch Chief of the Investigational Drug Branch, and other CT leaders.
iii. The main goal of the IDSC is to facilitate ETCTN collaborations and provide scientific and technical expertise related to experimental therapeutics development.
iv. The IDSC will work in concert with CTEP and the ETCTN Program Official to:
    a. Further the goals and objectives to treat, control, and cure cancer.
    b. Clinically evaluate investigational agents with an emphasis on translational research to elucidate molecular targets and mechanisms of drug effects.
    c. Provide advice during all phases of drug development.
    d. Facilitate scientific dispute resolution.
v. The IDSC will meet at least quarterly.

This Committee may establish one or more Task Forces and/or Working Groups that focus on specific scientific areas of interest. General information on the NCI IDSC is available at: https://www.cancer.gov/about-nci/organization/ccct/steering-committees/investigational-drug.

C. NCI Clinical and Translational Research Operations Committee (CTROC):
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.

9. **Data safety and monitoring Board (DSMB)**
The Clinical Trials Monitoring Service coordinates the operation of a Data Safety Monitoring Board (DSMB) for the ETCTN for Phase 1/Randomized Phase 2 and Randomized Phase 2 studies. The focus of the ETCTN DSMB is on the randomized phase 2 studies.
https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_etctn_ctms.htm

10. **CORE the Clinical Oncology Research Enterprise- CTEP CORE supports CTEP, other NCI staff, and the extramural community in the following clinical trial domains:**
    - **Information Security**
    - **Study Administration and Logistics**
    - **Clinical Data Capture and Reporting**
    - **Correlative Study Data**
    - **Regulatory Monitoring and Reporting**
    - **Data Quality and Control**

1.II.2.H. Biomarker Review Committee (BRC)

With the current emphasis on biomarker-driven drug development, it is necessary to ensure that assays that measure biomarkers in CTEP-sponsored protocols have been reviewed and determined to be fit-for-purpose. To that end, the NCI Division of Cancer Treatment and Diagnosis (DCTD) has formed the Biomarker Review Committee (BRC), which is now responsible for reviewing the biomarker components of CTEP-sponsored clinical trials.

Definitions

An investigational laboratory assay is one that has not been cleared or approved by the FDA for the purpose for which it will be used in the trial.

Integral studies are defined as assays/tests that must be performed for the trial to proceed. Integral studies are inherent to the design of the trial from the outset and must be performed in real time for the conduct of the trial. Examples include tests to determine eligibility, tests to assign treatment or stratify randomization, and tests whose results serve as the primary endpoint of the trial. Integral biomarkers may require a CLIA-certified laboratory, which will be needed if the test results will be returned to the patient or their physician.

An integral assay that will be used to determine eligibility or treatment may need to be performed under an Investigational Device Exemption (IDE) from the FDA.

Integrated studies are defined as assays/tests that are clearly identified as part of the clinical trial from the outset and are intended to address the highest priority scientific question in the trial. Integrated studies in general should be performed on all the trial participants or on a pre-defined subset such as an expansion cohort. Plans for specimen collection, laboratory measurements, use of cutpoints, and statistical analysis should be pre-specified and should be based on sufficient preliminary data to ensure scientifically valid results from the trial.

In contrast, *exploratory* biomarkers may not be performed on all subjects in a trial, and collection of these exploratory markers may be voluntary. Exploratory biomarkers will not undergo BRC review, except when NCI funds are requested for collection or for the marker analysis. However, in some cases, the distinction between an integrated and exploratory biomarker may be difficult, and NCI may decide to review the biomarker in such cases.

LOI Review Process and Duties of the Investigator

LOIs for trials under CTEP INDs that are not reviewed by an NCI disease-specific steering committee will require BRC review and approval if they meet **any** of the following criteria:

- Integral or integrated biomarkers are proposed.
- CTEP funds are requested for sample collection and/or performance of the assay.
- Biomarker plan requires biopsy(ies) that are mandatory specifically for research.
- Biomarker procedure is burdensome on the patient (invasiveness, schedule, etc.)

In most instances the inclusion of biopsies or other invasive procedures in a trial will need to be justified by an integrated biomarker assay that has been approved as fit-for-purpose by CTEP.

The BRC may, at its discretion, review any assay judged to be of particular importance to the trial. Laboratory correlatives that are generally not reviewed by BRC include pharmacokinetic assays, anti-drug antibody assays, and flow cytometry of peripheral blood and bone marrow.

All biomarker studies that request to use NCLN resources will undergo a review by the NCLN Committee for approval.

An LOI may propose the use of an assay that has been previously reviewed and approved by the BRC. The BRC will determine whether the existing assay is fit-for-purpose for the new trial. Additional information may be required, for example to show that the existing assay works on a different type of tumor tissue. If the previously reviewed assay is approved for the new trial, a letter of commitment will be required from the laboratory.

To comply with OEWG timelines, BRC reviews will occur in parallel with CTEP's Protocol Review Committee (PRC) and will be coordinated by the CTEP Protocol Information Office (PIO). Comments from the BRC reviewers will be incorporated into CTEP BRC consensus reviews that will be sent to the investigators.

Note: Because integral biomarkers are critical to carrying out the clinical trial, BRC approval of the integral biomarker assays is necessary prior to LOI approval. Accordingly, CTEP strongly encourages investigators to include the assay information described below when submitting the LOI. Investigators are encouraged to discuss their biomarker plan with the Investigational Drug Branch (IDB) Medical Officer for an agent before submitting an LOI. A list of NCI IND agents and

corresponding Medical Officers (Drug Monitors) can be found at the following link: https://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm.

Integrated markers may be reviewed by the BRC after the LOI approval has occurred, although investigators must provide to PIO the information needed for BRC review and approval, generally before a protocol may be submitted.

When submitting the LOI, investigators should carefully complete both the biomarker table, which defines the purpose of each biomarker and assigns a biomarker to an assay, and the specimen collection table which shows how each specimen will be analyzed in reference to the proposed biomarkers. When a biospecimen is intended to be used in multiple assays, the priority of use of each specimen must be delineated. In addition, the funding source for each assay must be identified.

Investigators should be certain to provide sufficient information about assay methodology and operating characteristics to allow BRC reviewers to make an adequate assessment. The **Study Checklist for CTEP-Supported Early Phase Trials with CTEP-Supported Biomarker Assays** [at: http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm] provides templates for structured submissions for all assays that meet any of the bulleted criteria listed above, and submission of the completed checklist(s) as an appendix to the LOI will expedite the review. The information submitted to BRC reviewers should clearly state the purpose the biomarker will serve in the trial and provide data to demonstrate that the assay for the biomarker has analytic performance adequate for that purpose.

Please note that failure to provide sufficient information to allow NCI reviewers to evaluate the assay may delay LOI or protocol approval.

1.II.3. General Management & ETCTN Operating Principles

1.II.3.A. General Management

Direct programmatic oversight of the ETCTN is provided by the NCI, DCTD and its programs. The primary oversight and administration of the ETCTN Program is provided by the Investigational Drug Branch (IDB) in the Cancer Therapy Evaluation Program (CTEP) in DCTD. CTEP works closely with other staff within the DCTD for the ETCTN including representatives from the Biometric Research Program (BRP), the Cancer Diagnosis Program (CDP), the Cancer Imaging Program (CIP), and the Radiation Research Program (RRP), DCTD. Additional ETCTN collaborators include the Clinical Assay Development Network, NCLN, CIMAC, the Division of Cancer Biology, SPOREs, as well as other NCI Senior Scientific and Administrative staff from all CTEP branches, and other DCTD and NCI programs and offices. The NCI ETCTN Administration and Grant Manager and IDB Clinical Operations Manager work closely with the ETCTN Program Official to oversee the ETCTN.

NCI Division of Cancer Treatment and Diagnosis (DCTD): https://dctd.cancer.gov/
NCI/DCTD Cancer Therapy Evaluation Program (CTEP): https://ctep.cancer.gov/
NCI/DCTD Biometric Research Program (BRP): https://brb.nci.nih.gov/
NCI/DCTD Cancer Diagnosis Program (CDP): https://www.cancerdiagnosis.nci.nih.gov/
NCI/DCTD Cancer Imaging Program (CIP): https://imaging.cancer.gov/
NCI/DCTD Radiation Research Program (RRP): https://rrp.cancer.gov/

NCI/DCTD National Clinical Laboratories Network (NCLN):
https://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm

1.II.3.B. ETCTN Operating Principles

The purpose of the ETCTN is to provide a standing, consolidated, and integrated infrastructure for an experimental therapeutics program. ETCTN participating institutions will collaborate with each other and with NCI to achieve the objectives of the Network. The NCI will provide centralized support for program management, centralized registration, data management, centralized IRB review, auditing, and other support for approved, early phase trials originating inside and outside the Network.

1.II.3.C. Opening a Trial in the ETCTN

Checklists for each of the "Steps to Activating an ETCTN Trial for the Coordinating Center" and "Steps to Site Participation in ETCTN Trials" respectively detail actions to be taken by the Coordination of Clinical Trials and Associated Activities Component and Study PI leading up to ETCTN study activation, and by the site to participate in an ETCTN study; these checklists are available in the Appendices.

1.II.3.D. ETCTN Education and Training

ETCTN education and training resources are available online via the CTSU, including slide sets (such as "ETCTN CTMS Systems Build" and "ETCTN Protocol Development: From Approval on Hold to Activation," both of which are available in the Appendices). Information sheets, which are also included in the Appendices, provide ETCTN brief procedural outlines/summaries and are maintained by the CTSU.

1.II.3.E. Grant Funding for ETCTN

In general, the allowable costs can support expenditures associated with personnel (*e.g.*, operational staff, scientific and administrative committee leaders, PIs for specific trials), travel, and other operational costs related to the conduct of clinical trials. However, costs for recruitment are permitted in the competing continuation RFA (RFA-CA-19-007). See section IV, R&R budget, 3rd paragraph under "General determination of overall funding. Routine patient care, laboratory tests, and reference laboratory research are not allowed under the award funding for the ETCTN, unless approved by the ETCTN Program Official and Associate Director, CTEP, for exceptional circumstances related to a specific trial. Funding for research laboratory tests may require support from other resources, including commercial and charitable funds, and/or specific administrative supplements to the Cooperative Agreements under the ETCTN in special situations.

1.II.3.F. Funding for Data Collection/Management and Biospecimen Collection

NCI funding for LAOs participating in all ETCTN trials to cover the costs related to data collection/management and biospecimen collection associated with enrolled patients is provided by award funding. LAOs are responsible for establishing subcontracts with their Integrated Components and AOs.

1.II.4. Terms and Conditions of Award for Cooperative Agreements

1.II.4.A. General Terms and Conditions of Award for ETCTN (UM1) (RFA-CA-19-007)

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, DHHS grant administration regulations at 45 CFR Part 75, and other DHHS, 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, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

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

1. Establishing an overall research strategy for ETCTN early phase clinical trials as well as all key components related to the conduct of approved clinical trials.
2. Overseeing the development, with CTEP assistance, of appropriate early phase experimental therapeutic clinical trial protocols.
3. Ensuring that the performance benchmarks are met including specifically:
    A. Accrue approximately 100 patients annually to ETCTN clinical trials, of which approximately 30% should be accrued to ETCTN trials not led by the institution or its affiliates
    B. Open approximately 30% of available ETCTN trials at the institution and/or at its affiliates, of which approximately 30% should be ETCTN studies not led by the institution or its affiliates
    C. Achieve approval-on-hold status of approximately two new Letters of Intent (LOIs) per year

4. Ensuring that each Disease-Focused Clinical Investigator (D-FCI):
    A. Is responsible for developing, opening, and supervising ETCTN studies within their discipline at their institution and other institutions in the proposed LAO(s) and AO(s).
    B. Opens a minimum of six ETCTN trials per year at LAO and AO sites.
    C. Accrues in their discipline a minimum of 10 patients per year to ETCTN disease specific clinical trials.
5. Ensuring each site has a clinical investigator with phase 1/phase 1 combinations expertise.
6. Ensuring the Interventional Radiologist performs risk assessments and obtains high quality research biopsies.
7. Ensuring the Research Pathologist reviews the quality of the biopsy specimens and assists in the biomarker assay development.

Disease-Focused Clinical Investigators (D-FCI)

The ETCTN D-FCI initiative aims to promote team-based collaborations among **Disease-Focused Clinical Investigators** at Experimental Therapeutics Clinical Trials Network (ETCTN) affiliated research sites (lead academic organizations and affiliated organizations). D-FCIs are ETCTN funded clinical trial investigators responsible for leading disease-specific accrual to ETCTN sponsored early-stage clinical cancer trials. D-FCI teams (e.g., ETCTN breast cancer specialists) are expected to attend bi-annual webinar meetings focused on enhancing disease-specific research collaborations to support ETCTN clinical trial accrual and clinical research objectives. D-FCI meeting agendas consist of disease-specific (e.g., breast cancer) portfolio updates, opportunities to explore and fill in research portfolio gaps, and highlight portfolio successes in collaboration with D-FCIs and ETCTN members.

For more information on ETCTN disease-specific portfolios, visit
https://ctep.cancer.gov/initiativesprograms/etctn_trials.htm

For general inquires contact ET-CTN@mail.nih.gov.

Additional Requirements for Senior/Key personnel to be maintained during the project period:

1. The LAO and AO(s) PDs/PIs must commit a minimum of 1.2 calendar months of effort per year.
2. Each LAO is required to have one Translational Scientist, one Interventional Radiologist, one Research Pathologist, and four Disease-Focused Clinical Investigators.
3. Each AO is required to have one Interventional Radiologist, and two Disease-Focused Clinical Investigators.
4. The designated Disease-Focused Clinical Investigators, Translational Scientist, Interventional Radiologist, and Research Pathologist are expected to commit a minimum of 0.6 calendar months of effort per year.
5. Disease-Focused Clinical Investigators should be either the site Clinical Trial PI or Co-Investigator.

Other Requirements:

1. PK assays are required for ETCTN clinical trials and will be assigned to one of the two U24 funded ETCTN Pharmacokinetics Reference Laboratories.
2. Assays whose results will be reported to patients or their physicians at any time (e.g., those for patient selection, stratification, or treatment determination) must be performed in a CLIA-certified laboratory and may be subject to FDA oversight as an Investigational Device Exemption (21 CFR 812).
3. As appropriate, each awardee is expected to utilize the various biospecimen, biomarker, and pharmacodynamic resources developed through the NCI.
4. Ensuring the NCI CIRB is the IRB of record for all studies conducted in the ETCTN at US sites.
5. A trans-ETCTN Biospecimen Working Group (EBWG will be established. ETCTN Translational Scientists, Interventional Radiologists and Research Pathologists are expected to form the EBWG for the acquisition of high-quality research specimens. Each Translational Scientist, Interventional Radiologist and Research Pathologist will be required to attend EBWG meetings.
6. The investigator(s) will be required to use systems developed and maintained by NCI/CTEP. These systems are the Clinical Trials Monitoring System (CTMS), Cancer Trials Support Unit (CTSU), Identity and Access Management (IAM), Cancer Therapy Evaluation Program Enterprise (CTEP Enterprise), Clinical Data Management System (CDMS), Adverse Event/Regulatory support, Oncology Patient Enrollment Network (OPEN), the NCI Early Phase Central Institutional Review Board (CIRB), the CTEP Adverse Event Expedited Reporting System (CTEP AERS), EET Biobank , and WebReporting for aggregated Adverse Event analysis. See: https://ctep.cancer.gov/initiativesPrograms/etctn_infrastructure.htm.
7. For clinical study participation, site Clinical Investigators and all site Sub-Investigator research staff must register with the NCI and re-register annually using the Registration and Credential Repository (RCR) see: https://ctepcore.nci.nih.gov/rcr
8. Staff must maintain an applicable, **active person-registration status** by submitting required documentation necessary for NCI to qualify research site personnel and to be added to the corresponding site roster in RSS to allow for participation in the clinical investigations and to

access all CTEP and CTSU websites and applications. Documentation submission requirements for qualifying personnel per person registration type are outlined on the CTEP website: https://ctep.cancer.gov/investigatorResources/default.htm. Staff must maintain the **Delegation of Tasks Logs (DTL)**.

9. Comply with the rules for the conduct of clinical research summarized in the following documents:
   A. NCI CTEP Investigator's Handbook (Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis, NCI): https://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf.
   B. NCI Guidelines for Monitoring the Experimental Therapeutics Clinical Trials Network (ETCTN) and Other Early Phase CTMS-Monitored Studies: https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Monitoring_Guidelines.pdf.
10. 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 ETCTN trials. 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.
11. Awardees can accept funds from non-governmental sources to support ETCTN 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 per case data management funding, support for correlative science studies that use biospecimen or image collections funded by the NCI/DCTD for trials under the ETCTN) and must be reported under the Terms and Conditions of Award for the ETCTN unless they are associated with an exempted category under the NIH grant policy for program income, available at: https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.3_management_systems_and_procedures.htm.
12. The Terms and Conditions of Award for all the Cooperative Agreements under the ETCTN 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. All key components of the ETCTN must report "Program Income" to the NCI on an annual basis (in the non-competitive Type 5 application (Research Performance Progress Report (RPPR)) and must indicate the clinical trial(s) that the funds are being used to support (or other functional component if the funds are not provided to support specific trials).
13. The contact PDs/PIs and all other PDs/PIs, as well as other senior investigators, will become members of the IDSC and will be required to attend all IDSC meetings.
14. The ETCTN UM1 awardees will be responsible for implementing and maintaining the NIH Genomic Data Sharing Policy, as well as assuring that an Institutional Certification is requested from the Institution's local IRB for any study performing molecular characterization or genetic analysis.

NIH staff have 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 Managers). The NCI Project Scientist(s)/Managers(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 an NCI waiver according to NCI procedures for management of conflict of interest.

Additionally, the ETCTN 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 staff may have substantial programmatic involvement (as Project Scientists/Coordinator). Program staff involved in this capacity will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications or will seek an NCI waiver as stated above.

The NCI Science Officer will be NCI program staff who will have substantial scientific involvement through technical assistance, advice, and coordination above and beyond normal program stewardship for these awards. This includes functioning as a peer with the Principal Investigators (PIs), facilitating the partnership relationship between NCI and the awardees funded under all Experimental Therapeutic Clinical Trials Network (ETCTN) Request for Applications (RFA), helping to maintain the overall scientific balance in the program commensurate with new research and emerging research opportunities, and ensuring that the activities of the ETCTN are consistent with the mission stated in all ETCTN RFAs.

The main responsibilities of substantially involved NCI staff members include, but are not limited to, the following activities:

1. Working with ETCTN Awardees to collaboratively manage issues associated with their participating in the conduct of clinical trials across the Network;
2. Working and performing the roles and responsibilities as the agent(s) sponsor as defined in the Code of Federal Regulations;
3. Informing the PDs/PIs of scientific opportunities resulting from NCI-supported clinical research programs and facilitating collaborations between the ETCTN and other NCI-sponsored programs;
4. Facilitating scientific involvement in oncology treatment research, including advanced imaging research and radiation oncology research, associated with ETCTN trials;
5. Monitoring/Auditing of ETCTN sites;
6. Reviewing accrual and overall performance of ETCTN clinical trials by site(s);
7. Reviewing compliance with applicable regulations for clinical research involving human research subjects;
8. Advising awardees concerning mechanisms established for quality control of therapeutic and diagnostic modalities used in ETCTN clinical trials;
9. Monitoring the progress and performance of the key components of the ETCTN;
10. The NCI ETCTN Program Official will periodically evaluate the actual patient accrual to ETCTN studies. The actual patient accrual will be a significant factor of consideration for the release of respective funds for “Patient Enrollment Costs” (see Section 1.III.5.C. Research Budget).
11. NCI leadership and NCI CTEP staff will review proposals from ETCTN investigators for correlative studies to enhance clinical trials and recommend approved studies for funding consideration;
12. Facilitating approval of ETCTN LOIs and protocols;
13. Reviewing all records relating to awardees’ performance under the award for appropriate collection, review, and distribution of biospecimens collected in association with ETCTN trials;
14. Assisting in the coordination of the IDSC and PDs/PIs participation.

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 review all records related to

awardees' performance under the award for appropriate collection, review, and distribution of biospecimens collected in association with ETCTN trials.

In case of insufficient patient accrual per the protocol specified, 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 the award budget, withhold support, suspend, or terminate the award.

Areas of Joint Responsibility

PDs/PIs of the ETCTN, NCI ETCTN Program Director(s)/Official(s), CTEP Medical Officers, and designated NCI staff will be members of the Experimental Therapeutics Clinical Trials Network. As part of the ETCTN, all members will:

1. Develop appropriate early phase experimental therapeutic clinical trial protocols.
2. Participate as active team members on drug development project teams led by IDB Medical Officers. They will meet quarterly to review studies performed under the award and more often to participate on and provide input for the IDSC, with respect to the drug development plans.
3. Discuss and resolve any issues raised during the initial review of Letters of Intent.
4. Collaborate on study development and conduct especially with respect to compliance with federal regulations for clinical trial research and participating in activities related to the collective management of the ETCTN, as appropriate.
5. Address other programmatic responsibilities jointly, as needed, by the ETCTN awardees and the NCI staff.
6. General aspects of collaboration on study development and conduct especially with respect to compliance with federal regulations for clinical trial research (*e.g.*, 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 (DSMBs) for randomized phase 2 trials and other trials with clear licensing potential, development of collaborative trials and international trials, and collective management of the ETCTN.
7. Review of recommendations from the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) on strategic directions for the ETCTN
8. PDs/PIs, including contact PDs/PIs, multiple PDs/PIs, co-investigators, will meet on a frequent basis to manage the award scientifically and financially. The cooperative agreement may function as a single institution or a consortium consisting of the contact PD/PI and all other PDs/PIs. For early phase trials the meetings should occur weekly or more frequently if necessary, and on an *ad hoc* basis to review all ongoing patients and trials. Later phase studies should be managed every other week or less frequently, depending on the complexity of the planned clinical investigation. This ETCTN coordination committee/team will be charged with the safe conduct of clinical trials based on Good Clinical Practice principle and will assure that all regulatory requirements and reporting are fully met for all trials they are conducting. The NCI monitors and audits all these trials in their position as IND sponsor. The ETCTN coordination team will be responsible for reviewing all trials open in the ETCTN that they accrue to which are open at their institution and that appropriate disease specific experts are identified to champion all disease specific phase 1 and 2 trials. This group along with the study PDs/PIs are required to work collaboratively with NCI Program staff to assure that competitive proposals are discussed and submitted to CTEP for review and decision.

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. A Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the ETCTN Group representatives chosen from the ETCTN Leadership without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two panel members. In the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does 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.

Note that in addition to these general rules for dispute resolution, the NCI Coordinating Center for Clinical Trials (CCCT) IDSC has a specific appeal process in place to adjudicate decisions regarding LOI disapproval for ETCTN study proposals. DCTD/CTEP/IDB has in place policies and procedures for the management of investigators who fail to meet terms of award including performance improvement plans, corrective action plan, and procedures to move to close-out for non-compliance with the terms of award.

1.II.4.B. Specific Terms and Conditions of Award

General rights and responsibilities for the ETCTN are described in RFA-CA-19-007. The following specific terms and conditions of award are described below. The following specific special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, 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 DHHS, Public Health Service (PHS), and NIH grant administration policies.

The dominant role and prime responsibility reside with the awardees for the project, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

1.II.4.B.1. Awardee Rights and Responsibilities

Throughout these specific Terms and Conditions of Award, research programs for the “NCI Experimental Therapeutics Clinical Trials Network” funded by UM1 awards are referred to as the “ETCTN.” The ETCTN comprises the organizational structure which is composed of the awardee institution(s), including the ETCTN sites and ETCTN site PIs and other key personnel, all of whom agree to collaborate on research goals of the early experimental therapeutics program.

The ETCTN is responsible for developing its specific clinical and laboratory research projects, including definition of objectives and approaches, planning, implementation, analysis, interpretations, and conclusions of studies, and publication of results. The ETCTN will continue to develop early phase experimental therapeutic clinical trial protocols in accord with the research interests, abilities, and goals of the early experimental therapeutics program, and submit these protocols to CTEP for review prior to their implementation.

