



THE NATIONAL CANCER INSTITUTE  
CANCER PREVENTION CLINICAL TRIALS NETWORK (CP-CTNet)  
PROGRAM GUIDELINES

**Division of  
Cancer Prevention**

**The National Cancer Institute  
Cancer Prevention Clinical Trials Network (CP-CTNet)**

**Program Guidelines**

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## I. Introduction

### a. Purpose of Program Guidelines

Program Guidelines for the Cancer Prevention Clinical Trials Network (CP-CTNet) have been developed by the National Cancer Institute (NCI), Division of Cancer Prevention (DCP) staff in consultation with the Office of Grants Administration (OGA) and NCI Division of Extramural Activities. The purpose of these guidelines is to describe and outline expectations for CP-CTNet grantees, investigators, and NCI/DCP staff. These guidelines are intended to be used as a resource for the CP-CTNet to efficiently design, conduct, and oversee all aspects of early-phase cancer prevention clinical research within NCI/DCP CP-CTNet. For more detailed information, see Funding Opportunity Announcement (FOA) links [RFA-CA-18-029](#) and [RFA-CA-18-030](#).

### b. CP-CTNet Background, Purpose, and Objectives

#### i. Background

The search for effective cancer preventive agents in the context of a rapidly advancing molecular understanding of the process of carcinogenesis has led to the study of an increasing number of agents that intervene in specific molecular pathways thought to be critical to cancer development. The prospect of an even better understanding of the early phases of cancer development provides a strong rationale for increased investment in cancer prevention. Similarly, the recognition of the importance of the role of the immune system in tumor development and the recent successes in cancer immunotherapy for the treatment of advanced malignancies have led to a resurgence of interest in immunoprevention. The increasing number and molecularly or immunologically targeted nature of new agents require an efficient clinical trials system for evaluation and screening. These complex trials must also include extensive biomarker analyses, investigation of the biologic effects of the agent on the intended target, and correlation with clinically relevant indicators of potential health outcomes.

The nature of cancer prevention clinical trials requires access to specialized high-risk populations who obtain their care from different subspecialists and expertise in tissue collection and biomarker analysis. A typical Phase II trial might examine the effect of an intervention on a histologically proven premalignancy in participants at risk for cancer. This requires the screening of multiple high-risk individuals with procedures such as a colonoscopy or bronchoscopy to identify those who harbor such premalignancies, followed by post-treatment procedures with biopsies to assess the intervention's efficacy. Other types of studies employed in cancer preventive agent development include (but are not limited to): Phase 0 micro-dosing trials, Phase I pharmacokinetic and pharmacodynamic trials, and window-of-opportunity trials performed prior to definitive cancer treatment. Cohorts participating in such studies include healthy volunteers, individuals at high risk for cancer either due to genetic predisposition or the presence of premalignant lesions, and cancer patients either prior to or after definitive surgical,

radiation, or chemoradiation treatment. Thus, multi-institutional groups of clinicians from diverse specialties, research nurses, pathologists, translational scientists, statisticians, data managers, and other personnel with expertise in cancer prevention, drug development, and biomarker analysis are needed to successfully perform increasingly complex cancer prevention clinical trials.

**ii. Purpose**

The purpose of the CP-CTNet is to perform and provide clinical trial support for the efficient conduct of early-phase clinical trials, evaluate the biologic effects of preventive agents and interventions, and determine clinically relevant correlates in order to advance their development for cancer prevention.