1.II.4.B.1.1 ETCTN Sites Key Components

1.II.4.B.1.1.1. Scientific Leadership and Site Organization

1.II.4.B.1.1.1.1. Scientific Leadership – ETCTN sites

Investigators in the ETCTN sites shall demonstrate scientific leadership for ETCTN trials as well as support of and participation in other ETCTN activities in a variety of ways through their membership in the ETCTN, including but not limited to, the following:

1. It is anticipated that the ETCTN site PI(s) will possess expertise in experimental therapeutics and be well integrated into the scientific and administrative senior leadership in clinical research, thereby fostering collaboration between the ETCTN and other clinical and translational research investigators. ETCTN site PI(s) should be well integrated into the scientific and clinical activities of other NCI clinical trials mechanisms.
2. Leading and participating in the IDSC Project Teams for drug development of individual experimental therapeutics.
3. Having primary responsibility for development of an overall research strategy for the development of ETCTN clinical trials, as well as all key components related to the conduct of approved clinical trials.
4. All participating ETCTN sites shall be responsible for screening, enrolling patients, collection and reporting of required clinical data on electronic case report forms (eCRFs), collecting required biospecimens, treating patients, and monitoring and reporting safety information throughout the conduct of their clinical trials. ETCTN sites will be able to enroll patients on all ETCTN trials open within the ETCTN irrespective of the specific Institution (LPO) which is leading the study. **Note:** International sites (i.e., non-U.S. sites apart from Canada) that are AOs may not be able to participate in all ETCTN trials because of special regulatory issues specific to the country of the international member or based on the decision of the pharmaceutical collaborator.
5. Establishing fiscal management arrangements to support ETCTN-related activities at each Integrated Component and AO (if applicable).
6. Establishing fiscal management of the administration of the PK/PD component through the U24 PK/PD Reference Laboratory, including the process for selecting laboratories to perform specific studies (a competitive process is encouraged when feasible).
7. Participating in major meetings of the ETCTN, including NCI Early Drug Development Meetings and other meetings deemed necessary for performance of the activities of ETCTN.
8. Establishing a process for the distribution of funds from the Coordination of Clinical Trials and Associated Activities component to AOs to support special clinical research costs for patients accrued onto ETCTN clinical trials.
9. Accomplish collaboration between all participating ETCTN sites and other clinical and translational research investigators locally, nationally, and internationally. ETCTN sites shall provide a mentorship program or activities to involve young investigators at their institution in clinical trial research and to help train them to eventually take on senior leadership responsibilities for components of clinical trial research at the institution.
10. Establishing procedures to allow non-ETCTN institutions to participate in the development and conduct of early phase experimental therapeutic trials in those limited situations in which an institution has distinctive expertise or capabilities that would contribute to successful conduct of a program study.
11. Timely publication of major findings.

1.II.4.B.1.1.1.2. Scientific Leadership – ETCTN LAOs

Investigators in the ETCTN shall demonstrate scientific leadership for ETCTN trials as well as support of and participation in other ETCTN activities in a variety of ways through their membership in the ETCTN, including but not limited to the following:

1. Having primary responsibility for development of an overall research strategy for the development of ETCTN clinical trials, as well as all key components related to the conduct of approved clinical trials.
2. Conducting high-quality trials evaluating novel treatments with innovative translational components.
3. Offering eligible patients participation in ETCTN studies and entering sufficient patients to meet accrual targets and enrollment of patients on ETCTN trials.
4. Participating in research design and protocol development for ETCTN studies, including nomination of IDSC Project Team members and engaging in collaborations between other ETCTN sites and NCI-supported programs and investigators, particularly at their institution, that may lead to an ETCTN trial.
5. Analyzing and disseminating trial results, including PK/PD and molecular characterization.
6. Acquiring high-quality biospecimen(s) for analysis of integral and integrated biomarkers.
7. Participating in major meetings of the ETCTN, including NCI Early Drug Development Meetings and other meetings deemed necessary for performance of the activities of the ETCTN.
8. LAO PI(s) are responsible for accrual to all trials conducted across the ETCTN.
9. Collaborating with NCI in managing the ETCTN, including but not limited to, participating in the CIRB, utilization of NCI support services, -the common data management system, monitoring, and auditing.
10. The LAO is responsible for coordinating all the scientific and administrative policies at the institution.
11. LAO PI(s) of all ETCTN awards shall serve on the NCI-sponsored panel, IDSC task forces and committees. The IDSC conducts strategic discussions regarding early phase experimental therapeutics drug development trials involving agents for whom CTEP holds an IND. IDSC participants will commit up to 12 days per year to IDSC activities. This commitment includes attendance at quarterly in-person meetings and teleconferences, and participation on task forces and committees.
12. The awardee and up to two additional individuals are required to attend the Early Drug Development meetings sponsored by CTEP. The awarded ETCTN site PIs are required to attend the bi-annual IDSC meetings.
13. Timely publication of major findings is central to the ETCTN mission and is a primary means by which the ETCTN's accomplishments can be evaluated. The ETCTN will have timelines for the development of abstracts and manuscripts based on its clinical trials and should have mechanisms for monitoring the performance of the ETCTN in meeting these timelines. Corrective action plans will be implemented when these timelines are not met. Publication or oral presentation of work conducted via the ETCTN requires appropriate acknowledgment of NCI support. For publications using an agent supplied under a Cooperative Research and Development Agreement (CRADA) or Clinical Trial Agreement (CTA), the CTEP pharmaceutical collaborator will have an opportunity for review prior to submission, as per CTEP Standard Protocol Language for CRADAs and CTAs. The NCI will have access to all data generated under this cooperative agreement and will periodically review the data.

1.II.4.B.1.1.1.3. Site Organization

Under the direction and leadership of the PI(s), the LAO is responsible for development and maintenance of a governance and organizational structure to coordinate ETCTN site activities at the institution. The organizational structure of the ETCTN sites should have the following attributes:

1. Be established with clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of any multiple PIs.
2. Establish and maintain site, investigator, and associate rosters with the CTSU.
3. ETCTN site PI(s) should be well integrated into the scientific and clinical activities of each of the NCI clinical trials mechanisms such as Cancer Centers and SPORE(s).
4. The AO is under the leadership of the Site PI(s), who coordinate(s) all the scientific and administrative policies at the institution related to ETCTN activities, as well as coordination with the Coordination of Clinical Trials and Associated Activities Component and other ETCTN sites.

1.II.4.B.1.1.2. Team Science for Project Development

ETCTN Sites are expected to lead and/or participate in multidisciplinary scientific teams during the development and implementation of ETCTN drug development plans.

1. The PI of the LAO (in his/her role as an IDSC member) may be asked to serve as the leader of IDSC Team(s) charged with the design, implementation, and conduct of drug development plans.
2. Each IDSC Team will focus on the development of a specific experimental therapeutic to understand its molecular mechanisms and will consist of the NCI Medical Officer and experts in a broad range of scientific areas, such as cancer biology, translational science, oncology, statistics, assay development, and molecular characterization.
3. IDSC Team drug development plans may include multiple distinct clinical trials, each headed by a LAO or LPO PI.
4. IDSC Team leaders will be expected to provide strong leadership and management of these diverse collaborative teams during preparation for IDSC presentation.

1.II.4.B.1.1.3. PK/PD, Biomarker Assays, and Molecular Characterization of Patients

ETCTN sites will comply with all ETCTN requirements for the PK/PD and molecular analyses during the conduct of ETCTN trials.

ETCTN sites may act as a central resource for the PK/PD performed by the PK/PD Reference Laboratory (U24), or molecular analyses specific to an ETCTN clinical trial. In those cases, the ETCTN site will:

1. Work with the NCI to provide the scientific and logistical infrastructure to receive, store, and analyze clinical samples from all ETCTN sites participating in a trial.
2. Be responsible for timely and accurate transmission of data generated from those analyses to the NCI.

The NCI will have access to all data (including molecular characterization and genomic/proteomic data, PK/PD, and imaging data) collected and/or generated under this Cooperative Agreement and will periodically review the data.

1.II.4.B.1.1.4. Coordination of Clinical Trials and Associated Activities

ETCTN sites are expected to have experience and expertise in the management of complex early phase clinical trials, including protocol development, patient screening and enrollment, data and specimen collection and management, and compliance with regulatory requirements related to human subject protections and privacy and FDA-regulated investigational agents.

A. Protocol Development

1. The LPO shall submit an LOI for review and approval prior to protocol development. Protocols for review and approval by NCI shall be preceded by a written LOI to the CTEP LOI Coordinator declaring interest in conducting a particular study. LOIs shall be submitted using the LOI template (LOI Submission Form).
2. The LAO SOPs should include timelines for the steps involved in the writing and electronic submission of LOIs as part of the IDSC project team and clinical protocols and should include mechanisms for monitoring the performance of the LPO in meeting these timelines. The LAO's SOPs should include corrective action plans outlining the steps to be taken when these timelines are not met. Data concerning the early phase experimental therapeutic program's performance in meeting timelines for protocol development should be provided in the Annual Progress Report (RPPR) and quarterly tabular updates.
3. It is the responsibility of the LPO to develop the details of the research design of the protocol, including definition of objectives and approaches, planning, implementation, analysis, interpretations, and conclusions of studies, and publication of results.
4. Clinical trial protocols should be developed, submitted, and implemented in accordance with the DCTD "Investigator's Handbook" (https://ctep.cancer.gov/investigatorResources/investigators_handbook.htm). Reference protocol development guidelines (See: http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf).
5. The LAO shall not expend NCI funds to conduct any study disapproved by CTEP unless CTEP's disapproval has been modified by the dispute resolution process.
6. The LAO is responsible, in accordance with the program's SOPs, for the preparation and implementation of procedures for development and timely submission of early phase clinical trial protocols that are not assigned to the CPWS to the CTEP Protocol Information Office (PIO) for NCI's review and approval.
7. The LAO is responsible for establishing routine electronic communication with ETCTN sites to facilitate clinical trial protocol development, study monitoring, and tasks of the Coordination of Clinical Trials and Associated Activities component. Relevant communication methods include website postings, e-mail, teleconferences, and video conferences.
8. The LAO is responsible for communicating the results of the CTEP PRC to relevant ETCTN site members and the LPO PI.
9. All clinical trials utilizing CTEP-sponsored investigational agents co-developed with a pharmaceutical collaborator shall be conducted in accordance with the terms of the "Intellectual Property Option Policy" (April 1, 2011) and the NCI Standard Protocol Language for CRADAs and CTAs. Foreign site participation is dependent on approval of the pharmaceutical collaborator and the foreign site's successful regulatory filing with the foreign health authority.
10. Individuals may be asked to participate on the NCI CIRB. Participants may be, but are not limited to, physicians, nurses, patient advocates, and ethicists.

B. Correlatives

The LAO is responsible for managing and coordinating the acquisition and shipping of protocol-specified tumor specimens and biological fluids (with relevant de-identified clinical data as indicated) to the appropriate laboratories and/or tumor/specimen repository or at the ETCTN site for storage of specimens for future research laboratory studies. The LAO is responsible for validation of all assays in the appropriate laboratory environment, and reporting PK/PD, biomarker assays, and molecular characterization assay study results.

1. All biospecimens collected for an ETCTN trial must be sent by the institutions/sites participating in the trial to the designated ETCTN laboratory unless an exception is approved by the NCI/DCTD to accommodate the needs of a specific trial.
2. The LAO is responsible for overseeing the timely collection and transmission of biospecimens from all its Integrated Components and AOs to ETCTN trials for patients that are credited to the ETCTN site.
3. Timely reporting of data to CTEP shall be done using CTMS (see CTMS Help Desk link (RAVE Other) at the following: https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Contacts.pdf. All ETCTN studies using CTEP IND agents will report bi-weekly using the CTMS-common data management system.
4. Biospecimen Sharing Policy: The LAO is required to follow the NCI/DCTD policy regarding review of requests for use of banked biospecimens collected in association with ETCTN trials by CTEP's PRC The LAO is 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 NCI ETCTN Program Official, Associate Director of CDP, and Program Official of the Tumor Banking Program for the ETCTN. This inventory should be consistent with standards established by the NCI/DCTD Biomarker Review Committee (BRC).

C. Data Management

The LAO, under the direction of the LAO PI, is responsible for coordinating clinical protocol development, protocol submission for review and approval, study conduct (including central data collection and analysis by services and tools provided (*e.g.*, -common data management system, OPEN, RSS, CTMS), QA including QC and study monitoring, protocol amendments/status changes, adherence to requirements regarding investigational drug management and federally mandated regulations, and protocol and performance reporting. Specific responsibilities are:

1. Study Monitoring:
   https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Monitoring_Guidelines.pdf
   The LAO or LPO in collaboration with CTMS is responsible for assuring accurate and timely monitoring of the progress of each study and, therefore, must adhere to the standard procedures for timely data collection and data management consistent with the intensive data requirements and the need for rapid reporting necessary for early phase studies. Standard procedures include (but are not limited to):
   a. Precise tracking of patient accrual and adherence to accrual goals defined by the clinical trial protocol. If the ETCTN wishes to continue accrual to a study beyond the total accrual goal for eligible and ineligible patients specified in the clinical trial protocol, the LAO shall seek approval from CTEP prior to continuing patient accrual. Timely accrual will be an important measure of success.
   b. Procedures for assigning dose level (for dose escalation studies) at the time a new patient is enrolled in a study and assuring that the required observation period has elapsed before beginning a higher dose level.
   c. Patient screening and assessment of patient eligibility and evaluability.
   d. Timely medical review and assessment of individual patient data.
   e. Timely submission of clinical trials data (*e.g.*, adverse events, anticancer response, etc.) and responses to data queries from all participating ETCTN sites. These measures should include procedures for monitoring compliance with the ETCTN's guidelines for data timeliness on an institution and a study basis, including summary reports of data submission timeliness to be

used for Institutional Performance Review and to be used for study monitoring. These summary reports shall be included in the Annual Progress Report (RPPR).
Failure to comply with timely submissions and query resolution may result in temporary suspension of site accrual and require submission of Corrective Action and Preventive Action (CAPA) plan.

f. Timely reporting of treatment-related morbidity/mortality information and measures to ensure communication of this information to all relevant parties. For investigational agents sponsored by CTEP, this involves reporting to IDB via CTEP-AERS according to CTEP guidelines specified in each protocol (http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm).
g. Preparation of study monitoring reports describing patient accrual and demographics, data timeliness, toxicity, and other items as appropriate using reports accessible through the Reporting Module in CTMS. Examples of study monitoring reports include reports prepared for study chairs, the annual reports for program meeting agendas, and reports for the Data and Safety Monitoring Committee (DSMC) (if one has been constituted).
h. Adequate policies and procedures for closure of studies. If the ETCTN wishes to close accrual to a study prior to meeting the initially established accrual goal, the interim results and other documentation should be made available to CTEP staff for review and concurrence prior to implementation of the decision. It is recommended that statistical guidelines for early closure be presented as explicitly as possible in the clinical trial protocol to facilitate these decisions.
i. Completion of molecular, imaging, or correlative study analysis within 45 days of study completion (all patients have completed protocol-defined therapy and meeting the 30-day safety reporting interval (unless defined differently in the protocol). Also, entering -the common data management system all data and query resolutions from ETCTN sites within 45 days of study completion).

2. Data Management Policies and Practices: The responsibilities of the Coordination of Clinical Trials and Associated Activities component for data management related to study monitoring include the following:
   a. Providing for central storage, security, processing, and retrieval of study results.
   b. Incorporating security features consistent with the guidelines of the U.S. DHHS https://www.hhs.gov/hipaa/for-professionals/security/index.html .
   c. Implementing procedures for backing up the ETCTN clinical and administrative data, including intermittent duplication of the database with storage at a remote facility.
   d. Protecting patient confidentiality at all steps in the submission and analysis of clinical trials data and ensuring the technical integrity and security of the data management systems.
   e. Providing CTEP in a timely manner, upon the request of the Program Official, true copies of data files and supporting documentation for all CTEP-supported protocols that have a major impact on patterns of care, as determined by CTEP.
   f. Providing verification of pathological diagnosis in cases where known variability in the accuracy of histological diagnosis is a potentially serious problem and where pathology data may provide important prognostic information.
   g. Providing review either concurrently or retrospectively of port films and compliance with protocol-specified doses for individual patients, where relevant. Determination of the adequacy of radiation delivery with the assistance of their respective radiological physics center, whose functions usually include equipment dosimetry, periodic institutional visits, and other aspects of physics review.

h. Providing review of pharmacy orders, drug administration, flow sheets, and drug distribution with determination of protocol compliance in dose administration and dose modification.
i. Providing assessment of adequacy of protocol-specified surgical procedures through review of operative notes and study-specific surgical forms where relevant.
j. Providing assessment of adequacy of protocol-specified imaging procedures. This assessment may include methods for acquisition and display of images, methods for monitoring quality of image interpretation (including quantitative measurement of lesions), and methods of data archiving and retrieval as appropriate to specific studies.
k. Establishing assay validation and QA/QC procedures for laboratory assays for PK/PD and other molecular assays. These procedures may include such elements as assay validation procedures, calibration curves, check samples, standards for accepting or rejecting data (*e.g.*, positive, and negative controls), and external QA/QC. Procedures for ensuring patient privacy and sample tracking must be established.
l. Reporting of PK/PD, biomarker assays, and molecular characterization assay results in real time during the study. The schedule for sample assay should be established in the written protocol.

D. Regulatory

The LAO is responsible for ensuring that it and the ETCTN sites follow all applicable federal regulations concerning the conduct of research involving human subjects. LAOs shall have policies and procedures for ensuring compliance with federal regulations for the protection of human subjects. These include the following policies and guidelines to be addressed:

1. Human Subjects Research
   A. OHRP Assurances: The LAO must ensure that it and each Integrated Component and AO has a current, approved Federal Wide Assurance (FWA) on file with OHRP. The LAO is responsible for assuring that it and the ETCTN sites follow all applicable federal regulations concerning the conduct of human subjects research. Policies and guidelines to be addressed include the following:
      i. The LAO must ensure that each member (this includes all ETCTN sites enrolling patients in ETCTN trials) has a current, approved, active FWA, on file with OHRP https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/irb-and-fwa-status/index.html. Information on assurances is available on the OHRP website at: https://www.hhs.gov/ohrp/. 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.
      ii. Assuring Appropriate Informed Consent: The LAO must ensure that each patient (or legal representative) gives written informed consent prior to entry on study. Ensure any substantive modification by the AO of sample consent information related to risks or alternative procedures is appropriately justified.
      iii. The ETCTN sites must have procedures in place to ensure that each 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

ETCTN 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 on the CTEP website at https://ctep.cancer.gov/protocolDevelopment/informed_consent.htm.

iv. GCP training is completed every 3 years and documented annually via the NCI Registration and Credential Repository.

v. Management, data analysis, and data and safety monitoring (DSM) systems are adequate, given the nature of the research involved.

vi. Sample protocols and informed consent documents are developed and distributed to each Integrated Component and AO.

vii. The Investigator's Handbook, a Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported CTEP, DCTD, NCI (and any subsequent modification to it) is hereby incorporated by reference as terms of award. This document describes the programmatic responsibilities for the conduct of the research supported by this cooperative agreement. https://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

viii. **Education on the Protection of Human Subjects:** NIH policy requires education on the protection of human subjects 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.

ix. **International Participating Sites:** Additional requirements may be required for any International Participating Site including: CTEP International Committee approval, a signed Technical Agreement, State Department clearance, etc.

As a public service, the NIH Office of Extramural Research offers a free tutorial on Protecting Human Research Participants (https://phrptraining.com/) that institutions may elect to use to fulfill the requirement for education in the protection of human subjects. A Spanish language version is also available.

2. Institutional Review Board

A. CIRB Review of ETCTN Protocols: The LPO must ensure that each clinical trial protocol is reviewed and approved by the NCI CIRB prior to activation and patient entry and must ensure that each clinical trial protocol undergoes continuing review by the CIRB no less than once per year until the trial qualifies for closure with the CIRB.

B. All participating institutions must ensure that regulatory approval for a given protocol at their site has been documented in the CTSU's Regulatory Support System (RSS), whether that be via the CIRB (expected, unless waiver issued as described immediately below), or via the site's local IRB. Of note, some studies will have protocol-specific requirements (PSRs) beyond IRB approval that must be complied with to enroll patients.

C. Exemption requests with supporting documentation of the timely IRB review from member institution/sites of the ETCTN must be submitted to the NCI ETCTN Program Official by the supporting LAO. If an exemption is granted, the Coordination of Clinical Trials and Associated Activities component is responsible for including reports of IRB timelines for their sites that have received an approved exemption in its annual progress report (RPPR) as well as any other pertinent information. The NCI ETCTN Program Official may withdraw the exemption and require that the institution/site use the NCI CIRB for applicable ETCTN studies if justification for the exemption is not warranted on a continuing basis.

D. The LAO must ensure that each ETCTN site submits its regulatory documents to the CTSU RSS; otherwise, the site shall not be allowed to enroll patients on ETCTN trials. For CIRB sites, this involves submission of the Study Specific Worksheet for Local Context via the CIRB's IRB Manager (which is then communicated directly to RSS) and the submission of any additional PSRs to the CTSU RSS. If an ETCTN site receives a waiver for participation in the NCI CIRB program, the LAO must ensure that each protocol for an ETCTN trial that one of its sites credits to the LAO is reviewed and approved by the site's local IRB prior to patient entry and ensure that each protocol is reviewed annually by the site's IRB until the trial qualifies for closure with the IRB. In these cases, IRB approval documentation (as well as any PSR-related documentation) is submitted to the CTSU RSS in the manner described in each protocol document. It is anticipated that the NCI CIRB will be the IRB of record in most cases.

E. IRB review of the LAO's entire research project proposed in the cooperative agreement application at the grant-holder's institution upon award has been eliminated. Only the research protocol requires review. See: https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-elimination-of-irb-review-of-research-applications-and-proposals/index.html. The IRB should determine and document that the Coordination of Clinical Trials and Associated Activities component has sufficient mechanisms in place to ensure that:
   i. oversight of data management and analysis are adequate, given the nature of the research involved;
   ii. sample protocols and informed consent documents are developed and distributed to each institution/site participating in a trial;
   iii. each institution/site holds or is covered under an applicable OHRP-approved FWA;
   iv. each protocol is reviewed and approved by the CIRB (or IRB with approved waiver) covering the member institution/site prior to the enrollment of subjects;
   v. any substantive modification by the institution/site of sample consent information related to risks or alternative procedures is appropriately justified; and
   vi. 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: https://www.hhs.gov/ohrp/.

3. Registrations

A. All ETCTN site investigators and sub-investigators performing trials involving CTEP investigational agents must be active NCI-registered investigators and have completed and submitted all required investigator registration documents (FDA Form 1572, Financial Disclosure Form, NIH Biosketch, and Agent Shipment Form as appropriate for their registration type) prior to participation in the clinical investigation. See the NCI Registration and Credential Repository at: https://ctep.cancer.gov/investigatorResources/investigator_registration.htm. All investigators must document that they have completed the protocol-specific training prior to enrolling patients. All orders for CTEP IND agents must be written by a study-eligible, NCI-registered physician Investigator or a study-eligible, NCI-registered Qualified Advanced Practice Provider (APP) registered as Non-Physician Investigators prior to agent dispensing and administration. APPs must be licensed and qualified per institutional policy, local state laws and regulations, including requirement as mandated for international sites.

B. Clinical Trials Reporting Program (CTRP)/clinicaltrials.gov Registration and Outcomes Reporting: All ETCTN trials must be registered and appropriate information updated in the NCI CTRP as described at: https://www.cancer.gov/about-nci/organization/ccct/ctrp as well as registered in the U.S. National Library of Medicine clinical trials database (i.e., at: www.clinicaltrials.gov). Trials must be reviewed for accuracy twice a year. Changes in the trial design and accrual, as well as results reporting from ETCTN trials are to be reported to clinicaltrials.gov as required under the Food and Drug Administration Amendments Act (FDAAA), Section 801. The LPO should work with its associated ETCTN sites to coordinate activities to ensure information on ETCTN trials is appropriately updated.

4. Safety Reporting
   A. The LAO must assure timely reporting of all serious and/or unexpected adverse events. For investigational agents sponsored by CTEP, this involves reporting to IDB, CTEP, via CTEP-AERS according to CTEP guidelines specified in each clinical trial protocol https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm. The regulation for expedited adverse event reporting is 21CFR 312.32.

      Adverse events should be reported using the CTCAE v4.0 or most recent version available.

   B. Serious adverse event reporting for all ETCTN trials should follow the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) INDs and IDEs" available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.
   C. For studies with immediate safety issues that are under monitoring by a Data and Safety Monitoring Plan (DMSP) or Data Monitoring Committee (DMC):
      i. Immediate notification should be made to the DMC Chair and the NCI ETCTN Program Official as described in the approved DSMP.
      ii. For therapeutic studies that are not under DMC monitoring, immediate notification should be made to the Medical Officer in the IDB at CTEP (along with the agent liaison physician in the IDB at CTEP for studies being conducted under a CTEP IND) with a copy to the NCI ETCTN Program Official.
      iii. For imaging studies that are not under DMC monitoring and/or those being conducted under a CIP IND, immediate notification should be made to the imaging agent liaison physician in the Clinical Trials Branch at CIP with a copy to the NCI ETCTN Program Official.
      iv. The Coordination of Clinical Trials and Associated Activities component is required to send a listing (or an email with internet access link to a listing) of all DMC recommendations accepted by the NCI ETCTN Program Official after every scheduled DMC meeting. DMC recommendations accepted by the LAO PI(s) after *ad hoc* DMC meetings/calls must be communicated to the NCI ETCTN Program Official.
      v. The LAO must establish a DSMP for the clinical trials conducted by the ETCTN Sites in compliance with NIH and NCI guidelines for data and safety monitoring for clinical trials (see: https://grants.nih.gov/policy/humansubjects/policies-and-regulations/data-safety.htm, with additional description at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html and the NCI policy at: https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf). Any changes/modifications to the plan must be submitted to and approved by the NCI ETCTN Program Official.

D. For early experimental therapeutic studies using CTEP IND agents, CTMS comprehensive or routine reporting procedures will be used, which capture demographic, adverse event information (by course), and response data. See: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm.

5. Policy Compliance
   A. 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 IDB at CTEP or the Clinical Trials Branch at CIP if a CIP IND imaging agent is involved before any action is taken.
   B. NIH policy requires that women and members of minority and ethnic subgroups be included in all NIH-supported biomedical and behavioral clinical research projects involving human subjects, as described at: https://grants.nih.gov/grants/funding/women_min/women_min.htm. Compliance with this policy requires appropriate study designs, planned enrollment 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 ETCTN sites conduct multiple 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: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: https://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.)
   C. A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial categories 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 (RPPR). The LAO shall report this data for all patients enrolled on studies it leads or participates in where the LAO UM1 funds are used to support enrollment, regardless of whether it is credited with the patient enrollment.
   D. NIH policy requires that children (i.e., individuals under 18 years of age) must be included in all human subject's research, conducted, or supported by the NIH, unless there are clear and compelling reasons not to include them. For cancer clinical research, ETCTN sites conducting research in adult cancers can provide a rationale for not including children because most children with cancer in the United States are already accessed by Network Sites devoted to pediatric cancer research. 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.
   E. The purpose of the **Inclusion Across the Lifespan Policy** is to ensure individuals are included in clinical research in a manner appropriate to the scientific question under study so that the knowledge gained from NIH-funded research is applicable to all those affected by the researched diseases/conditions. The policy expands the Inclusion of Children in Clinical Research Policy to include individuals of all ages, including children and older adults. The policy also requires that the age at enrollment of each participant be collected in progress reports (see: https://grants.nih.gov/policy/inclusion/lifespan.htm). The Inclusion Across the Lifespan

policy is now in effect and applies to all grant applications submitted for due dates on or after January 25, 2019.

F. Conflict of Interest Policy: The LAO must establish a Conflict-of-Interest Policy that follows all of the DHHS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: https://grants.nih.gov/grants/policy/coi. This policy should ensure that there is no reasonable expectation that any investigator or staff member of the ETCTN 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 be in compliance with NCI/DCTD/CTEP's Conflict of Interest Policy for ETCTN Clinical Trials found on the CTEP website at: https://ctep.cancer.gov/investigatorResources/docs/Conflict_Of_Interest_Policy.pdf.

G. **Other Federal Regulations:** Information on other federal regulations (and their associated citations/URLs) that may be applicable to ETCTN research is provided in Part 3.XIII.2: Appendices.

H. 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: httsp://publicaccess.nih.gov/.

I. The Lead Study Principal Investigator and Study Team are responsible for results reporting, reporting and publication to ClinicalTrials.gov. FDAAA requires reporting of elements defined in the final rule including participant flow, demographics, baseline characteristics, outcomes and statistical analyses, adverse events, the protocol and statistical analysis plan and administrative information. Grantees must also follow NIH policy which requires registration and results reporting of all NIH-funded clinical trials in Clinicaltrials.gov as specified at: https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm

6. Data Sharing

A. The *Intellectual Property Option to Collaborator* document (and any subsequent modification to it) is hereby incorporated by reference as terms of award. This document describes the programmatic responsibilities for the conduct of the research supported by this cooperative agreement and can be found at: https://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations or may be obtained from the Regulatory Affairs Branch, CTEP, DCTD, NCI, at telephone number (240) 276-6580.

B. Clinical trials data must be directly submitted by performing institutions using the CTMS electronic data capture systems (ACESR or CDS, CTEP-AERS, or CaAERs).

C. Monitoring activities must be conducted to guarantee data integrity and compliance with protocol and regulatory requirements.

D. Since it is expected that all data on patients enrolled on ETCTN site trials will be transmitted to the appropriate LAO, those LAOs should address data sharing plans that will be applied to the patient data from the ETCTN Sites. All LAO data-sharing plans should comply with the NIH Data-sharing Policy as described in httsp://grants.nih.gov/grants/policy/data_sharing.

E. **Data-sharing Policy:** The LAO should address a plan for sharing research data; see https://grants.nih.gov/grants/policy/data_sharing. The LAO's policy for data sharing will be

subject to approval by the NCI ETCTN Program Official. Per this policy, requests for data will only be considered once the primary study analyses have been published.

F. 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 and the Pharmaceutical Collaborator (i.e., the NCI ETCTN Program Official in conjunction with the NCI/DCTD Regulatory Affairs Branch).

G. **Institutional Support (Facilities, Equipment, and Programs):** The ETCTN site 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 ETCTN that will enhance ETCTN research.

1.II.4.B.1.1.5 Research Pharmacy Management

ETCTN sites must have established procedures for investigational pharmacy operations to adequately fulfill obligations related to investigational agents. These obligations and requirements include, but are not limited to, the following elements.

1. Policies/Procedures
   A. Access to approved protocol documents and amendments and notification of protocol activation at the site.
   B. Notification of patient enrollment to a given protocol, including notification of signed informed consent prior to agent dispensing.
   C. Ability to order and receive agent(s) from the supplier as instructed in the clinical protocol.
   D. Agents are available when needed.
   E. Policies and procedures for safe and secure handling, preparation and disposal of dangerous goods, hazardous substances, and infectious substances.
   F. Policies and procedures related to safe transport of investigational agents within the facility or to approved satellite dispensing area facilities.
   G. Proper documentation of agent transfer to another NCI-sponsored trial and/or final disposition of investigational agents.
   H. Adherence to local, state, and federal regulations and laws.
   I. Continuous training of staff and written training documentation.
   J. Written SOPs related to investigational agent management, including agent receipt, storage, accountability, and final disposition. Written procedures regarding authorized dispensing of investigational agents to eligible study subjects on approved protocols.
   K. Procedures to ensure NCI-supplied investigational agents are only prescribed by physician Investigators or Non-Physician Investigators who are registered and have an active registration status on file with the Pharmaceutical Management Branch, CTEP, and are authorized prescribers for the trial.
   L. Procedures for reconciling deviations.
   M. The ability to properly order, receive, store, and maintain investigational agents.
   N. Existing procedures for reconciling deviations.
   O. Procedures for assuring that the ETCTN sites follow CTEP requirements described in the DCTD Investigators' Handbook for storage and accounting for investigational agents

[including NCI Drug Accountability Records (DAR) procedures] and follow FDA requirements for investigational agents.

2. Infrastructure/Equipment
   A. Availability of secured access storage space and storage unit(s) necessary to meet storage conditions of agent(s), including controlled room temperature, refrigerator (2 °C to 8 °C), freezer (-10 °C to -20 °C). and ultralow freezer (-70 °C) storage.
   B. Maintenance of continuous proper storage conditions of agent(s) according to supplier instructions, including validation documentation such as temperature logs or temperature recordings and access to emergency back-up power supplies.
   C. Ability to store and segregate agents by protocol, strength, unit, formulation, and investigator.
   D. Adequate security of agent(s) with controlled access to authorized personnel.
   E. Accurate completion of NCI's DARF, NIH-2564, https://ctep.cancer.gov/forms/ as the primary record of all transactions related to the investigational agent(s).
   F. Limited access areas for secure and safe preparation of investigational agents.
   G. Access to appropriate primary containment equipment, personal protective equipment, and safety equipment.
   H. Secured access to storage space and storage units(s) necessary to meet storage conditions of agent(s).
   I. Research pharmacy personnel experienced in the preparation, storage, handling and dispensing of investigational agents.

1.II.4.B.1.1.6 Performance

The LAO is responsible for submitting annual progress reports to the NCI that describe activities and accomplishments during the previous year of the ETCTN sites. The report will use the RPPR and include:

1. A summary of the overall performance of the LAO's Coordination of Clinical Trials and Associated Activities component in meeting their responsibilities for clinical trial protocol development, study monitoring, and complying with Federal regulations.
2. Summary data on performance of each Integrated Component and AO, including clinical trial accrual, quality, and timeliness of submitted data, and involvement in clinical trial protocol development activities.
3. Research plans, changes in procedures and/or staff, and the proposed budget for the coming year.
4. Use of tables is strongly recommended for the purpose of reporting annual progress.

The awardee retains custody of and have primary rights to the raw 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 CRADAs with biotechnology and pharmaceutical partners, as governed by NCI-approved Data-sharing plans and NCI-approved review for use of biospecimens collected in association with ETCTN trials.

Pharmaceutical and biotechnology companies will have access to all data generated under CTEP Collaborative Agreements; however, the companies may contract directly with the CTEP support contractors with prior approval from NCI for access to data files or other reports not routinely provided.

1.II.4.B.2. NIH Responsibilities

The NCI Project Scientist(s), ETCTN Science Officer(s), ETCTN Program Official and additional relevant NCI staff, as needed, will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards. The NCI ETCTN Program Official, or designee, will be the main NCI contact for all facets of the scientific interaction with the awardees and will provide advice to the awardee on specific scientific and/or analytic issues. NCI scientific or program staff will assist, guide, coordinate, or participate in project activities.

The role of the NCI/DCTD staff, as described throughout these Terms and Conditions of Award, is to assist, facilitate, and ensure optimal coordination of ETCTN activities. The ETCTN is part of a larger NCI-sponsored clinical trials program that includes investigational agent development. The CTEP staff has very specific and well-defined responsibilities for the oversight and review of ETCTN Site clinical trials and for investigational agent development that meets DCTD/CTEP responsibilities as sponsor of INDs and IDEs as defined in the Code of Federal Regulations (CFR) 21 Part 312 and Part 812. The responsibilities of NCI/DCTD staff are described below.

NCI Program Staff Responsibilities will include:

1.II.4.B.2.1 Scientific Leadership

1. The **NCI responsibilities** are related to research efforts of the ETCTN and include, but are not limited to, the following activities:
   A. Drug sponsor for investigational agent or device development for NCI-sponsored or co-sponsored IND and/or IDE clinical trials.
   B. Act as scientific liaisons to awardees in the ETCTN and participate in drug development meetings.
   C. Informing ETCTN investigators of scientific opportunities resulting from NCI-supported clinical research programs.
   D. Oversight of data and safety monitoring plans and boards for ETCTN clinical trials.
   E. Oversight of data management and monitoring programs for ETCTN trials, as well as onsite auditing programs and QA/QC programs for the ETCTN.
   F. Facilitating coordination of the clinical trial activities and collaborations between the ETCTN and other NCI-sponsored programs and investigators.
   G. Review of clinical trial project proposals, PK/PD, integral, integrated molecular assays, and study requests for use of biospecimens collected in association with ETCTN trials.
   H. Ensuring compliance with FDA requirements for investigational agents, OHRP, and other federal requirements and regulations for research involving human research subjects.
   I. Advising awardees concerning mechanisms established by the awardees for QC of therapeutic and diagnostic modalities.
   J. Monitoring the progress and performance of the key components of the ETCTN.
   K. Oversight of services provided under contract to support the ETCTN.
   L. Regulatory issues for the protection of patient privacy as it relates to the collection and analysis of molecular characterization and genotyping information.

   Additional NCI staff members may be designated to have substantial involvement (*e.g.*, in the role of Project Managers). The NCI Project Scientist(s)/Managers(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 an NCI waiver according to the NCI procedures for management of conflict of interest.

2. The ETCTN Program Official (PO), or designee, is responsible for the overall design, organization, implementation, direction, and evaluation of the ETCTN. For issues concerning the overall ETCTN, the ETCTN Program Official serves as a resource person for prospective applicants, grantees, the IC, NIH, other offices of the Federal government, and the public. The ETCTN Program Official will be the NIH/NCI Program Official of record and provides approvals, submissions, and responses as required by the NIH Grant Policy. The ETCTN Program Official will designate the ETCTN Science Officer.

   The ETCTN Program Official will be responsible for:
   A. Exercising normal stewardship and oversight responsibilities of an NIH/NCI Program Official.
   B. Carrying out continuous review of all activities to ensure objectives are being met.
   C. Attending Investigational Drug Steering Committee meetings as a non-voting participant, if not also participating as a Science Officer.
   D. Recommending and providing program approval for the withholding or reduction of support from any ETCTN institution/organization that substantially fails to achieve its goals according to the benchmarks agreed to at the time of the award, fails to maintain state-of-the-art capabilities, or fails to comply with the Terms and Conditions of the award.
   E. Attending Peer Review meetings for applications submitted in response to a solicitation or request applicable to their Program.
   F. Providing overall coordination with, and background information to Scientific Review Officers (SROs) in the Center for Scientific Review (CSR) and the IC. This includes providing recommendations to SROs of individuals to serve on scientific review groups.

3. The ETCTN Science Officer will be NCI program staff who will have substantial scientific involvement during the conduct of this activity, through technical assistance, advice, and coordination above and beyond normal program stewardship for grants. This includes functioning as a peer with the PIs, facilitating the partnership relationship between NCI and the awardees funded under all ETCTN RFAs, helping to maintain the overall scientific balance in the program commensurate with new research and emerging research opportunities, and ensuring that the activities of the ETCTN are consistent with the mission stated in all ETCTN RFAs.

   The ETCTN Science Officer will be the resource person for prospective applicants, grantees, and the public for their assigned Program and will be included as a primary point of contact in the Notice of Grant Award.

   The ETCTN Science Officer will be responsible for the following:
   A. Providing relevant scientific expertise and overall knowledge.
   B. Assisting in avoiding unwarranted duplication of effort across institutions/organizations.
   C. Coordinating collaborative research efforts that involve multiple institutions/organizations.
   D. Reviewing and commenting on critical stages in the research program before subsequent stages are implemented.
   E. Assisting in the interaction between the awardee and investigators at other institutions.
   F. Providing information about ongoing NCI and NIH-supported research and resources.
   G. Ensuring there are consistent policies, guidelines, and procedures for dealing with recurrent situations that require coordinated action.

H. Assisting in the group process of setting research priorities and milestones, deciding optimal research approaches and protocol designs, and contributing to the adjustment of research protocols or approaches as warranted. The ETCTN Science Officer will assist and facilitate the group process and not direct it.
I. Serving as scientific liaison between the awardees, other NIH program staff, and the Drug Development Project Teams.
J. Recommending additional research endeavors within the constraints of the approved research and negotiated budget, including the awarding of administrative supplements to further the goals of the program.
K. Recommending re-allocation of NCI ETCTN support among awardees, as scientific goals evolve.
L. Consulting with non-NIH experts in the field as needed to help carry out these duties.
M. Attending Investigational Drug Steering Committee meetings as a non-voting participant.
N. Serving as primary point of contact for activities within the assigned Program.
O. Addressing ETCTN issues within their assigned Program.
P. Working with CTEP leadership to ensure that CTEP program priorities are being addressed by the ETCTN.
Q. Attending the IDSC as NCI liaisons for the ETCTN.

4. **The ETCTN Science Officer and the ETCTN Program Official will be jointly responsible for:**
   A. Developing ETCTN RFAs, guidelines, and application instructions.
   B. Providing ETCTN oversight of post award administration, including review and assessment of progress reports submitted by grantees.
   C. Participating in site visits.
   D. Establishing ETCTN goals for new programs and plans of action for implementation.
   E. Developing internal CTEP operating procedures for ETCTN activities.
   F. Addressing ETCTN issues across the Network.

5. Monitoring ETCTN and site progress. Actions necessary for monitoring may include, but are not limited to, the following: regular communications with the LAO PI(s) and staff; periodic site visits for discussions with LAO research teams; response audits to confirm therapeutic activity reported from a clinical trial; review of audit reports; observation of field data collection and management techniques; fiscal review; review of clinical trial reports submitted to NCI; review of the ETCTN site annual progress report; and attendance at early phase experimental therapeutic meetings. The NCI retains, as an option, periodic external review of progress.

6. Scientific Liaison: Serving as a resource with respect to other ongoing NCI activities that may be relevant to the ETCTN research efforts to identify promising new leads, to facilitate compatibility with other NCI research projects, and to avoid unnecessary duplication of effort.

7. The NCI ETCTN Program Official, ETCTN Science Officers and NCI CTEP Medical Officers will attend biannual Early Drug Development meetings to discuss relevant scientific information, to discuss progress in the clinical trials, and to discuss the status of newly available investigational agents and other research opportunities to plan future activities. Other NCI staff [*e.g.*, from IDB, Clinical Investigations Branch, Radiation Research Program, and CIP] will attend as needed.

8. CTEP Assistance in Clinical Trial Development: The clinical trial protocol must be a detailed written plan of a clinical experiment mutually acceptable to the LPO and to the CTEP Protocol Review Committee (PRC). Communication at the various stages of protocol development is encouraged as it is necessary to promote protocol development and implementation. Following review, the NCI staff will provide a consensus review to the LAO and LPO and will address the following issues:
   A. The existence and nature of concurrent clinical trials in research, pointing out possible duplication of effort.
   B. Information, including relevant PK and PD data, concerning investigational agents.
   C. Availability of investigational agents.
   D. The PRC's assessment of the scientific rationale and value of the proposed study, its design, and statistical requirements.
   E. Appropriate inclusion of CTEP Standard Protocol Language for CRADAs and CTAs in the protocol.
   F. The implementation of the study, if indicated.

9. CTEP Review of LOIs and Protocols: All ETCTN LOIs and protocols will be reviewed by the PRC, which meets weekly and is chaired by the Associate Director, CTEP. *Ad hoc* reviewers, external to NCI, will be utilized when deemed appropriate by the PRC chairperson. Protocols should be preceded by a written LOI from the LPO site declaring interest in conducting a particular study. For further discussion of these mechanisms, see the DCTD Investigator's Handbook at: http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf). The PRC will formally review the LOI. NCI staff will provide the PI with a PRC consensus review that describes recommended modifications and other suggestions, as appropriate (see the DCTD Investigator's Handbook regarding protocol review at CTEP). LOIs approved by PRC go to the pharmaceutical partner for approval of drug provision prior to final CTEP approval. The NCI CTEP Medical Officer and/or CTEP ETCTN Program Official will be available to assist the LPO in developing a mutually acceptable protocol, consistent with the research interests, abilities, and strategic plans of the program and of the NCI.

   The major considerations relevant to Protocol Review by CTEP include:
   A. Strength of the scientific rationale supporting the study.
   B. Clinical importance of the question being posed.
   C. Avoidance of unnecessary duplication with other ongoing studies.
   D. Appropriateness of study design.
   E. Consistency with development plans for IND agents.
   F. Satisfactory projected accrual rate and follow-up period.
   G. Patient safety.
   H. Compliance with federal regulatory requirements.
   I. Adequacy of data management.
   J. Appropriateness of patient selection, evaluation, assessment of adverse events, response to therapy and follow-up.
   K. Method of monitoring and reporting to NCI to be used will be CTMS.

   If a proposed clinical trial protocol is disapproved, the specific reasons for lack of approval will be communicated in writing by the NCI Project Scientist to the LAO and LPO as a consensus

review within 30 days of protocol receipt by the NCI. NCI will not provide investigational agents or permit expenditure of NCI funds for a clinical trial that has not been approved.

10. CTEP Protocol Amendment Review: Any change to the protocol document subsequent to its approval by CTEP must be submitted in writing for review and approval prior to implementation (See "The Investigator's Handbook", http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf, Part 3: Attachment 9, for further discussion of these procedures).

11. Requests for Use of the ETCTN Infrastructure Services: The infrastructure of the ETCTN, including NCI/DCTD-supported contract services, may be used only for ETCTN trials approved by NCI/DCTD under this Cooperative Agreement. In special circumstances, the LAO may request limited use of certain services (*e.g.*, the RSS, the Oncology Patient Enrollment Network [OPEN] for a related research effort associated with a specific ETCTN clinical trial that is supported by charitable funds or a related oncology research study funded by another NIH-funded program). Final approval by the CTEP Associate Director will be required. These requests must be reviewed and approved by NCI/DCTD via an official written approval by the NCI ETCTN Program Official and then final review and approval by the Associate Director, CTEP. The agreements proposed to support such requests must also be reviewed and approved by the Regulatory Affairs Branch, CTEP, NCI. It is anticipated that only requests that are compatible with and are anticipated to benefit the overall research goals of the ETCTN would be approved, subject to the availability of ETCTN resources/funding and other DCTD/CTEP resources.

12. CTEP Involvement in Clinical Trial Protocol Closure: Protocol closure is primarily the responsibility of the LAO and LPO. The NCI CTEP Medical Officer, ETCTN Program Official and ETCTN Science Officers or staff will monitor clinical trial protocol progress and may request protocol closure to further patient accrual if necessary, including the following reasons:
    A. Insufficient accrual rate per the protocol-specified timelines and/or NCI/DCTD slowly accruing guidelines for trials.
    B. Accrual goal met.
    C. Poor protocol performance.
    D. Patient safety or regulatory concerns.
    E. Study results are already conclusive.
    F. Emergence of new information that diminishes the scientific importance of the study question.
    G. Lack of availability of the IND agent.
    H. Research misconduct.
    I. Misuse of funds.
    J. NCI will not provide investigational agents or permit expenditures of NCI funds for a study after requesting closure (except for patients already on-study).

13. ETCTN Meetings: NCI is responsible for the organization of biannual meetings to review ETCTN progress, establish priorities, and plan future activities. Additional meetings between ETCTN members and meetings with NCI staff may be held as needed. Relevant responsibilities for meeting organization include:
    A. Arranging for appropriate meeting space and accommodations for attendees.
    B. Developing and distributing meeting agendas.

C. Ensuring that copies of the Report of Studies (electronic and/or hard copy) are distributed to ETCTN members and NCI program staff.
D. Preparing summaries as appropriate after each meeting to be sent to ETCTN members and NCI Program Staff.

14. 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. NCI/DCTD staff with support from the CCCT will assist in coordinating the organization of IDSC meetings under the auspices of the IDSC. NCI/DCTD staff may support *ad hoc* scientific meetings to achieve consensus on critical clinical problems. The IDSC and *ad hoc* meetings will be composed of investigators with established expertise in the 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 IDSC meetings. The ETCTN will be encouraged to address these priorities.

15. The NCI ETCTN Program Official and ETCTN Science Officers may request and receive budgetary and administrative materials from the ETCTN. The NCI ETCTN Program Official will frequently perform liaison activities concerning budgetary and administrative matters interfacing with the primary Administrators for the ETCTN Sites.

16. 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 ETCTN Sites 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 ETCTN trials.

17. NCI/DCTD staff, including the Associate Director, CTEP, the Chief, IDB/CTEP, the NCI ETCTN Program Official, and ETCTN Science Officers serve as liaisons to the IDSC. The IDB physician in the related drug area for the IDSC or CIP representative has special responsibilities on the NCI IDSC. These responsibilities include developing meeting agendas with the IDSC Co-Chairs, preparing the Consensus Evaluations for proposals evaluated by the committees, and working with the IDSC Co-Chairs on the scientific direction of the committee.

18. Any change in the policies and procedures of the IDSC related to composition of committee membership, conflict of interest, and evaluation/prioritization procedures for ETCTN clinical trials requires review and approval by the NCI Center for the Coordination of Clinical Trials (CCCT), the NCI ETCTN Program Official, the ETCTN Science Officers, the Branch Chief of IDB and the Associate Director, CTEP, DCTD/NCI.

19. The NCI Program Staff will ensure that U.S. State Department approvals are in place for sites from foreign countries that will be participating in the research even though federal funds will only be used to support the participants from the ETCTN Sites enrolling patients on study. U.S. State Department clearance is required for foreign sites participating in the ETCTN, regardless of receipt of ETCTN funds for their participation.

1.II.4.B.2.2 Team Science for Project Development

1. Initially, the NCI Medical Officers will collaborate e with the pharmaceutical partners to establish the preliminary list of important development questions.
2. The NCI Medical Officer will request PTAs, to determine interest in participating on the IDSC drug-specific Project Team. In their PTA, ETCTN sites will be asked to provide documentation to identify a senior PI or young investigator with mentor to coordinate and conduct the trial from their site.
3. The NCI Medical Officer will participate in the organization and leadership of the IDSC Project Team (agent, drug development plan), and contribute to the design, implementation, and conduct of drug development plans.

1.II.4.B.2.3 PK/PD, Biomarker Assay, and Molecular Characterization of Patients

ETCTN sites will comply with all ETCTN requirements for the PK/PD, biomarker assay, and molecular analyses of clinical samples during the conduct of ETCTN trials. When scientifically appropriate, ETCTN sites may act as a central resource for the PK/PD Reference Laboratories or molecular analyses specific to an ETCTN clinical trial. In those cases, the ETCTN site will:

1. Work with the NCI to provide the scientific and logistical infrastructure to receive, store, and analyze clinical samples from all ETCTN sites participating in a trial.
2. Be responsible for timely and accurate transmission of data generated from those analyses to the NCI.

1.II.4.B.2.4 Coordination of Clinical Trials and Associated Activities

1. Protocol Review
   A. CTEP must review and approve every protocol involving CTEP-supplied study agents or studies receiving NCI support or funding. CTEP reviews each protocol for completeness, scientific merit, duplication of existing studies, patient safety, and adequacy of regulatory and human subjects protective aspects. If the protocol is incomplete, or the investigator/institution is ineligible under the proposed category of sponsorship, then CTEP will not review the study for scientific content. Protocol review and approval by the PRC is detailed in the DCTD Investigators' Handbook.
   B. Any change to the protocol document after its approval by CTEP must be submitted to CTEP's Protocol Information Office (PIO) in writing for review and approval by CTEP prior to implementation of the change, apart from administrative updates. Additional information on the procedures for protocol amendment can be found in the Investigator's Handbook.
   C. Access to agents for Pre-Clinical Testing: For CTEP-sponsored IND agents, CTEP RAB will facilitate transfer of material to investigators with a Materials Transfer Agreement (MTA).

2. Laboratory and Imaging Biomarker Studies
   A. Laboratory and imaging studies embedded in ETCTN clinical trials at the time of initial proposal submission will be appropriately designed as **integral, integrated, or exploratory studies** with fit-for-purpose assays or procedures (imaging), robust statistical designs and analysis plans that address specific and important scientific hypotheses. Integral, integrated and some exploratory biomarker assays will require approval by the NCI/DCTD-approved ETCTN Biomarker Review Committee (BRC). Correlative laboratory studies requesting use of biospecimens from any ETCTN clinical trial that **has not** yet reported out primary results will

be evaluated by CTEP's PRC (usually as an amendment during the conduct of the study). The study may be sent for evaluation to the NCI/DCTD Biomarker Review Committee (BRC).

B. All correlative laboratory studies requesting use of biospecimens from any ETCTN clinical trial that **has** reported out primary results (i.e., request for use of "banked" biospecimens) are reviewed by the NCI/DCTD Biomarker Review Committee (BRC) and the pharmaceutical collaborator.

C. The NCI/DCTD BRC will evaluate and provide recommendations for integrated, integral, and exploratory biomarker studies in received proposals. Membership will include, but is not limited to, the following:
   i. Standing:
      a. Chair: Director, DCTD
      b. Members:
         1. Deputy Director, DCTD
         2. Associate Director, CTEP
         3. Associate Director, CDP
         4. Deputy Associate Director, CDP
         5. Associate Director, Developmental Therapeutics Program (DTP)
         6. Biomarker biostatistician
         7. Director, Laboratory of Human Toxicology & Pharmacology (LHTP)
         8. Chief, Diagnostics Evaluation Branch, CDP
         9. Chief, Clinical Trials Branch, CIP
         10. Chief, RAB, CTEP
         11. Chief, IDB, CTEP
         12. Associate Branch Chiefs, IDB, CTEP
         13. Chief, CIB, CTEP
   ii. *Ad hoc*:
      a. Lead reviewer for clinical trial (IDB or CIB)
      b. Members of standing members' programs, as required
      c. Subject matter experts (may be non-NCI, when required)
      d. Grant Program Official(s)
   iii. Support:
      a. PIO
      b. CTEP Project Manager
      c. IDB CRS

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

E. Banked biospecimens in NCI-funded or other tumor banks tied to ETCTN 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.

3. Data Management

A. Data Management and Analysis Review: Biometric Research Program staff will review mechanisms established for data management and analysis. When deemed appropriate, the NCI ETCTN Program Official or staff will make recommendations to ensure that data collection and management procedures are adequate for QC and analysis and are as concise as appropriate to encourage maximum participation of physicians entering patients and to avoid unnecessary expense. The NCI will have access to all data although they remain the property of the awardee institution. Data must be available for external monitoring as required by NCI's agreement with the FDA relative to the NCI's responsibility as drug sponsor.
B. Data and Safety Monitoring Plans: The NCI ETCTN Program Official, assisted by the BRP staff, will assess compliance with NCI and NIH established policies on Data and Safety Monitoring Plans. The NCI Project Scientist must review and approve the DSMPs, see: https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf
C. Access to and Monitoring of Data: The NCI will have access to all data generated under this cooperative agreement and may periodically review the data. Data must be available for external monitoring as required by NCI's Drug Master File Agreement with the FDA relative to the responsibility of CTEP as an IND sponsor. The awardee will retain custody and primary rights to the data consistent with current DHHS, PHS, and NIH policies. The awardee will comply with the data access provisions of applicable CTAs and CRADAs. When these agreements are in place, the pharmaceutical collaborator will have complete access to the data for any and all regulatory filings.

4. Regulatory
   A. CTEP sponsorship of IND Applications: The NCI ETCTN Program Official and ETCTN Project Scientist, assisted by the Chief of the RAB, CTEP, and staff will advise investigators of specific requirements and changes in requirements concerning IND or IDE issues that the FDA may mandate. Investigators performing trials under cooperative agreements will be expected, in cooperation with CTEP, to comply with all FDA requirements for investigational agents and assays.
   B. CTEP Review of Federally Mandated Regulatory Requirements: The CTMB and RAB, through the NCI ETCTN Program Official and ETCTN Project Scientist, will advise the program regarding mechanisms to meet FDA and OHRP requirements for the protection of human subjects by program institutions.
   C. IDB and CIB staff will provide updated information to the ETCTN Sites on the efficacy and adverse events associated with new investigational agents supplied to ETCTN site members under a CTEP-sponsored IND. IDB staff will advise the ETCTN sites of potential agents/interventions that will be relevant to new avenues of cancer therapy.
   These requests may 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.
   D. The protocol document must be reviewed and approved by the NCI CIRB and CTEP/DCTD prior to distribution by an ETCTN site to other sites for local IRB review and trial activation (i.e., opening the study to patient enrollment after approval of the study by at least the CIRB or one IRB).
      i. All adult study protocols require approval by the NCI CIRB **before** approval of the final protocol document by CTEP.

ii. Any changes/modifications requested by the NCI CIRB at the time of its initial review may require a revision to the study. Changes submitted in response to the CIRB will be routed to CTEP by the CIRB Operations Office for final CTEP approval.
iii. All protocol amendments submitted on the trial require NCI CIRB approval prior to final approval of the amendment by CTEP.
iv. Phase 2 trials will 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 ETCTN.

5. Data Sharing
   Requests for use of clinical data only from an ETCTN clinical trial are subject to the CTEP-approved data-sharing policy of the ETCTN site that leads/led the trial and the pharmaceutical collaborator notification and review of the proposal.

6. Research Pharmacy Management
   NCI staff will monitor these activities.

7. Career Development and Mentored Training of Junior Investigators
   NCI staff will monitor these activities.

8. Performance
   The NCI ETCTN Program Official, and/or designee, will monitor and review annual progress reports. Performance of each ETCTN site will be reviewed based on the information provided at the semi-annual and other meetings, in the annual progress reports (RPPR), and in the Clinical Data System (CDS) reports submitted to CTEP for each of the clinical trials. Insufficient patient accrual or progress, or noncompliance with the Terms and Conditions of Award, may result in a reduction of budget, withholding of support, suspension, or termination of the award.

1.II.4.B.3. Collaborative Responsibilities

The cooperative agreement awardee shall, with CTEP assistance as described in the above terms for the NCI staff responsibilities, develop appropriate early phase experimental therapeutic clinical trial protocols. The protocols must be acceptable to the CTEP PRC.

PIs of the ETCTN awards, NCI ETCTN Program Official, ETCTN Project Scientists and CTEP Medical Officers will be members of the ETCTN. ETCTN sites will become members of the ETCTN upon release of the Notice of Award. ETCTN sites will be expected to participate as active team members on the drug development project teams. They will meet quarterly to review studies performed under the award and more often to participate on and provide input for the IDSC, with respect to forming drug development plans.

In general, all ETCTN sites should be prepared to participate in all ETCTN protocols. It is anticipated that some studies will be initiated as limited Institutional studies, which may require expansion to all ETCTN sites to meet accrual targets. Awardees may collaborate to perform specific pharmacologic, correlative, molecular or imaging studies. For example, to minimize duplication of effort in assay validation and QA procedures, researchers based at one ETCTN site may perform assays and correlative studies on biopsies provided by another ETCTN site. CTEP scientists will assist investigators in the ongoing coordination required for such cross-award collaborations.

Areas of Joint Responsibility include:

1. **Scientific Leadership**
   A. ETCTN members in conjunction with NCI staff will collaborate cooperatively to achieve ETCTN objectives outlined previously.
   B. The ETCTN sites will be involved in developing collaborations with other ETCTN sites as well as other NCI-sponsored programs and investigators (*e.g.*, SPOREs, Cancer Centers, R01/P01 investigators) to augment and enhance the drug development plans and research productivity on clinical trials conducted in the ETCTN. The LAO is responsible for participating in the collective management of the ETCTN, including participation in appropriate ETCTN activities and initiatives (*e.g.*, NCI CIRB, IDSC, and NCI Support Services) by making recommendations on NCI drug development.
   C. The LPO, working with the LAO, will collaborate with other ETCTN sites to name co-PIs for studies that the LPO leads to augment accrual via collaboration on its ETCTN trials.
   D. The NCI will collaborate and cooperate with the ETCTN sites to ensure collective management of the ETCTN as needed.

2. **Team Science for Project Development**
   A. The NCI will form Project Teams that include representatives from extramural ETCTN sites to work cooperatively to formulate initial drug development plans of new agents accepted for NCI-assisted development through the NCI NExT program.
   B. The list of important questions and the development plan will be sent to the full IDSC for comment prior to implementation.
   C. ETCTN clinician members of the Project Teams may be invited to submit individual LOIs to address each important question.
   D. ETCTN Sites are expected to lead and/or participate in multi-disciplinary scientific and general aspects of collaboration on study development.
   E. The ETCTN will accomplish its objectives by forming multi-institutional, multi-disciplinary project teams to define drug development with the support of the IDSC.

3. **PK/PD, Biomarker Assays, and Molecular Characterization**
   ETCTN sites will comply with all ETCTN requirements for the PK/PD and molecular analyses of clinical specimens during the conduct of ETCTN trials. When scientifically appropriate, ETCTN sites may act as a central resource for the validated PK/PD Reference Laboratories (U24), biomarker assays or molecular analyses specific to an ETCTN clinical trial.

4. **Protocol Development**
   A. Because of the significant resource, regulatory, and general administrative issues involved in ETCTN key component activities and to ensure required compliance with other federal regulations and federal agencies, the ETCTN sites and other key components of the ETCTN should collaborate closely with NCI/DCTD staff.
   B. This collaboration should occur early in the development of trials, general research strategies, and new initiatives.
   C. NCI/DCTD staff and the ETCTN site should work collaboratively to develop protocols meeting GCP standards.
   D. All parties (ETCTN site, NCI/DCTD staff, and company collaborators) should be involved in any conference calls and/or meetings involving the FDA during the development and conduct of any approved ETCTN trial with licensing potential, regardless of whether the

study is being conducted under CTEP IND to ensure that all sponsors are involved in discussions regarding the trial.

E. Both the ETCTN sites 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 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.

5. **Correlatives**
The NCI, DCTD, CTEP and the ETCTN will work cooperatively together in a collaborative fashion to prioritize, review, and perform *in vitro* molecular assays and imaging studies in the context of early experimental therapeutics trials.

6. **Data Management**
   A. Accrual Credit: All accrual credit requests shall be discussed and agreed upon with the NCI ETCTN Program Official prior to study initiation and documented in writing or electronically. Suitable subjects for accrual credit include but are not limited to:
      i. Enhanced enrollment to early experimental therapeutic trials based on race/ethnicity.
      ii. Recruitment to high complexity clinical trials.
      iii. Recruitment to trials for rare or orphan cancers.
   B. Both the ETCTN sites and NCI/DCTD share responsibility to collaborate on initiatives to promote accrual to ETCTN trials.
   C. The ETCTN sites are required to use specific ETCTN common services and tools, including but not limited to those listed below, for all ETCTN trials for the trials to be approved for activation:
      i. ETCTN Common Data Management System for data collection.
      ii. ETCTN Specimen Tracking System for tracking biospecimen collection from ETCTN trials.
      iii. ETCTN OPEN via CTMS's Interactive Web Response System (IWRS).
      iv. ETCTN RSS via the CTSU.
      v. Establish and maintain site, investigator, and associate rosters with the CTSU.
      vi. Establish and maintain a protocol-specific Delegation of Task Log.
      vii. NCI CIRB Review for studies as required under these Guidelines.

7. **Legacy Studies**
Legacy studies supported by the ETCTN will be conducted under the same ETCTN Terms and Conditions of Award as those studies that commence under the ETCTN. Hence, the awardees of any of the key components of the ETCTN are bound by the Terms and Conditions of their Award under the ETCTN when working on legacy studies that are supported by the ETCTN.

8. **QA/QC of Early Phase Clinical Trials**
The CTEP CTMB provides direct oversight of CTEP-sponsored QA/QC programs. The ETCTN is responsible for complying with implemented mechanisms to ensure the accuracy and reliability of its clinical trials data. Key items that should be addressed concerning QA/QC procedures include:
   A. Institutional performance evaluations. Performance factors to be considered include:
      i. Accrual of adequate number of eligible patients onto trials.
      ii. Timely, accurate submission of required data.

iii. Rigorous adherence to clinical trial protocol requirements.
iv. Participation in study development and in timely publication of study findings.

B. Procedures will be in place for putting ETCTN sites on probation for inadequate performance and for removing such institutions from the early experimental therapeutics program if performance is not adequate by the end of the probationary period or at any time that the institution (or participating site) does not meet established ETCTN standards and/or terms of award.

C. Educational functions that address data collection, data management, and overall data quality include, but are not limited to, the following elements:
   i. Training for new CRAs and ongoing training for all CRAs should be provided. Training may be provided by CTMS for new CRAs in the ETCTN's data submission policies and ongoing training for all CRAs concerning changes to program procedures and instructions for data submission in new protocols.
   ii. Instruction should be provided for LAO/LPOs on their responsibilities for study monitoring.
   iii. Instruction should be provided for Integrated Components and AO PIs and research personnel on their responsibilities in complying with the ETCTN's SOPs and Federal regulations at their institution.
   iv. Training/guidance should be provided to all research personnel on how to comply with NCI/NIH policies and procedures (*e.g.*, Ethics, Conflict of Interest, etc.) in addition to the policies and procedures of other governmental agencies important to the conduct of clinical trials (*e.g.*, OHRP, FDA).

D. Procedures for central review of major elements that impact the outcome of clinical trials. This will include central review of claimed responses and adequacy of imaging studies submitted by ETCTN sites, central review of submitted data with determination of protocol compliance in dose administration and dosage modification, and additional review as necessary.

E. The CTMB, CTEP, NCI is responsible for monitoring and oversight of the ETCTN QA/QC programs. The CTMS administers the early phase experimental therapeutic data management and auditing functions on behalf of CTMB. Activities and responsibilities include:
   i. Onsite auditing of ETCTN sites will occur approximately three times/year for studies assigned to CTMS Comprehensive monitoring, with the timing of audits to be based in part on ETCTN site accrual. Phase 2 studies may be assigned to CTMS routine monitoring with the timing of audits to occur every 12-24 months. The onsite audit will address issues of data verification, protocol compliance, compliance with regulatory requirements for the protection of human subjects and investigational agent accountability.
   ii. The LAO's Coordination of Clinical Trials and Associated Activities component will be responsible for logistical coordination and ensuring follow-up of audit findings.
   iii. Any serious problems with data verification or compliance with Federal regulations must be reported to the CTMB immediately. Otherwise, written reports by CTMS must be submitted within 4 weeks of each audit to CTMB.
   iv. The LAO's Coordination of Clinical Trials and Associated Activities component will be responsible for coordinating development of and compliance with the Corrective and Preventive Action Plan (CAPA) in response to audits. If the NCI determines that any component of an ETCTN site failed to adequately comply with NCI guidelines for conduct of clinical trials, accrual of new patients to ETCTN protocols at the ETCTN sites

shall be suspended immediately upon notice of the NCI determination. The suspension will remain in effect until the LAO conducts the required audit and NCI accepts the audit report or CAPA.

v. The LAO will be responsible for notifying any affected Integrated Component and/or AO of the suspension. During the suspension period, no funds from this award may be provided to the ETCTN sites for new accruals, and no charges to the award for new accruals will be permitted.

vi. Any data irregularities identified through QC procedures at an ETCTN site or through the monitoring/auditing program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB, CTEP, NCI. For data irregularities:
    a. The CTMB must be notified immediately by telephone or email 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.
    b. Any data irregularities identified through other QC procedures suspicious and/or suggestive of intentional misrepresentation of data must be immediately reported to CTMB.
    c. It is the responsibility of the LAO 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 ETCTN clinical trials.
    d. **The irregularity/misrepresentation does not need to be proven; a reasonable level of suspicion suffices for CTEP CTMB notification.**
    e. Involved individual(s) and/or institutions should follow their own institutional misconduct procedures in these matters.

Clinical Trials Operations – Conduct of Clinical Trials & Data Management: The ETCTN sites should have a clearly articulated process for prioritizing ETCTN trials at their institutions. Investigators at ETCTN sites form the cornerstone of the research programs for the ETCTN and must perform at a high level through submission of accurate and timely clinical data, as well as ancillary materials necessary to support the ETCTN (*e.g.*, tumor specimens, imaging studies, pathology slides). The PI(s) at each ETCTN site is responsible for the performance at their institution which includes timely submission of data and for assuring adherence to ETCTN, NCI, OHRP, and FDA policies and procedures. International standards for the conduct of clinical trials (ICH E6: Good Clinical Practices at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1) should be observed and followed by all research personnel involved in conducting the study.

It is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, -common data management system. This includes:

1. All ETCTN sites must utilize -the CTMS common data management system as the -electronic data capture system.
2. Patients must be registered and treated at an approved ETCTN site.
3. Research staff at the Participating Institution will require an IAM password to access the CTMS common data management system and other CTEP systems. See: http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

4. Data are to be submitted via CDMS to CTMS on a real-time basis, but no less than once every 2 weeks.
5. All patients who are consented to ETCTN studies (including patients who are found to be screen failures) will be registered prospectively using OPEN.
6. The submitted data will undergo a centralized clinical QA review at CTMS. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN site to resolve.
7. A protocol-specific eligibility electronic Case Report Form (eCRF) will be completed by the enrolling institution and electronically transmitted to CTMS via the OPEN.
8. The eligibility Electronic Case Report Form (eCRF) may include collection of molecular profiling/genotyping information which will be stored and maintained by the CTMS common data management system and may be used to identify additional protocols that the patient may be eligible for enrollment. The eCRF will be built in the CTEP clinical data base management system (CDMS) by the CTMS and available to all ETCTN sites at the time of protocol activation. eCRFs will include but may not be limited to the following:
    a. Eligibility and Enrollment
    b. Prior therapies
    c. Concomitant Medications/Interventions
    d. Baseline Medical History and Physical Exam
    e. Baseline Symptoms
    f. Baseline and Follow-up Extent of Disease
    g. Course Initiation
    h. Study Drug Administration
    i. Adverse Events
    j. Course Assessment
    k. Laboratory Evaluations
    l. PK/PD
    m. Correlative (biomarker, molecular and imaging) Studies
9. CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant. Customized eCRFs will be included when appropriate to meet unique study requirements. The LPO PI is encouraged to review the eCRFs working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

F. The timeliness of data submissions and in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due. If delinquent data issues persist and are not resolved at the time of the following quarterly assessment, registration privileges to the ETCTN may be suspended until all delinquent data are submitted and a corrective action plan for ensuring timely data submission is submitted and approved by CTMS and the NCI ETCTN Program Official.

G. QA and Onsite Monitoring/Auditing:
    i. Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and human subjects who participate in research studies. The following should be adhered to in the ETCTN:
        a. Good Clinical Practice (GCP) is an International ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials results that involve

the participation of human subjects. Information on GCP standards in FDA-regulated Clinical Trials is provided at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/good-clinical-practice.

b. Ensuring adequate safeguards is particularly important when conducting early phase clinical trials where the mechanism of action of the agent and/or adverse event profile for the agent may be less understood.

ii. ETCTN sites 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/participants are protected, and that the data generated from the clinical trial are credible. The integrity of the clinical trial is a function of the entire process of data collection and analysis. Vigilance to detect honest errors, whether systematic or random, as well as data fabrication and/or falsification are especially important when conducting clinical trials since independent replication of most trials is not feasible. Goals of the QA Program should be:

a. To prevent problems.
b. To select responsible investigators and research staff.
c. To detect problems by implementing routine monitoring procedures. The system should make detection of both random errors and systematic errors feasible during data collection. Procedures for data audit and statistical methods should be implemented to detect certain types of problems, but purposeful fraud may be very difficult to detect.
d. To take appropriate action in a timely and effective manner. It should be recognized that some errors will remain undetected and uncorrected regardless of the QC, editing, and auditing procedures in place.
e. To serve as a valuable educational vehicle. The onsite visit team should use the opportunity to share with the local staff GCP techniques and data management and QC systems that have been successfully implemented at other institutions. The local staff can use the results of the onsite audit to identify operational areas for improvement.

iii. Data from the CTEP clinical data base management system (CDMS) and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials. To assist the CTEP in fulfilling its regulatory responsibilities as an IND sponsor and to ensure protocol compliance and source data verification, the CTMS contractor performs the Audits of ETCTN participating institutions:

a. Audit will closely follow the policies outlined in section 16 of the Investigator's Handbook (see: http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf and the CTMB Guidelines:https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_etctn_ctms.htm.
b. Representatives from the CTMS will, depending on enrollment, conduct two data audits per year and one annual site visit per year to each of the ETCTN participating institutions. Audits shall be scheduled at a minimum of 4 weeks in advance of the anticipated audit date. The minimum requirements for the initial audit or

subsequent audits will include a meeting between the Contractor Physician/CRC or CRA and the investigator to review his/her understanding of FDA regulations and DCTD policies/procedures for conducting investigational agent trials. These include:

1. FDA regulations concerning GCP, IRB obligations, Informed Consent Regulations and Obligations of Sponsors, Monitors, and Investigators.
2. DCTD, CTEP requirements for submission, review, and approval of protocol and amendments prior to clinical trial activation at an institution.
3. DCTD's Expedited Adverse Event Reporting Requirements via CTEP-AERS and procedures and the use of DCTD's CTCAE 4.0 or subsequent versions.
4. NCI DARFs and pharmacy procedures for proper drug accountability.
5. Review of DCTD required protocol patient data capture procedures and QC review of submitted data.
6. Review of the scope of the investigator's research efforts and the adequacy of facilities for conducting the research. The Physician/CRC/CRA monitor shall collect the institution's laboratory normal values.
7. Review of regulatory procedures and documentation of approval for:
    a. Verification of initial IRB approval for each protocol and all amendments, as well as the required continuing annual IRB approvals and safety reports.
    b. Review of the local consent form to ensure that it is consistent with the informed consent form approved by the CTEP, PRC. A review shall be conducted to determine if the consent form being used is the current IRB approved version.
    c. Review of the Delegation of Task Log. The DTL is a listing of anyone who contributes significant trail-related duties.

b. The data verification audit encompasses the submitted patient data component of the audit. The CTMS auditor will review protocol compliance to ensure patient cases are treated in accordance with protocol specifications and that data have not been omitted from submission.
c. The Patient Case Review will include:
    1. Comparison of source documents to the protocol patient data capture submissions electronically.
    2. For all patient cases reviewed, verification of the presence of an IRB-approved, properly signed and dated informed consent form.
    3. Verification of patient eligibility.
    4. Assessment of compliance with protocol treatment requirements, including the presence of proper documentation of treatment administration and adherence to dose/treatment modification requirements.
    5. Verification that the response is assessed in accordance with the criteria described in the protocol.
    6. Review of patient records to ensure the timely reporting of adverse events requiring expedited reporting via CTEP-AERS. The CTMB is to be promptly notified of any unreported adverse event during the audit that required expedited reporting.
    7. Verification that protocol-required parameters (labs, exams, scans, etc.) were obtained in accordance with the protocol.
    8. A review of the NCI Investigational Drug Accountability Record Forms (DARFs) and of procedures for storage, distribution, and the security of investigational agents to include:

a. A comparison of actual shelf inventory (vial count) versus the NCI DARFs.
b. For the patient cases selected for audit, a comparison of agent dispensed as recorded on the NCI DARFs, versus that recorded as administered in patient source records.

A comparison of the NCI DARFs with the protocol registration listing along with dates to ensure all patients who received investigational agents were registered on the specified protocol.1.II.5. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) annually and financial statements as required in the *NIH Grants Policy Statement*.

A final RPPR, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act) includes a requirement for awardees of Federal grants to report information about first tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at https://www.fsrs.gov/ on all subawards over $25,000. See the NIH Grants Policy Statement for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceeding's information will be made publicly available in the designated integrity and performance system (currently FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

1.II.6. Additional Information

1.II.6.A. Requests for Use of Clinical Data

Requests for use of clinical data only from an ETCTN clinical trial is subject to the CTEP-approved data-sharing policy of the LAO. These requests may be subject to review and approval by NCI Program staff (or "CTEP collaborator" instead) and review by the pharmaceutical 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).

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1.II.6.B. Protocol LOI Review/Approval

Evaluation/Review Outcome: In general, CTEP's PRC discusses the submitted LOI with all assigned reviewers and committee members and decides on the study proposal from one of the four options provided below. A similar process is followed for CTEP's PRC review of non-intervention study proposals (i.e., correlative science studies requesting use of biospecimens collected in association with an ETCTN trial). All approved proposals are sent to the pharmaceutical collaborator for review and approval to supply drug if it is a clinical trial.

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.

Provisional Approval 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 is not set back to a pending review status when the modification is straightforward.

On Hold – The CTEP PRC has significant questions about the proposed study. The proposed study can be approved if the investigators satisfactorily address the concerns included in the written consensus review/evaluation adequately (i.e., comments requiring a response).

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

All Project Team study proposals that are prioritized by the IDSC must undergo review by CTEP before final approval is given. This is done 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 a routine manner (approximately 2 weeks) in most cases as designated NCI/DCTD staff participate as full members on the IDSC or the NCI/DCTD ETCTN BRC. Significant issues in these areas are incorporated into the evaluation/prioritization discussion.

Any approved ETCTN early phase trial is submitted to FDA for comment. Any approved ETCTN LOI with an investigational device/biomarker may also be submitted to the FDA for comment even if the study is not identified as being specifically designed for a licensing indication for an agent or device.

1.II.6.C. Protocol Development Review/Approval and Amendment Review/Approval

The protocol document must be reviewed by NCI/DCTD and granted Approval on Hold (AOH) prior to being submitted to the NCI CIRB for their review. All ETCTN study protocols require approval by the NCI CIRB prior to being granted Final CTEP Approval and being released for activation (i.e., being posted on the CTSU website and opened to patient enrollment). Upon study activation, sites using their local IRB for study review/approval may access the protocol documents for submission to their IRBs.

Any changes/modifications requested by the NCI CIRB at the time of its initial review may require an amendment to the study prior to activation if CTEP believes any of the requested changes/modifications should be in the master protocol document (either in the informed consent or in other sections of the protocol document) prior to granting final CTEP Approval. Minor changes in the informed consent document may be limited to the approved CIRB version of the informed consent document for its sites only. After the trial is activated, all protocol amendments submitted for the trial require NCI CIRB approval prior to final approval of the amendment by CTEP.

Any change to the protocol document after its approval by CTEP must be submitted to CTEP's PIO in writing for review and approval by CTEP prior to implementation of the change. CTEP final approval of changes to the protocol document is contingent upon CIRB approval of the changes following a process like that described above for new protocols.

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

1.II.6.D. 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 already on treatment or in follow-up).

1.II.6.E. Data and Safety Monitoring Boards (Data Monitoring Committees) and Data Safety Monitoring Plans

The focus of the ETCTN DSMB is on the randomized phase 2 studies.
https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_etctn_ctms.htm

The ETCTN Program Official or Senior Scientific Officer and the Chief of the Clinical Trials Monitoring Branch should approve each LPO's policy regarding its data and safety monitoring plans for all ETCTN studies.

1.II.6.F. Data Management, Analysis Review & Use of Standard ETCTN Tools and Services

At the request of CTEP, the Biometric Research Program (BRP) staff, in consultation with other NCI/DCTD staff, will review mechanisms established by the Network site for data management and analysis. When deemed appropriate, BRP staff will make recommendations to ensure that data collection and management procedures are adequate for QC and analysis, yet sufficiently simple to encourage maximum participation of physicians entering patients onto studies and to avoid unnecessary expense. The NCI will have access to all Network site data although the data will remain the property of the awardee institution under the Cooperative Agreement. Data must 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 ETCTN tools and services are used. Network site trial protocols will be periodically audited by NCI/DCTD to ensure that the tools related to common data elements in compliance with the ETCTN

approved sections of the data dictionary for common data elements in caDSR are used in the data collection instruments for the ETCTN trials. If issues with compliance are identified, the NCI/DCTD will work with the ETCTN Site to develop a corrective action plan.

1.II.6.G. Description of Programs, Branches, and Services used in NCI Investigational Agent Development

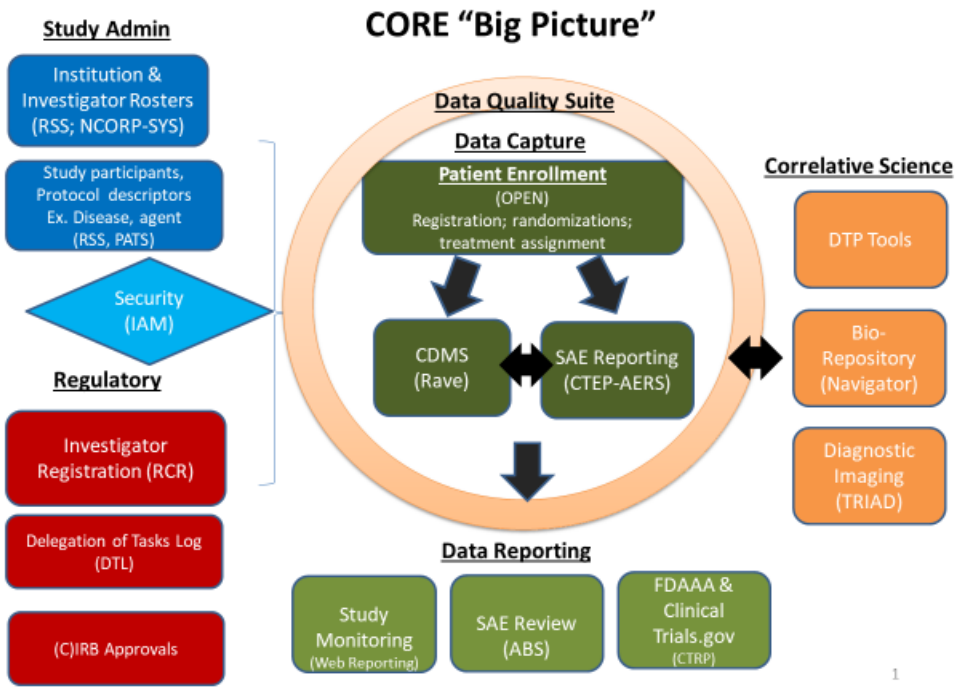
The clinical development of new anticancer agents is a highly important use of ETCTN site resources. The ETCTN sites are a vital component of the research apparatus necessary for the clinical development of the many new investigational agents sponsored by NCI/DCTD. Various branches and contractor services within DCTD share the responsibilities for investigational agent development, as described below.

1. Biometric Research Program (BRP): BRP assesses proposed study designs for evaluating the benefits of investigational agents.
2. Cancer Diagnosis Program (CDP): CDP, with other offices in DCTD, may be involved in planning and oversight of correlative biomarker plans for clinical trials.
3. Cancer Trials Support Unit (CTSU): CTSU coordinates roster management, collection of study specific regulatory documentation, patient enrollment and other ETCTN support activities.
4. Central Institutional Review Board (CIRB): CIRB coordinates initial, annual, and amendment reviews of protections for human research participants.
5. Clinical Data Management System (CDMS): The NCI standard clinical data management system for the ETCTN is CDMS. CDMS is an application for data entry, data analysis, and clinical trial management.
6. The Clinical Investigations Branch (CIB): CIB is involved in promoting agents that are first developed into disease-based Phase 2 and 3 clinical trials.
7. Clinical Trials Branch in the Cancer Imaging Program (CIP): 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 the ETCTN.
8. Central Protocol Writing Service (CPWS): CPWS provides support to develop protocol documents, for selected trials, once an LOI has been approved. CPWS support is discontinued once a protocol has been approved.
9. Clinical Trials Monitoring Branch (CTMB): CTMB verifies adherence by the ETCTN to the Quality Assurance (QA) procedures of investigational agent trials.
10. Clinical Trials Monitoring Service (CTMS): CTMS coordinates data management, quality assurance and onsite auditing.
11. Investigational Drug Branch (IDB): 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.
12. Oncology Patient Enrollment Network (OPEN): OPEN provides controls for patient registration, determination of site and investigator eligibility to participate in a particular study, and assessment of patient eligibility according to parameters established in the protocol.
13. Pharmaceutical Management Branch (PMB) at DCTD: PMB provides for the distribution of investigational new agents for which DCTD is the IND sponsor, registration of all investigators and sub-investigators participating in CTEP clinical trials, and the maintenance of all registration records.

14. Regulatory Affairs Branch (RAB): 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.

Regulatory Support Service (RSS): The Regulatory Support System (RSS) serves as a centralized repository for the regulatory documents for all NCI-supported multi-center clinical trials. The RSS provides a streamlined and comprehensive approach to collecting and maintaining site registration, person, and institution documentation essential to the management of clinical trials.

RSS integrates with several NCI systems (e.g., IAM, OPEN, -Common Data Management System, TRIAD, CTE_ESYS, CIRB-Manager) to enforce authorization rules to facilitate regulatory compliance. RSS maintains protocol information including funding and protocol specific requirements and IRB approvals.



As previously stated, NCI/DCTD (including CTEP and CIP) uses a system of Letters of Intent (LOIs) and PTMAs as a mechanism for developing rational strategies for investigational drug/agent development studies as described in the Investigator's Handbook 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.

1.II.6.H. 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 Networks to meet FDA regulatory requirements for studies involving DCTD/CTEP-sponsored investigational agents and OHRP requirements for the protection of human subjects.

1.II.6.I. Changes in Principal Investigator(s) for Any Key Component of the ETCTN

The NCI ETCTN Program Official must approve any proposed changes in the PI for any key component for the ETCTN under the Cooperative Agreement. The institution's business office should forward the name of the proposed PI in a memorandum to the ETCTN Program Official requesting approval, with a copy to the NCI ETCTN Administration and Grants Manager. The curriculum vitae (CV), biosketch, contact information (address, phone, and email) of the proposed PI should be included as an attachment. The memorandum should be countersigned by the current PI (if available), the LAO's Business Office Official who has responsibility to sign for the cooperative agreement, and the proposed PI. The request to change the Principal Investigator can be sent from the email address of the Institute's Business Office Official with the request memorandum attached with a note from the Institute Business Office Official stating concurrence with the request.

The request for *prior* approval of any additional or substitute PD/PIs or Senior/Key Personnel named in the Notice of Award, or change from a multiple PD/PI model to a single PD/PI model, must be *submitted promptly, and must be* accompanied by a strong scientific justification related to the scientific project, including any proposed changes in scope, the biographical sketch of any new individuals proposed and other sources of support, and any budget changes resulting from the proposed change. A new or revised Leadership Plan is required if the request is to change from a single PD/PI model to a multiple PD/PI model, or to change the number or makeup of the PD/PIs on a multiple PD/PI award. The Commons ID must be provided for any new PD/PIs. In addition, because NIH recipients are expected to provide safe and healthful working conditions for their employees and foster work environments conducive to high-quality research, the request for approval should include mention as to whether change(s) in PD/PI or Senior/Key Personnel is related to concerns about safety and/or work environments (e.g., due to concerns about harassment, bullying, retaliation, or hostile working conditions). NIH will in turn be better positioned to enable informed grant-stewardship decisions regarding matters including, but not limited to, substitute personnel and institutional management and oversight.

1.II.6.J. Changes in Awardee Institution for Any Key Component of the ETCTN

Only under exceptional circumstances will NCI permit transfer of a Cooperative Agreement from one institution to another. The NCI ETCTN Program Official, NCI ETCTN Administration and Grants Manager, and the appropriate NCI Office of Grants Administration Grant Specialist should be consulted for further advice if the LAO contemplates such a transfer request. Any such request, if accepted, will require a detailed plan regarding policies and procedures related to personnel issues, resources, etc., and approval and oversight by the ETCTN Program Official and Associate Director, CTEP.

NIH prior approval is required for the transfer of the legal and administrative responsibility for an NIH funded- project or activity from one legal entity to another before the expiration of the approved project period (competitive segment). A request for a change of grantee organization must be submitted to the NCI Office of Grants Administration (OGA). The original institution must include an Official Statement Relinquishing Interests and Rights in a Public Health Service Research Grant (PHS 3734) (relinquishing statement). The relinquishing statement may be submitted in paper or electronically via the eRA Commons. Final FFR Expenditure Data and a Final Invention Statement are due to NIH from the relinquishing organization no later than 90 days after the end of NIH support of the project. Final FFR Expenditure Data should not be submitted until the original institution has received a revised NoA for the relinquished grant.

The proposed new awardee institution must provide the NCI OGA with a change of institution application (Type 7 application). Instructions for applying for a change in awardee institution are found at https://grants.nih.gov/grants/guide/pa-files/PA-18-590.html. Applicants must prepare applications using current forms in accordance with the Application Guide.

The application from the proposed new awardee institution should include, at a minimum, the following:

1. The appropriate Face page as indicated in the Application Guide.
2. Budget pages (current and future years). Budgets should not exceed the direct costs (plus applicable F&A costs) previously recommended for any budget period. For transfers in the middle of a budget period, the budget for the initial year may be based on the total costs relinquished only if the grantee has been instructed to do so by the awarding IC. For these applications, grantees will also need to include the Other Project Information and the Senior/Key Personnel components.
3. Updated biographical sketches for the PDs/PIs and existing senior/key personnel and biographical sketches for any proposed new senior/key personnel.
4. If transferring on the anniversary date, include the progress report for the current year including a statement regarding the goals for the upcoming year. For all transfer applications include a statement indicating whether the overall research plans/aims have changed from the original submission, and, if so, provide updated information.
5. Updated "other support" page(s), if necessary.
6. Resources page, including probable effect of the move on the project.
7. Checklist page.
8. Certification of IRB/IACUC approval, including OHRP and OLAW assurance numbers, if applicable.
9. Detailed list of any equipment purchased with award funds to be transferred to the new organization (inclusion of this list in the transfer application from the new organization indicates its acceptance of title to that equipment).

NIH expects that requests for change in recipient institution should include mention as to whether the change in recipient institution is related to concerns about safety and/or work environments (e.g., due to concerns about harassment, bullying, retaliation, or hostile working conditions) involving the PD/PI. NIH will in turn be better positioned to enable informed grant-stewardship decisions regarding matters including, but not limited to, substitute personnel and institutional management and oversight. The NIH expects both the relinquishing and applicant organizations to disclose whether a Change of Recipient Organization is occurring within the context of an ongoing or recent investigation of misconduct of any kind, including but not limited to professional misconduct or research misconduct.

For more information see:
https://grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.1.2_prior_approval_requirements.htm#Change3 and https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-124.html.

1.III. Other NCI Administrative Considerations

1.III.1. Program Staff Administration of the ETCTN

Within NCI/DCTD, major scientific policy and programmatic decisions concerning the ETCTN are made only after appropriate consultation with and involvement by the responsible NCI ETCTN Program Official, the Scientific Officers of the ETCTN, the Project Scientists, NCI/DCTD Branch Chiefs and Program Chiefs that are involved in the ETCTN, and the Associate Director, CTEP, DCTD, as necessary and appropriate. Routine programmatic administration is the responsibility of the NCI ETCTN Program Official, or designee, who assures uniformity of implementation across the various key components in conjunction with the Scientific Officers of the ETCTN and the Project Scientists.

The ETCTN Program Official 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 ETCTN Program Official will administer these tasks in conjunction with the Grants Specialist in the Office of Grants Administration (OGA) and will be assisted by the Scientific Officers of the ETCTN, the Project Scientists for the key components of the ETCTN, as well as the NCI ETCTN Administration and Grants Manager.

1.III.2. Administration and Grants Manager for the ETCTN

The NCI ETCTN Administration and Grants Manager assists the ETCTN Program Official with administrative activities in support of the ETCTN, which include but is not limited to reviewing administrative materials supporting ETCTN site 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 ETCTN awardees. The NCI ETCTN Administration and Grants Manager exchanges information with the sites for the key components of the ETCTN, and with OGA and various NCI staff on administrative actions, changes, and priorities.

1.III.3 Investigational Drug Branch Clinical Operations Manager

The NCI/DCTD IDB Clinical Operations Manager assists the ETCTN Program Official with clinical trial related activities in support of the ETCTN. These activities include, but are not limited to, managing and tracking LOIs and protocols through the approval process, roster maintenance, and ETCTN accrual tracking.

1.III.4. NCI Office of Grants Administration (OGA)

The Grant Specialist in the NCI Office of Grants Administration (OGA) is responsible for the fiscal and administrative aspects of each application and award. The OGA Grant Specialist works closely with the responsible NCI ETCTN Program Official and NCI ETCTN Administration and Grants Manager 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.

1.III.5. Miscellaneous Budgetary Considerations

1.III.5.A. Carryover Requests

Carryover requests will be considered 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.

1.III.5.B. Requests for Non-competing Supplemental Funding (Administrative Supplement Requests)

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 may be initiated by the LAO PI. Electronic submission of administrative supplement requests is required. Supplement requests should be submitted under Funding Opportunity Announcement (FOA) PA 20-272 https://grants.nih.gov/grants/guide/pa-files/PA-20-272.html. See "Section IV. Application and Submission Information" in the FOA for details on electronic submission.

If an administrative supplement is being submitted under a non-ETCTN parent award for an ETCTN related activity or study, use the same FOA as above. Once the supplement is submitted, an email should be sent to the ETCTN Program Official with a copy to the ETCTN Administration and Grant Manager to notify them of the supplement submission. In the email notification, include the award ("grant") number of the parent award, the NCI Program Official's name, and the date of the supplement submission.

1.III.5.C. Research Budget

Senior/Key Persons and Other Personnel:

Costs should include estimated costs of salary support (based on level-of-effort) for the PDs/PIs, Disease-Focused Clinical Investigator(s), Translational Scientist, Interventional Radiologist, Research Pathologist, and other collaborators responsible for various aspects of early drug development (but not personnel costs directly related to the conduct of clinical trials at the clinical level).

Each individual designated as a PD/PI must commit a minimum of 1.2 calendar months of effort per year. This minimal effort level must be maintained throughout the entire project period.

The designated Disease-Focused Clinical Investigators, Translational Scientist, Interventional Radiologist and Research Pathologist are expected to commit a minimum of 0.6 calendar months of effort each per year. Disease-Focused Clinical Investigators listed as Senior/Key Persons should receive partial salary support. The effort level requested should be commensurate with the projected scale of accrual to and opening of clinical trials.

General determination of level of overall funding:

The applicant can request more (or less) than the estimated amounts with appropriate budget justification. However, budgets are based on estimated ranges for the infrastructure costs associated with per case management. To justify the budget, the applicant needs to describe in detail in the budget justification the number of patients expected to be accrued for treatment trials, for primary imaging trials, and for one patient biospecimen collection for each enrollment on a treatment or primary imaging trial by category site type (main academic site and integral components versus affiliates).

The budget should include funding to be allocated to support research and development, and ETCTN collaboration efforts (in addition to support for scientific leadership, administrative and regulatory activities, data management and analysis, etc.). All costs for on-site data management using -the common data management system and services provided by CTMS must be fully justified. All costs for the timely development of electronic medical/hospital records to launch early phase clinical trials and mailing or handling research-related patient specimens, forms, and materials should be included. Other consulting costs should be outlined. Costs for protocol development and statistics and data

management for the institution(s) is to support the non-accrual responsibilities associated with participating in early-phase experimental therapeutic clinical trials (*e.g.*, CIRB submission, amendment distribution and continuing review, site training, pharmacy set-up, and site administration) that must be met even if patients are never enrolled on a study at an institution. An annual accrual rate of at least 100 patients per year per UM1 LAO is required. Accrual at each UM1 LAO by its ICs and AOs is counted towards the accrual rate of 100 patients per year.

Provide the cost for each main budget category (personnel, supplies, travel, etc.) as needed for organizational harmonization; the coordination of ETCTN clinical trials; clinical support and recruitment, regulatory, data management, Electronic Medical Record (EMR) builds, and other organizational activities. Costs of the integration of the informatics system with the services provided by the Clinical Trials Monitoring Service (CTMS, see http://ctep.cancer.gov/branches/ctmb/resources.htm) may be included but only for well-justified on-site expenses.

Funds for travel:

The ETCTN Site PDs/PIs will be required to travel to two meetings per year. Include travel funds for two NCI/CTEP Early Drug Development (EDD) meetings per year for four representatives from the ETCTN site (at least one of whom must be the LAO PD/PI). Travel costs for two presenters for major national/international meetings should be included in the budget.

Clinical Trials Research Operations and Research Related Hospital Charges:

Requested funds for clinical trials operations must be to support institutional costs of research that are not considered a “cost of treatment” by medical insurers, and therefore are not reimbursed by insurers (*e.g.*, blood and urine collection and shipping, tumor tissue handling and shipping to the tissue bank, performing research imaging studies, etc.).

In planning these expenses, applicants should consider patient Enrollment Costs. Estimated costs of patient accrual for clinical trials should be included. Provide a detailed breakout of costs used to estimate the reimbursable per-patient accrual costs in the budget justification. The net per-patient cost for accrual to ETCTN clinical trials regardless of phase (i.e., excluding the costs of laboratory studies and biospecimen handling) multiplied by the expected number of patients to be accrued (at least 100 per year) should be approximated as part of the entire budgetary request.

Tissue Acquisition:

The budget request should include costs for the acquisition of high-quality research biopsies and other clinical specimens, as well as biospecimen handling. The anticipated total annual expenses should be based on per-patient costs of the accrual, assuming at least 100 patients per year.

The requested budget items shall NOT include or reflect any costs for the following activities:

- Correlative studies and biomarker assays to enhance specific clinical trials; such studies will be prioritized and supported as needed by separate NCI Administrative Supplements or other funding sources;
- The NCI-provided standardized central operational, regulatory, and administrative support, as these services will be provided by the NCI at no cost to the applicant; and
- Any costs that are not solely research-related and could be considered "a cost of treatment" by medical insurers.

Part 2: Guidelines for Submission of Research Performance Progress Reports (Non-competing Continuing Applications, Annual Progress Reports)

2.I. Pre-Application Consultation and Application Submission Instructions

Each ETCTN LAO is required to submit, on an annual basis, a non-competing continuation application (Type 5 Application/Research Performance Progress Report [RPPR]) *i.e.*, the Annual Progress Report. Applicants should consult the RPPR Instruction Guide at: https://grants.nih.gov/grants/RPPR/rppr_instruction_guide.pdf for up-to-date information on NIH requirements for completing the annual RPPR. The RPPR is required for every year of award, including the year in which a competing continuation application (Type 2 Application) may be submitted.

The RPPR should contain the basic information needed to allow the NCI ETCTN Program Official, or designee, to monitor the progress and performance of all ETCTN Sites.

The submission procedures for the RPPR are described below.

SENDING AN RPPR TO THE NIH:
If the award is an annual award for each fiscal year of the project period, two (2) months before the start of the budget period, submit the RPPR via the RPPR module in eRA Commons. Grantees may access their progress report that is due using the Status page in eRA Commons and selecting the Tab "List of Applications/Grants." The far-right column on the resulting table entitled “Action” will include an RPPR link if a progress report is due. Select the RPPR link to access and initiate the RPPR form.

The RPPR instruction guide is available at: https://grants.nih.gov/grants/RPPR/rppr_instruction_guide.pdf. The information provided in the RPPR, however, should be focused on the specific activities of the ETCTN LAO, ICs, and AOs (*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).

A multi-year funded (MYF) award is one in which the project period and budget period are the same and are longer than one year, and the award is funded from a single appropriation. If the award is a multi-year funded award, RPPRs for multi-year funded awards are due annually on or before the anniversary of the budget/project period start date of the award. NIH will send an email notification to the PD/PI two months before the anniversary of the award requesting that the RPPR be submitted. Currently, UM1 mechanism awards will not have a link in eRA Commons to submit the RPPR.
It has been determined that due to the system issue which does not provide the Research Performance Progress Report (RPPR) link for the competing continuation (type 2) multiyear funded ETCTN UM1s, three alternatives for creating the RPPR are available:

1. Use a blank RPPR form if available at your institution
2. Use a previous RPPR in pdf or Word that can be edited to create the report
3. Use the PHS 2590 form found at https://grants.nih.gov/grants/funding/2590/2590.htm

Enrollment data can be updated using the link to the Human Subjects System (HSS) in eCommons for your application. To access the link, login to eCommons, click on the status tab, find the row for your UM1 (2UM1CAXXXXXX-06). The link to HSS (Human Subjects or HSS) should be in the “Available Actions” column. For clinical study information entered in HSS, the information entered in the data fields in HSS must match the corresponding data fields in clinicaltrials.gov. If those fields

do not match **prior to** the issuance of an award, HSS will prevent the issuance of the award until the data fields match. If a clinicaltrials.gov data field is changed after submission of HSS data to NIH, then data in the corresponding HSS field must be revised as soon as possible to match the clinicaltrials.gov data change and the revised HSS data must be resubmitted to NIH via HSS.

Once the enrollment data has been updated in HSS, your Signing Official should submit it to NIH via HSS. Inclusion Enrollment tables are not required in the RPPR, as this data should be provided to NIH via HSS.

Submit the RPPR from the email address of the UM1 LAO's institutional Signing Official with a note of concurrence with the RPPR submission to the OGA Specialist for your award with a copy to the ETCTN Program Official and the NCI ETCTN Administration and Grants Manager.

The following sections include instructions on the types of information that should be included in an RPPR.

2.II. RPPR Format

The information included in an RPPR should be provided in formats similar to the ones presented in this part of the Guidelines and should follow the requirements of the RPPR as stated in the RPPR Instruction Guide: http://grants.nih.gov/grants/RPPR/rppr_instruction_guide.pdf.

Providing the information in a standard format will allow the NCI ETCTN Program Official, Scientific Officers, and Project Scientists to evaluate the progress of the ETCTN more easily and to identify areas that need attention. The instructions on the following sections provide summaries of key information to provide in the RPPR for the ETCTN.

It is anticipated that additional instructions/modifications for specific required information to be included in the annual RPPR may be given to awardees by the ETCTN Program Official prior to submission of the first annual progress report, especially with respect to streamlining the report.

For those using the RPPR link in eCommons, once an RPPR is initiated its status becomes *PDs/PIs Work in Progr*ess and becomes available for editing. The PDs/PIs or delegate should use the **Edit** option for viewing and completing the report. For RPPRs with multiple PDs/PIs (MPI awards), only the Contact PDs/PIs has access to the **Edit** feature unless the Contact PDs/PIs has granted progress report authority to other PDs/PIs. Without this authority, MPIs can only view the RPPR PDF and its routing history.

2.III. Overview of RPPR Sections

2.III.1. Section A – Cover Page

The *Cover Page* includes tabs at the top and links at the bottom of the page for navigating to the other sections (*e.g.*, **Accomplishments, Participants, etc.**), which may be completed in any order. Before navigating to and from any of these sections, it is always necessary to select the **Save** button to save all changes on the current page. Navigating away from any page on the RPPR without selecting **Save** results in the loss of any information entered prior to the last save.

2.III.2. Section B – Accomplishments

Accomplishments allow NCI to assess whether satisfactory progress has been made during the reporting period. List the major goals of the project as stated in the approved application or as approved by NIH. *Goals* are equivalent to *specific aims*. If the awarding agency approved changes to the major goals/specific aims during the reporting period, provide a revised description of those revised goals and objectives. Explain any significant changes in approach or methods from those in the initial competing award. Written prior approval from the NCI ETCTN Program Official, or designee, is required for significant changes in the project or its direction. For the reporting period describe: 1) major activities; 2) specific objectives; 3) significant results, including major findings, developments, or conclusions (both positive and negative); and 4) key outcomes or other achievements. Include a discussion of stated goals not met.

a. Competitive Revisions/Administrative Supplements
Identify the Revision(s)/Supplements(s) by grant number (*e.g.*, 3R01CA4567895-01S1) or title and describe the specific aims and accomplishments for each Revision/Supplement funded during this reporting period.

b. Opportunities for Training and Professional Development
Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. *Training* activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency.

c. Dissemination of Results to Communities of Interest
Describe how the results have been disseminated to communities of interest. Include any outreach activities that have been undertaken to reach members of communities who are not usually aware of these research activities. Reporting the routine dissemination of information (*e.g.*, websites, press releases) is not required.

d. Plans for the Next Reporting Period
Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

2.III.3. Section C – Products

This section allows NCI to assess and report products to Congress, communities of interest, and the public.

a. **Publications**
The NIH Public Access Policy requires scientists to submit final peer-reviewed manuscripts that result from direct costs funded by NIH, and that are accepted for publication on or after April 7, 2008, to PubMed Central. Compliance with the NIH Public Access Policy is a legal requirement (Consolidated Appropriations Act of 2008, Public Law 110-161, Division G, Title II, Section 218) and a term and condition of an award. If a grantee has failed to materially comply with the terms and conditions of award, NIH may suspend the award pending corrective action, or may terminate the award for cause (per 45 CFR 74.61, 74.62, and 92.43).

PDs/PIs are required to report all publications that arise from their NIH award. Publications listed in other parts of the RPPR will not be tracked as award products. If there are publications

to report, ensure that the "Associate with this RPPR" box is checked as appropriate. The tables draw information from the PDs/PIs' My NCBI account. Grantees are responsible for ensuring publications comply with the Public Access policy even if they were provisionally compliant (listed as *in Progress*) when previously reported.

Only those publications resulting directly from activities of the ETCTN should be reported.

Ensure the following:

1. **If the manuscript(s) were accepted for publication on or after April 7, 2008, please enter these documents into PubMed Central as soon as possible.** Information on how to submit manuscripts can be found at: https://publicaccess.nih.gov/submit_process.htm.
2. You can confirm compliance by including the PubMed Central reference number (PMCID) in the list of publications. Please see the NIH Public Access Policy Frequently Asked Questions (FAQ) if you have questions about how to use PMCIDs or if the PMCID has not been assigned yet. You should include the PMCID when citing these papers in any subsequent report. Please see: Guide Notice NOT-OD-08-119 for more information and alternatives. If you have any questions about the Policy, please check the Website or send a note to PublicAccess@nih.gov

b. **Inventions, Patent Applications and/or Licenses**
Reporting of inventions through iEdison is strongly encouraged. For more information on iEdison go to https://public.era.nih.gov/iedison/public/login.do?TARGET=https%3A%2F%2Fpublic.era.nih.gov%2Fiedison%2Finit.do

c. **Accrual and Clinical Trial Performance**
Accrual and clinical trial performance described below apply to the annual RPPR for the ETCTN Awardees**.**

Provide documentation of important capabilities and available resources for specific functional components of the ETCTN LAO, ICs, and AOs. Relevant information may be provided in tabular form as listed below. Applicants are strongly encouraged to use, as appropriate, table templates provided in Part 3.III - Appendices (Appendices Tables).

Table 1.	**Completed and Ongoing Phase 1 and Phase 2 Clinical Trials** List ETCTN early phase clinical trials that have been completed during the reporting period of the RPPR and any ongoing clinical trials for which significant research findings are available. For each trial listed, provide respective National Clinical Trial identifier (NCT number).
Table 2.	**Other Scientific Achievements for Clinical Trials** List early phase clinical trial scientific achievements that have occurred during the reporting period of the RPPR
Table 3.	**List Molecular Characterizations Performed During Conduct of ETCTN Early Phase Clinical Trials**

	Describe biomarker assays, molecular characterization, and other correlative laboratory studies performed on patient tissue during the reporting period of the RPPR, especially those that included surgical or image-guided biopsies.
Table 4.	**Summary Accrual for Screened and Treated Patients on Early Experimental Therapeutic Clinical Trials** Describe the number of patients screened and treated on early phase clinical trials during the reporting period of the RPPR, that were/are led by the LAO and/or AOs or where the LAO and/or AO accrued patients to an ETCTN early phase clinical trial but was not the lead on the protocol
Table 5.	**Summary of Letters of Intent Submitted and Approved, and Protocols Submitted** List clinical trial protocol development activities for the reporting period of the RPPR, including relevant dates and milestones with timelines for specific steps in the clinical trial development process.
Table 6.	**Inclusion Enrollment Report** Total aggregate annual accrual, for the RPPR reporting period, to ETCTN early phase clinical trials by gender and ethnicity/race composition should be described in the PHS 398 Cumulative Inclusion Enrollment Report form http://grants.nih.gov/grants/funding/phs398/CumulativeInclusionEnrollmentReport.pdf Accrual should be grouped by phase of study.
Table 7.	**Operational Timelines for Activation of Clinical Trial Proposals** List timelines for the LAO, ICs, and any AOs (if applicable). List actual timelines for specific steps in the clinical trial protocol development process during the reporting period of the RPPR, including accrual rate projected and achieved, total accrual, study duration and submission of abstracts and manuscripts.

i) Clinical Trial Performance
LAOs should summarize the timeliness of CTEP-AERS reports submission, the date of the last audit for institutional members (or Lead Academic Participating Site), compliance with specimen submission, *etc*., in the RPPR.

ii) Progress & Summary of Research Achievements of the ETCTN site (Table 1 and 2)
The RPPR for the ETCTN site should report on the site's progress regarding the goals and activities outlined in the research plan of the awarded competing application. This should include information on how the ETCTN site has contributed to the goals of the ETCTN, with emphasis on accomplishments during the current funding period.

iii) Operational Timelines for Activation of Clinical Trial Proposals (Table 7)
The RPPR should list protocol development activities during the current funding period for ETCTN sites, in terms of submitted and approved Letters of Intent (LOIs), submitted and approved protocols, activated and completed trials with associated OEWG timelines.

The Products Section of the RPPR should provide a brief, narrative description of the contributions of the ETCTN site to ETCTN clinical trials and research goals and other ETCTN activities and initiatives, including important collaborations, during the current funding period. This section should be adequate to convey the important facets of the activity and any significant findings. In all cases, brief and concise descriptions in the products section of the RPPR are encouraged.

2.III.4. Section D – Participants

This section allows the NCI to know who has worked on the project to gauge and report performance in promoting partnerships and collaborations. Provide or update the information for: (1) PDs/PIs; and (2) each person who has worked at least one calendar month per year on the project during the reporting period, regardless of the source of compensation. **Senior/key personnel** are defined as the PDs/PIs and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether they receive salaries or compensation under the award. Calendar months reported on the RPPR are intentionally rounded to the nearest whole number to provide for generalized reporting consistent across federal agencies that support research activities.

The provision of the partial Social Security number and month/year of birth are voluntary.

All multiple PDs/PIs awards have a Leadership Plan that describes the roles and areas of responsibility of the named PDs/PIs, the process for making decisions concerning scientific directions, allocation of resources, disputes that may arise, and other information related to the management of the proposed team science project. If there has been any change in the governance and/or organizational structure of the Leadership Plan, provide a description, including communication plans and procedures for resolving conflicts, and any changes to the administrative, technical, and scientific responsibilities of the PDs/PIs. If the RPPR includes a change in the Contact PDs/PIs (*Cover Page, A.1*) address this change and the impact, if any, the change has on the administrative, technical, and scientific responsibilities of the PDs/PIs.

A change of the contact PI requires prior approval by the ETCTN Program Official.

2.III.5. Section E – Impact

This section will be used to describe ways in which the work, findings, and specific products of the project have had an impact during the reporting period. Describe ways, if any, in which the project made an impact, or is likely to make an impact, on physical, institutional, and information resources that form infrastructure.

2.III.6. Section F – Changes

Describe any challenges or delays encountered during the reporting period and actions or plans to resolve them. Describe only significant challenges that may impede the research (*e.g.*, accrual of patients, hiring of personnel, need for resources or research tools) and emphasize their resolution. Describe significant deviations, unexpected outcomes, or changes in approved protocols for human subjects, vertebrate animals, biohazards and/or select agents during this reporting period.

Significant changes in objectives and scope require prior approval of the agency.

2.III.7. Section G – Special Reporting Requirements

The Special Reporting Requirements section addresses NCI-specific award terms and conditions, as well as any award specific reporting requirements.

For electronic submission of the RPPR via the link in eCOMMONS:

a. Editing Inclusion Enrollment Data (Section G4.b)

When inclusion monitoring is required and no IDRs exist, the RPPR system will NOT allow the submission of the progress report without IER(s).

For more information on utilizing the Human Subjects System see:
https://era.nih.gov/files/HSS_user_guide.pdf.

For more information on the RPPR system see:
https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf

If there are changes from the planned enrollment originally approved for funding, contact the NCI ETCTN Program Official, or designee, to discuss updating/revising the planned enrollment. The NCI ETCTN Program Official must approve the change in planned enrollment prior to revising planned enrollment in HSS.

Grantees are **strongly** encouraged to view the RPPR prior to submission to ensure that the correct information and attachments are provided. The RPPR is validated for systemic and business rules. If there are any validation failures, they are indicated by error messages on the *RPPR Menu* screen. Errors must be corrected to submit the RPPR.

If assistance is needed with reporting inclusion enrollment data and/or with resolving error messages, contact the NCI ETCTN Administration and Grants Manager.

b. Project/Performance Sites

If there are changes to the project/performance site(s) displayed, edit the RPPR as appropriate.

The ETCTN site must alert the NCI ETCTN Administration and Grants Manager and the Office of Grants Administration (OGA) Grant Specialist for the ETCTN UM1 LAO award when a non-competing application (RPPR) involves any new international (non- U.S.) component, regardless of whether the component receives federal funding under the awardee's cooperative agreement. In such cases, advance clearance from the U.S. Department of State is required for each non-U.S. component prior to participation of the site in the research project. The information required by the U.S. Department of State for each foreign component/site is listed below (this information should also include all non-U.S. subcontracts).

1. Estimated annual Total Cost dollar award for the non-U.S. component
2. Name, organization, address, city, country, email, and telephone number of the International (non- U.S.) Principal or Collaborating Investigator(s)
3. Biosketch and Curriculum Vitae (CV) for both the domestic PI and the international PI
4. OHRP Federal-wide Assurance (FWA) number for the non-US component
5. Summary of responsibilities and activities of the foreign component.

For international sites collaborating with an ETCTN site on trials sponsored under the ETCTN (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 ETCTN and the other country.

2.III.8. Section H – Budget

To complete the detailed budget for this award, select the "SF424 Research and Related Budget" and follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Form, to complete the R&R budget and the R&R Cumulative Budget,

a. Non-Competing Budget Adjustments

Out-year budget commitments, as reflected in each Notice of Grant Award, are based on 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 ETCTN awardee or a change in the funds available to the government for distribution. Requests for the adjustments are initiated by the ETCTN site 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 affect an adjustment rests with the NCI Grants Management Specialist in the NCI OGA on the recommendation of the NCI ETCTN Program Official. Funding adjustments are facilitated by the NCI ETCTN Administration and Grants Manager.

Electronic submission of RPPRs for annual awards are due at the NCI 60 days prior to the award date. The RPPR for multi-year funded awards is due annually on or before the anniversary of the budget/project period start date of the award. Sufficient time should be allotted to permit timely receipt of RPPRs in line with any request for redistribution/restructuring or carryover. In connection with this timeline, it should be noted that OGA generally requires a formal, updated budget when changes of more than 25 percent are requested.

b. Budget Adjustments by NCI/DCTD for ETCTN Sites

Adjustments may be made by NCI/DCTD in the funding of ETCTN sites 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 ETCTN Program Official, who works in conjunction with the NCI ETCTN Administration and Grants Manager.

Budget commitments for the non-competing years are based upon the funding level for the competing year. Increases or decreases in funding for any ETCTN site may be made based on changes in performance relative to that approved in the competing application or in the previous year. The actual monies awarded are always 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.

The ETCTN site will undergo assessment with possible decrement in funding after 2 years of performance based on the awardee's accrual to ETCTN trials.

2.IV. PDF Attachments

Grantees should generate text attachments using any word processing software and then convert those files to PDF before attaching the files to the appropriate section in the RPPR. The PDF format

is used to preserve document formatting. All PDF attachments must be submitted as individual files. Although some software packages allow bundling of multiple PDFs into a single file, eRA systems cannot support "Bundling" or "Portfolio" features at this time. Use of these features may result in delays in NCI acceptance of the RPPR. Paginated PDF files are discouraged since they can interfere with system pagination of the entire RPPR document upon submission to NIH. File names will be used and displayed in the assembled PDF submitted to NIH.

Save all files with descriptive file names of 50 characters or less and be sure to only use standard characters in file names: A through Z, a through z, 0 through 9, and underscore (_). Do not use any special characters (examples include &, -, *, %, /, and #) or spacing in the file name, and for word separation use an underscore (*e.g.*, My_Attached_File.pdf).

Use an Arial, Helvetica, Palatino Linotype, or Georgia typeface, a black font color, and a font size of 11 points or larger. (A Symbol font may be used to insert Greek letters or special characters; the font size requirement still applies.) Type density, including characters and spaces, must be no more than 15 characters per inch. Type may be no more than six lines per inch.

Use standard paper size (8 ½" x 11). Use at least one-half inch margins (top, bottom, left, and right) for all pages. No information should appear in the margins, including the PI's name and page numbers.

Part 3: Appendices

3.I. NCI/DCTD Policies for the ETCTN (URLs to Websites)

NCI Experimental Therapeutics Clinical Trials Network (ETCTN) Website
https://ctep.cancer.gov/initiativesPrograms/etctn.htm

NCI ETCTN Guidelines *(this document; click link to obtain the most recent version)*
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Program_Guidelines.pdf

Investigator's Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI)
https://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

IP Option Policy
https://ctep.cancer.gov/industryCollaborations2/default.htm

Operational Efficiency Working (OEWG) Policy and Timelines
https://ctep.cancer.gov/SpotlightOn/OEWG.htm

Policy on Contract Review
https://ctep.cancer.gov/industryCollaborations2/guidelines.htm
(Under NCI Standard Protocol Language for Collaborative Agreements)

Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies
https://ctep.cancer.gov/protocolDevelopment/cde_data_policies.htm
(Under CDE / Data policies / CDUS – Slow Accrual Guidelines for Phase 3 Trials)

Adverse Event Expedited Reporting System (CTEP-AERS)
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Information on Common Data Elements (CDE) Approved for Use in CTEP-sponsored Clinical Trials
https://cdebrowser.nci.nih.gov/cdebrowserClient/cdeBrowser.html#/search

NCI's Common Terminology Criteria for Adverse Events (CTCAE)
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

NCI Clinical Trials Cooperative Program Guidelines for the Development, Conduct and Analysis of Clinical Trials with International Collaborating Institutions (Under Guidelines & Policies)
https://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/nci_clin_intl_guidelines.pdf#search=%22international%22

CTEP Conflict of Interest Policy for Cooperative Phase 3 Clinical Trials (Under Guidelines and Policies)
https://ctep.cancer.gov/investigatorResources/docs/Conflict_Of_Interest_Policy.pdf

NCI Templates for Protocols and Informed Consent Documents for ETCTN Trials

https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm

Guidelines for Auditing of Clinical Trials for Experimental Therapeutics Clinical Trials Network (ETCTN)
https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_etctn_ctms.htm
The National Institutes of Health (NIH) Genomic Data Sharing Policy
https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing/

The National Cancer Institute (NCI) Genomic Data Sharing
https://datascience.cancer.gov/data-sharing/genomic-data-sharing/about-the-genomic-data-sharing-policy

Privacy and Progress in Whole Genome Sequencing
https://bioethicsarchive.georgetown.edu/pcsbi/node/764.html.

3.II. ETCTN Help Contacts

A listing of contacts for assistance with the ETCTN Program is available at the following link:
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Help_Contacts.pdf.

3.III. Suggested Formats - Tables for New & Non-Competing Applications

The tables provided in this section are to assist in the documentation of important capabilities and available resources for specific functional components of the ETCTN LAO. **Applicants are strongly encouraged to use, as appropriate, table templates.**

Current and/or relevant information in the past 5-6 years for new or competing continuation applications and within the reporting period for noncompeting applications (RPPR) should be used in the tables unless otherwise indicated.

Template Table 1: Completed and Ongoing Phase 1 and Phase 2 Clinical Trials
MM/YYYY to MM/YYYY

List ETCTN early phase clinical trials that have been completed and any ongoing clinical trials for which significant research findings are available. For each trial listed, provide respective National Clinical Trial identifier (NCT number). Add rows as needed.

Cancer Site	Trial Phase	Year (publication 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

Template Table 2: Other Scientific Achievements for Clinical Trials
MM/YYYY to MM/YYYY

List early phase clinical trial scientific achievements that have occurred. Add rows as needed.

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

Template Table 3: List Molecular Characterizations Performed During Conduct of ETCTN Early Phase Clinical Trials

MM/YYYY to MM/YYYY

Describe biomarker assays, molecular characterization, and other correlative laboratory studies performed on patient tissue, especially those that included surgical or image-guided biopsies. Add rows as needed

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)

Template Table 4: Summary Accrual for Screened and Treated Patients on Early Experimental Therapeutic Clinical Trials

Describe the number of patients screened and treated on early phase clinical trials that were/are led by the LAO and/or AOs or where the LAO and/or AO accrued patients to an ETCTN early phase clinical trial but was not the lead on the protocol. Add rows as needed.
S=Screened S&T = Screened and Treatment Tx = Treatment

Study Accrual Period (MM/YYYY) to MM/YYYY)	Pilot and/or Exploratory IND Studies (Phase 0) Tx Studies			Phase 1 Tx Studies			Phase 1 Combination Tx Studies (Includes phase ½ studies)			Phase 2 Tx Studies			Phase 2 Combination Tx Studies		
	S	S&T	Total	S	S & T	Total	S	S & T	Total	S	S & T	Total	S	S & T	Total
Study Title and Protocol Number #1															
Accrual **to Trial Led** by Applicant															
Accrual **to Trial NOT Led** by Applicant															
Study Title and Protocol Number #2															
Accrual **to Trial Led** by Applicant															
Accrual **to Trial NOT Led** by Applicant															
Total	Sum of Total **column**														
Grand Total (across all studies)	(Sum of all totals in "Total" **row**)														

Template Table 5: Summary of Letters of Intent (LOI) Submitted and Approved, and Protocols Submitted
MM/YYYY to MM/YYYY

List clinical trial protocol development activities, including relevant dates and milestones with timelines for specific steps in the clinical trial development process. Add rows as needed.

	LOI Number Designation	Date Submitted	Date Approved/ Disapproved	Date Protocol Submitted	Date Protocol Approved	Date Trial Activated	Date Trial Completed	Type of Novel Trial Design
Study Title #1								
Study Title #2								
	# of LOIs	# Submitted	#Approved	# Submitted	# Approved	# Activated	# Completed	
Total (across all studies)								

Template Table 6: Cumulative Inclusion Enrollment Report

MM/YYYY to MM/YYYY

Total aggregate annual accrual during the RPPR reporting period to ETCTN early phase clinical trials by gender and ethnicity/race composition should be described in the PHS 398 Cumulative Inclusion Enrollment Report form (http://grants.nih.gov/grants/funding/phs398/CumulativeInclusionEnrollmentReport.pdf) Accrual should be grouped by phase of study. Do not modify the table.

Racial Categories	**Ethnic Categories**									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			**Total**
	Female	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	
American Indian/ Alaska Native										
Asian										
Native Hawaiian or Other Pacific Islander										
Black or African American										
White										
More than One Race										
Unknown or Not Reported										
Total										

Template Table 7: Operational Timelines for Activation of Clinical Trial Proposals MM/YYYY to MM/YYYY

List timelines for the LAO, ICs, and any AOs (if applicable). List actual timelines for specific steps in the clinical trial protocol development process, including accrual rate projected and achieved, total accrual, study duration and submission of abstracts and manuscripts. Add rows as needed.

IND Studies – Pilot and/or Exploratory IND Studies (Phase 0)

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 1

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 1 Combination

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 2

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

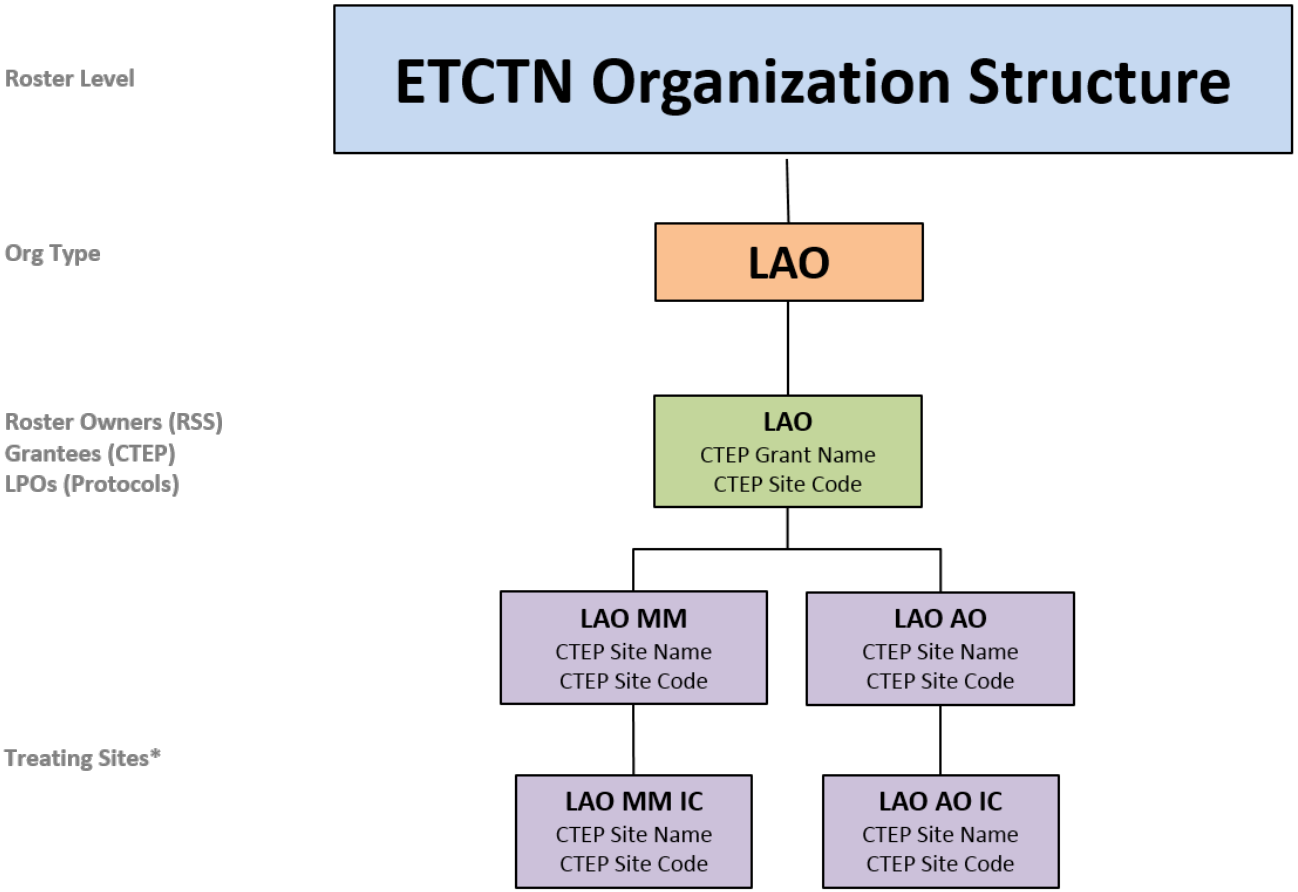
IND Studies – Phase 2 Combination

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

3.IV. ETCTN Organization Structure

The ETCTN Organization Structure is provided in the diagram contained in this section.

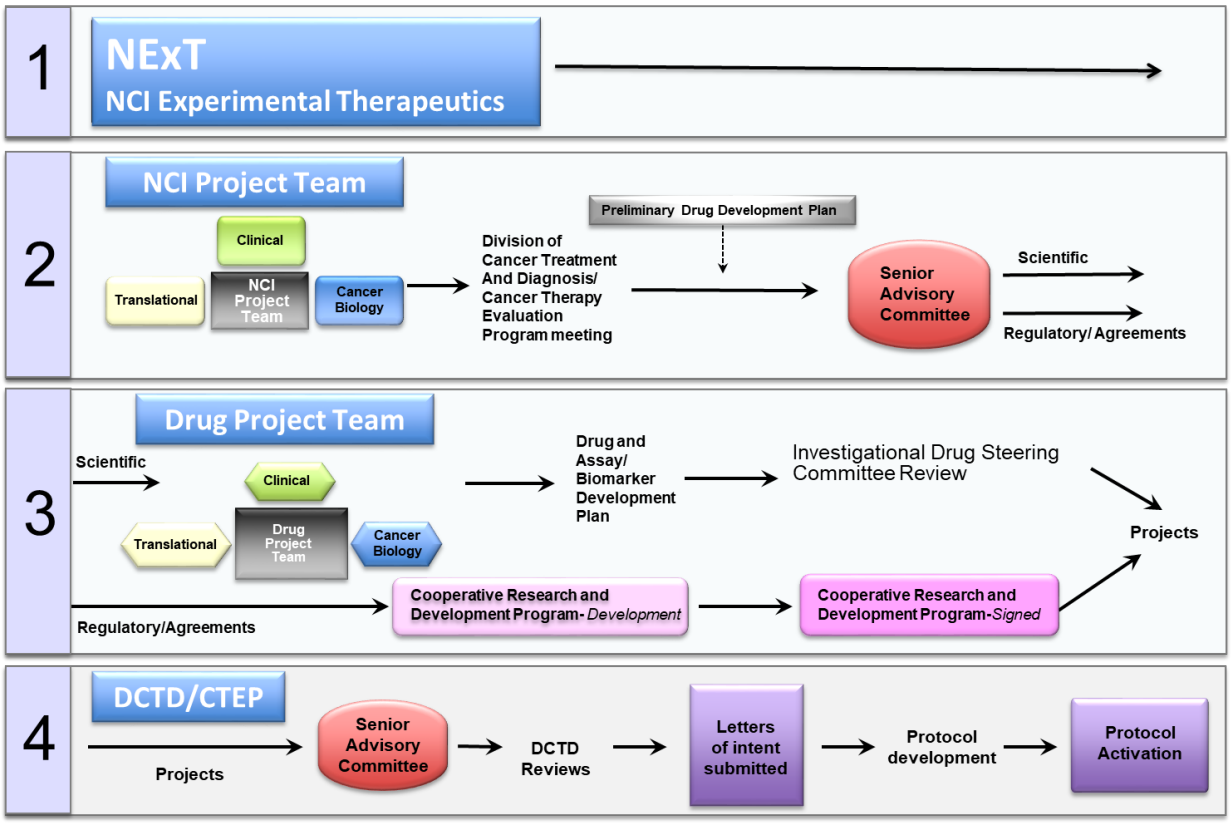
March 2016

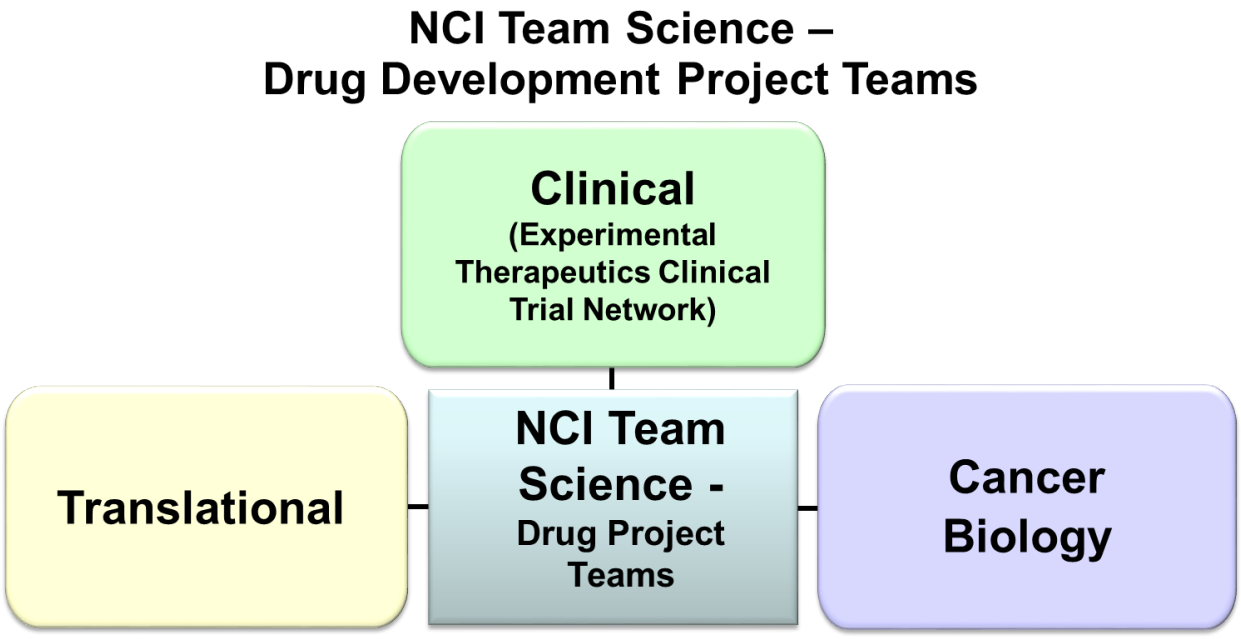


*The treating site roster is defined by the LAO grant (i.e., updates require an amendment to the grant and to the LAO grant package in CTEPESYS).

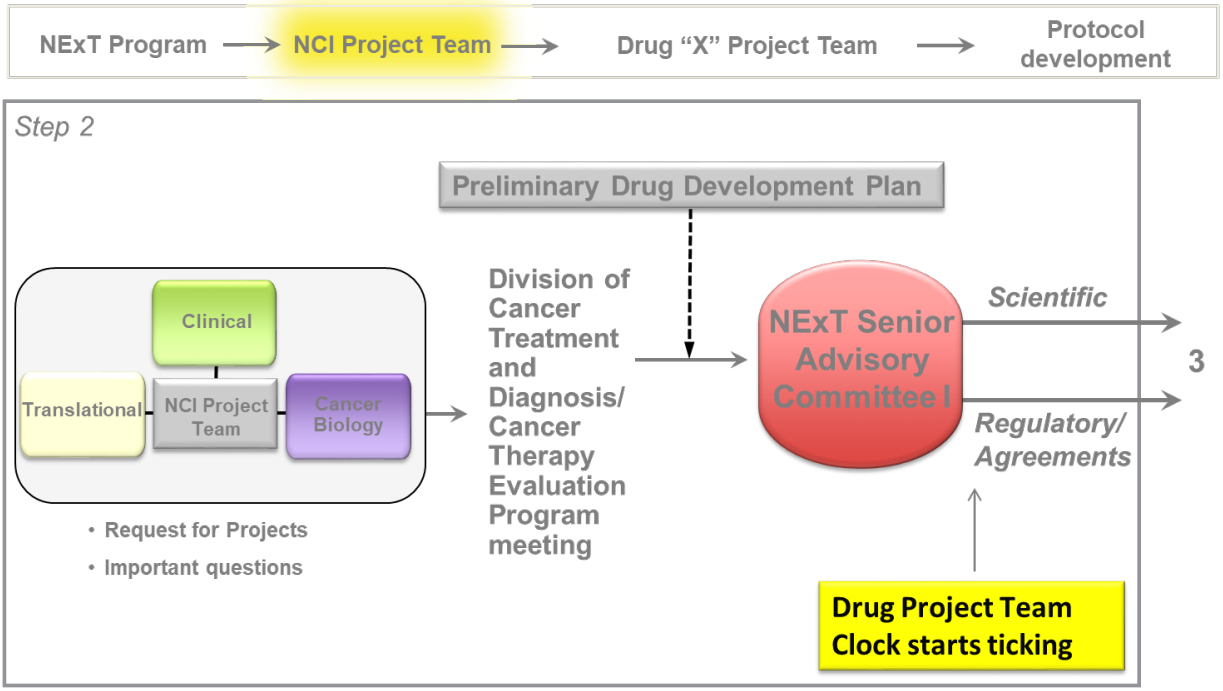
ETCTN – Experimental Therapeutics Clinical Trials Network
LAO – Lead Academic Organization (UM1); **MM** – Main Member; **AO** - Affiliated Organization; **IC** – Integrated Component

3.V. Process for Initial Development of NCI IND Agents

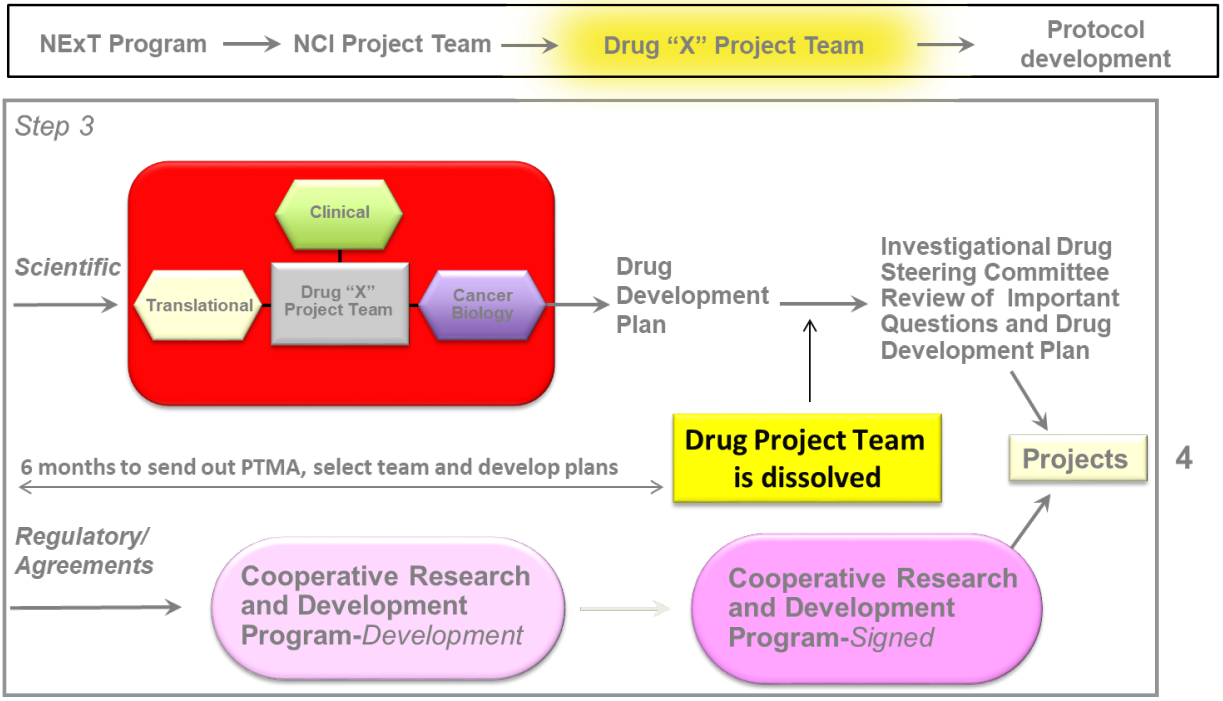



NCI Team Science –
Drug Development Project Teams
Clinical
(Experimental Therapeutics Clinical Trial Network)
Translational
NCI Team Science -
Drug Project Teams
Cancer Biology

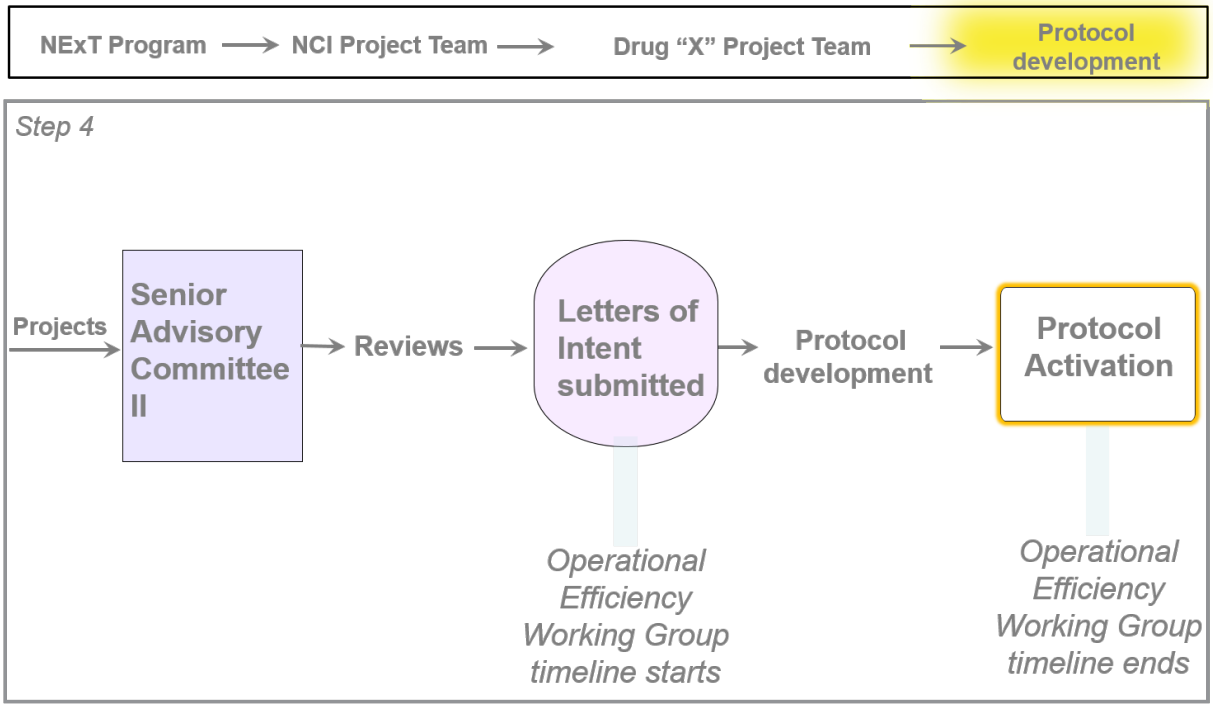
NCI Team Science-Project Development: Step 2 – NCI Project Team



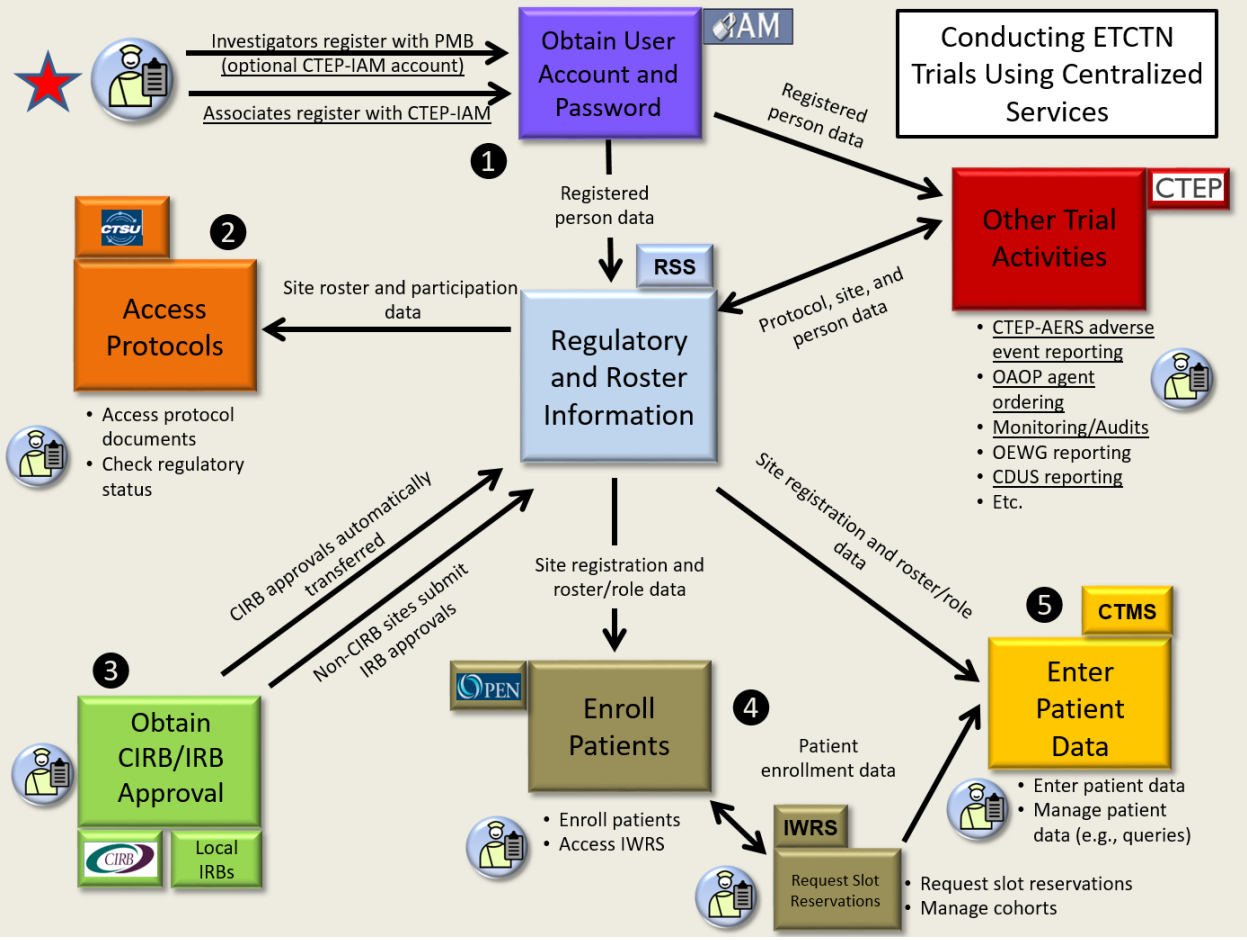
NCI Team Science-Project Development: Step 3- Investigational Drug Steering Committee Project Team

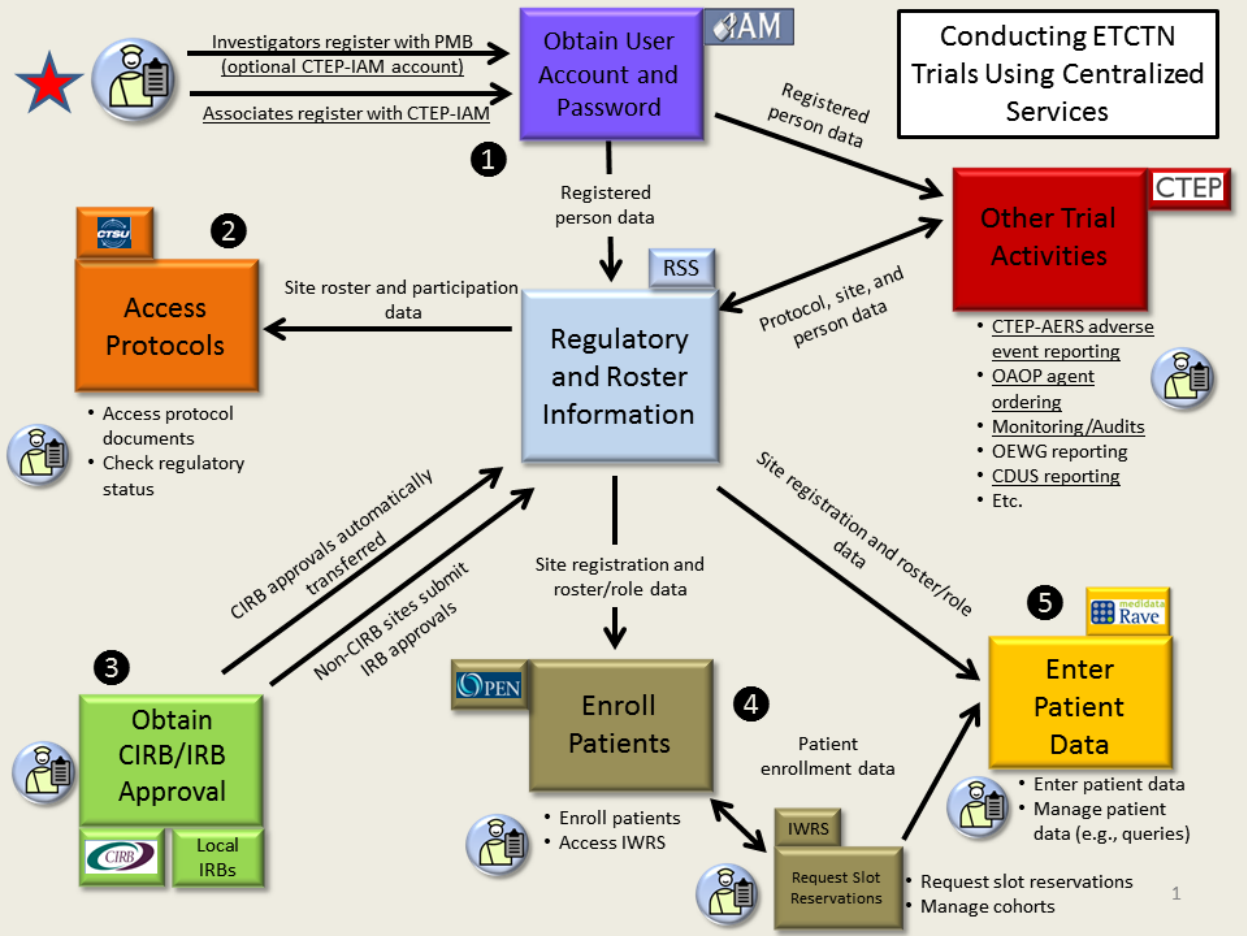


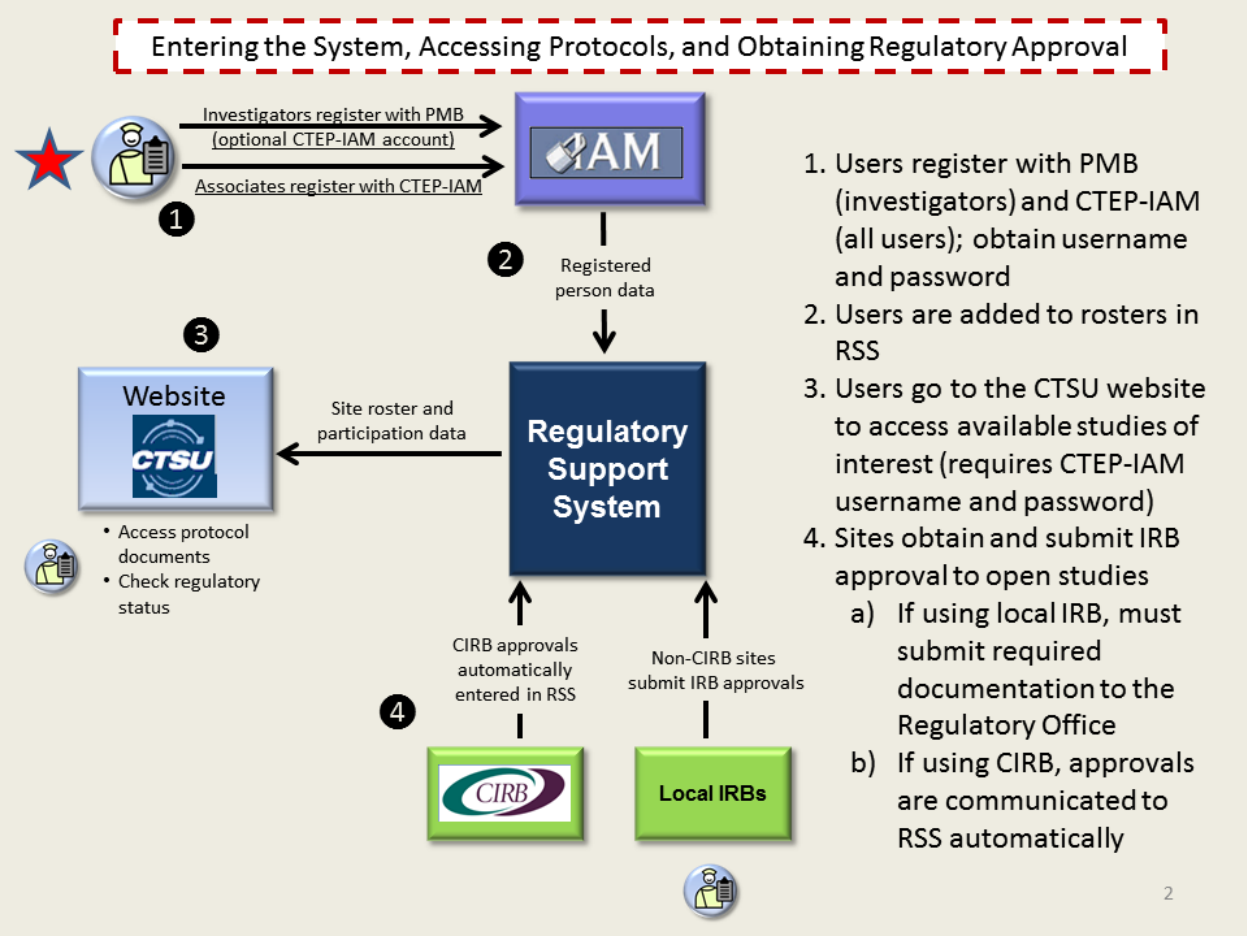
NCI Team Science-Project Development: Step 4 – Protocol Development

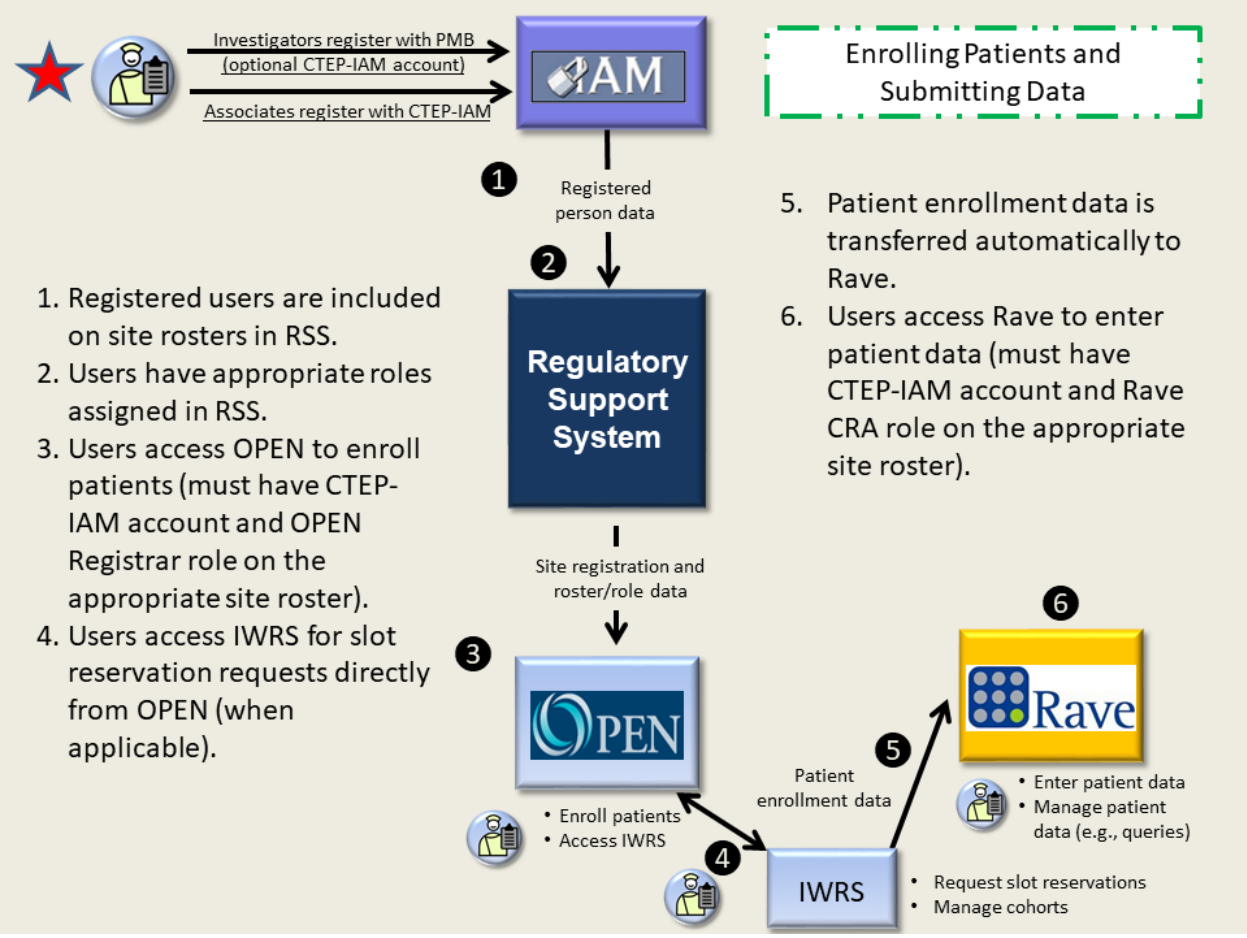


3.VI. ETCTN Centralized Services Workflow


Conducting ETCTN Trials Using Centralized Services
Investigators register with PMB (optional CTEP-IAM account)
Associates register with CTEP-IAM
Obtain User Account and Password
IAM
1
Registered person data
Registered person data
CTEP
Other Trial Activities
• CTEP-AERS adverse event reporting
• OAOP agent ordering
• Monitoring/Audits
• OEWG reporting
• CDUS reporting
• Etc.
RSS
Regulatory and Roster Information
Protocol, site, and person data
Site roster and participation data
2
CTSU
Access Protocols
• Access protocol documents
• Check regulatory status
CIRB approvals automatically transferred
Non-CIRB sites submit IRB approvals
Site registration and roster/role data
Site registration and roster/role data
5
CTMS
Enter Patient Data
• Enter patient data
• Manage patient data (e.g., queries)
3
Obtain CIRB/IRB Approval
CIRB
Local IRBs
PEN
Enroll Patients
4
Patient enrollment data
• Enroll patients
• Access IWRS
IWRS
Request Slot Reservations
• Request slot reservations
• Manage cohorts


Conducting ETCTN Trials Using Centralized Services
Investigators register with PMB (optional CTEP-IAM account)
Associates register with CTEP-IAM
Obtain User Account and Password
IAM
1
Registered person data
Registered person data
Other Trial Activities
CTEP
• CTEP-AERS adverse event reporting
• OAOP agent ordering
• Monitoring/Audits
• OEWG reporting
• CDUS reporting
• Etc.
2
Access Protocols
• Access protocol documents
• Check regulatory status
Site roster and participation data
RSS
Regulatory and Roster Information
Protocol, site, and person data
CIRB approvals automatically transferred
Non-CIRB sites submit IRB approvals
Site registration and roster/role data
Site registration and roster/role data
5
Rave
Enter Patient Data
• Enter patient data
• Manage patient data (e.g., queries)
3
Obtain CIRB/IRB Approval
CIRB
Local IRBs
OPEN
Enroll Patients
4
Patient enrollment data
• Enroll patients
• Access IWRS
IWRS
Request Slot Reservations
• Request slot reservations
• Manage cohorts
1


Entering the System, Accessing Protocols, and Obtaining Regulatory Approval
Investigators register with PMB (optional CTEP-IAM account)
Associates register with CTEP-IAM
IAM
1
2
Registered person data
3
Website
CTSU
Site roster and participation data
Regulatory Support System
• Access protocol documents
• Check regulatory status
CIRB approvals automatically entered in RSS
Non-CIRB sites submit IRB approvals
4
CIRB
Local IRBs
1. Users register with PMB (investigators) and CTEP-IAM (all users); obtain username and password
2. Users are added to rosters in RSS
3. Users go to the CTSU website to access available studies of interest (requires CTEP-IAM username and password)
4. Sites obtain and submit IRB approval to open studies
a) If using local IRB, must submit required documentation to the Regulatory Office
b) If using CIRB, approvals are communicated to RSS automatically
2


Investigators register with PMB (optional CTEP-IAM account)
Associates register with CTEP-IAM
IAM
Enrolling Patients and Submitting Data
1
Registered person data
2
Regulatory Support System
1. Registered users are included on site rosters in RSS.
2. Users have appropriate roles assigned in RSS.
3. Users access OPEN to enroll patients (must have CTEP-IAM account and OPEN Registrar role on the appropriate site roster).
4. Users access IWRS for slot reservation requests directly from OPEN (when applicable).
5. Patient enrollment data is transferred automatically to Rave.
6. Users access Rave to enter patient data (must have CTEP-IAM account and Rave CRA role on the appropriate site roster).
Site registration and roster/role data
3
OPEN
• Enroll patients
• Access IWRS
4
IWRS
• Request slot reservations
• Manage cohorts
Patient enrollment data
5
6
Rave
• Enter patient data
• Manage patient data (e.g., queries)

Acronyms Glossary

- CIRB: [NCI] Central IRB
- CTEP: Cancer Therapy Evaluation Program
- CTEP-AERS: CTEP Adverse Event Reporting System
- CTEP- IAM: CTEP Identity and Access Management
- CTSU: Cancer Trials Support Unit
- IWRS: Interactive Web Response System
- OAOP: Online Agent Order Processing
- OPEN: Oncology Patient Enrollment Network
- PMB: [CTEP] Pharmaceutical Management Branch
- RSS: Regulatory Support System

4

3.VII. Final Genomic Data Sharing Policy

3.VII.1. National Institutes of Health Genomic Data Sharing Policy

https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing/

3.VII.2. National Cancer Institute's Supplemental Information to the National Institutes of Health Genomic Data Sharing Policy

NCI Genomic Data Sharing: https://datascience.cancer.gov/data-sharing/genomic-data-sharing

3.VIII. Steps for Coordinating Centers to Open ETCTN Trials

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_StepsforCoordinatingCenters.pdf

3.IX. Steps for Participating Sites in ETCTN Trials

3.IX. 1 Affiliated Organizations and Integrated Components
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_StepsforParticipatingSites.pdf

3.IX.2 Early Drug Development Opportunity Program Organizations
https://ctep.cancer.gov/initiativesPrograms/eddop.htm

3.X. ETCTN Education and Training Materials

3.X.1. ETCTN Protocol Development

Developing an ETCTN Trial Concept Form Letter of Intent to Study Activation:
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Protocol_Development.pdf

Protocol Revision and Amendment
Process:https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Protocol_RevisionAmend.pdf

Protocol Access and Communication:
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Protocol_AccessComm.pdf

3.XI. ETCTN Auditing Guidelines

https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_etctn_ctms.htm

3.XII. ETCTN Information Sheets

Available Information Sheets are as follows:

Protocol Development Tools

Protocol Revisions and Amendments Information Sheet

Cancer Trials Support Unit (CTSU) Information Sheet

Person Registration

Rosters and Roles Information Sheet

Protocol Access and Communication Information Sheet

Regulatory Processing Information Sheet

NCI CIRB Initiative Information Sheet

Patient Enrollment Information Sheet

Agent Ordering Information Sheet

Data Management Information Sheet

Serious Adverse Event Reporting Information Sheet

Monitoring and Auditing Information Sheet

Links to access the most current Information Sheets from the CTSU members' website (username and password required) (https://www.ctsu.org/) are provided on the respective pages in this section.

3.XII.1. Protocol Development Tools

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Protocol_Development.pdf

3.XII.2. Protocol Revisions and Amendments Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Protocol_RevisionAmend.pdf

3.XII.3. ETCTN Cancer Trials Support Unit (CTSU) Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_CTSU.pdf

3.XII.4. Person Registration

https://ctep.cancer.gov/investigatorResources/default.htm

3.XII.5. Rosters and Roles Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Rosters_Roles.pdf

3.XII.6. Protocol Access and Communication Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Protocol_AccessComm.pdf

3.XII.7. Regulatory Processing Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Regulatory_Processing.pdf

3.XII.8. NCI CIRB Initiative Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_CIRB.pdf

3.XII.9. Patient Enrollment Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Patient_Enrollment.pdf

3.XII.10. Agent Ordering Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Agent_Ordering.pdf

3.XII.11. Data Management Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Data_Management.pdf

3.XII.12. Serious Adverse Event Reporting Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_SAE_Reporting.pdf

3.XII.13. Monitoring and Auditing Information Sheet

https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Audit_Monitoring.pdf

3.XIII. 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.

3.XIII.1. Website URLs referenced in these Guidelines

NCI Website
http://www.cancer.gov/

ETCTN Website
https://ctep.cancer.gov/initiativesPrograms/etctn.htm

NCI Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)
https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp/

NCI Cancer Trials Support Unit (CTSU) Website
https://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
https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-504.html

NCI Cancer Diagnosis Program's Website
http://cdp.cancer.gov/

NCI Center for Coordinating Clinical Trials
https://www.cancer.gov/about-nci/organization/ccct

NCI Central IRB Website
http://www.ncicirb.org

NCI Clinical Trials and Translational Research Advisory Committee (CTAC)
https://www.cancer.gov/about-nci/organization/ccct/ctac

NCI CTWG Steering Committee System (Information on NCI Scientific Steering Committees)
https://www.cancer.gov/about-nci/organization/ccct/steering-committees

NCI Clinical Trials Reporting Program (CTRP)
https://www.cancer.gov/about-nci/organization/ccct/ctrp

NCI Data and Safety Monitoring guidelines
https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf

NCI Guide to Information on Other NCI Divisions/Branches
https://www.cancer.gov/about-nci

FDA Regulations Relating to Good Clinical Practice and Clinical Trials
https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

Clarification of Instructions Regarding Inclusion of Publications as Appendix Materials
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

NCI Data Sharing Policy
https://datascience.cancer.gov/data-sharing/policies

NIH Freedom of Information Act Office
https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/freedom-information-act-office

NIH Grants Policy Statement
http://grants.nih.gov/grants/policy/policy.htm

NCI Guidelines for Auditing of Clinical Trials for the ETCTN
https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_etctn_ctms.htm

NIH Grant Policy for Program Income
https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.3.2_program_income.htm

NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October 2001 (COMPLETE COPY OF UPDATED GUIDELINES)
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

NIH Guide Notice on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (Amendment November 28, 2017).
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html

NIH Policy 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 and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (3/6/98)
https://grants.nih.gov/grants/guide/notice-files/not98-024.html

Inclusion of Children in Clinical Research: Change in NIH Definition (10/13/15)
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html

NIH Policy on Inclusion Across the Lifespan
https://grants.nih.gov/policy/inclusion/lifespan.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 Policy on Financial Conflict of Interest
http://grants.nih.gov/grants/policy/coi

NIH Public Access Policy (and Manuscript Submission System)
http://publicaccess.nih.gov

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

Spanish On-line Tutorial on Human Research Participants Protections
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-139.html

Updated Instructions Regarding Inclusion of Publications as Appendix Materials:
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-098.html

3.XIII.2. Other Federal Citations for NIH Grants Involved in Human Subjects Research & Websites

NIH Sharing Policies and Related Guidance on NIH-Funded Research Resources

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public. PIs and funding recipient institutions are expected to make the results and accomplishments of their activities available to the research community and to the public at large. The following are a few NIH policies and related guidance on sharing of research resources developed with NIH funding:

a. Genomic Data Sharing
b. Availability of Research Results
c. Data Sharing Policies
d. Genome-Wide Association Studies (GWAS) Policy

e. Public Access Policy
f. Model Organism Sharing Policy
g. Research Tools Policy

For additional information and a complete list of policies go to:
https://grants.nih.gov/grants/sharing.htm

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. For more information see the NIH Grants Policy Statement at:
https://grants.nih.gov/grants/policy/nihgps/html5/section_8/8.3.2_program_income.htm.

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 2020
In December 2010, the Department of Health and Human Services launched Healthy People 2020, which has four overarching goals:

- Attain high-quality, longer lives free of preventable disease, disability, injury, and premature death;
- Achieve health equity, eliminate disparities, and improve the health of all groups;
- Create social and physical environments that promote good health for all; and
- Promote quality of life, healthy development, and healthy behaviors across all life stages.

Healthy People 2020 (HP2020) tracks approximately 1,300 objectives organized into 42 topic areas, each of which represents an important public health area. In addition, HP2020 contains the Leading Health Indicators, a small focused set of 12 topics containing 26 objectives identified to communicate and move action on high-priority health issues.
Additional information can be found at: https://www.cdc.gov/nchs/healthy_people/hp2020.htm

Authority and Regulations
This program is described in the Assistance Listing Numbers (formerly called the Catalogue of Federal Domestic Assistance) at:
https://sam.gov/content/assistance-listings 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: https://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: https://www.lrp.nih.gov/.

3.XIII.3. Important Abbreviations Referenced in these Guidelines

ABBREVIATION	FULL TERM
AD	Associate Director, CTEP, DCTD
AO	Affiliated Organization
ARA	Awaiting Receipt of Application
BIQSFP	Biomarker, Imaging and Quality of Life Studies Funding Program
BRC	Biomarker Research Committee
BRP	Biometric Research Program (in DCTD; formerly the Biometric Research Branch [BRB])
caDSR	Cancer Data Standards Registry and Repository
CAERS	Cancer Adverse Event Reporting System
CAPA	Corrective and Preventive Action Plan
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)
CDS	Clinical Data System
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
CLIA	Clinical Laboratory Improvement Amendments
COI	Conflict of Interest
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
CrDL	Career Research and Development LOI
CSA	Clinical Supply Agreement
CSR	Center for Scientific Research (at NIH)
CT	Cooperative Team
CTA	Clinical Trial Agreement
CTAC	Clinical Trials and Translational Research Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program (in DCTD)
CTEP-AERS	Cancer Therapy Evaluation Program Adverse Event Reporting System
CTMB	Clinical Trials Monitoring Branch (in CTEP)
CTMS	Clinical Trials Monitoring Service
CTSA	Clinical and Translational Science Award
CTSU	Cancer Trials Support Unit
CTRP	Clinical Trials Reporting Program
CTWG	Clinical Trials Working Group

DAR	Drug Accountability Record
DARF	Drug Accountability Record Form
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)
DR	Diagnostics Evaluation Branch (in CDP)
DSM	Data and Safety Monitoring
DSMB	Data and Safety Monitoring Board (also known as Data Monitoring Committee)
DSMC	Data and Safety Monitoring Committee
EBWG	ETCTN Biospecimen Working Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
ETCTN	Experimental Therapeutics-Clinical Trial Network
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FOA	Funding Opportunity Announcement
FOIA	Freedom of Information Act
FWA	FederalWide Assurance (for OHRP)
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IAM	Identity and Access Management
IB	Investigator Brochure
IDB	Investigational Drug Branch (in CTEP)
IDE	Investigational Device Exemption
IDSC	Investigational Drug Steering Committee
IMS	Inclusion Monitoring System
IND	Investigational New Drug Application
IP	Intellectual Property
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LAO	Lead Academic Organization
LOI	Letter of Intent
LPO	Lead Protocol Organization
MTA	Material Transfer Agreement
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
NME	New Molecular Entity

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	Pharmacodynamics
PDs/PIs	Program Director(s)/Principal Investigator(s)
PHS	Public Health Service
PI	Principal Investigator
PIO	Protocol Information Office (in CTEP)
PK	Pharmacokinetics
PMB	Pharmaceutical Management Branch (in CTEP)
PRC	Protocol Review Committee (in CTEP – also known as NCI/DCTD PRC)
PSC	Purchase Service Agreement
PTA	Project Team Application
PTMA	Project Team Member Application
QA/QC	Quality Assurance/Quality Control
RAB	Regulatory Affairs Branch (in CTEP)
RPPR	Research Performance Progress Report
RRP	Radiation Research Program (in DCTD)
RSS	Regulatory Support System (in CTSU)
SEP	Special Emphasis Panel
SOP	Standard Operating Procedures
SPORE	Specialized Programs of Research Excellence
SRO	Scientific Review Officer
SSC	Scientific Steering Committee
URL	Uniform Resource Locator (internet address of resource)

3.XIII.4. Glossary

For this FOA, the following terms are defined as follows:

Affiliated Organization (AO): an institution collaborating with the LAO. For multiple PDs/PIs applications, an Affiliated Organization is defined as academic sites lead by the designated multiple PDs/PIs on the application, other than the LAO institution.

Biomarker: a biomarker is a validated indicator of a specific molecular disease state.

Correlative biomarker: a correlative biomarker is a validated biomarker with predictive and/or prognostic significance indicative of treatment outcome.

CTEP Identity Access Management (IAM): a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). It provides user accounts (usernames and passwords) required to access NCI and CTSU systems.

ETCTN sites: All sites rostered to participate on ETCTN studies. These include the LAO Main Members (MM), Affiliated Organizations (AO) and Integrated Components (MM IC and AO IC).

Integral biomarker assay: an assay or test that must be performed for the trial to proceed. Integral studies are inherent to the design of the trial from the outset and must be performed in real time for the conduct of the trial. Examples include tests to determine eligibility, tests to assign treatment or stratify randomization, and tests whose results serve as the primary endpoint of the trial. Integral biomarkers may require a CLIA-certified laboratory, which will be needed if the test results will be returned to the patient or their physician.

Integrated biomarker assay: an assay or test that is clearly identified as part of the clinical trial from the outset and is intended to address the highest priority scientific question in the trial.

Lead Academic Organization (LAO): The institution receiving the award under this FOA. A LAO may have Integrated Component(s), i.e., a component of the institution receiving the award, which may be at a different location. The institution must be the same legal entity as the LAO.

Lead Protocol Organization (LPO): An LPO is the organization of the investigator who leads the clinical trial.

Project Team Member Application (PTMA): An application submitted in response to an NCI request (Project Team Announcement [PTA]) that states the applicant's capabilities for participation on a Drug Project Team.

Proof of principle studies (for target effects): Such studies are done to demonstrate that an investigational agent hits its intended target and has its expected molecular effect.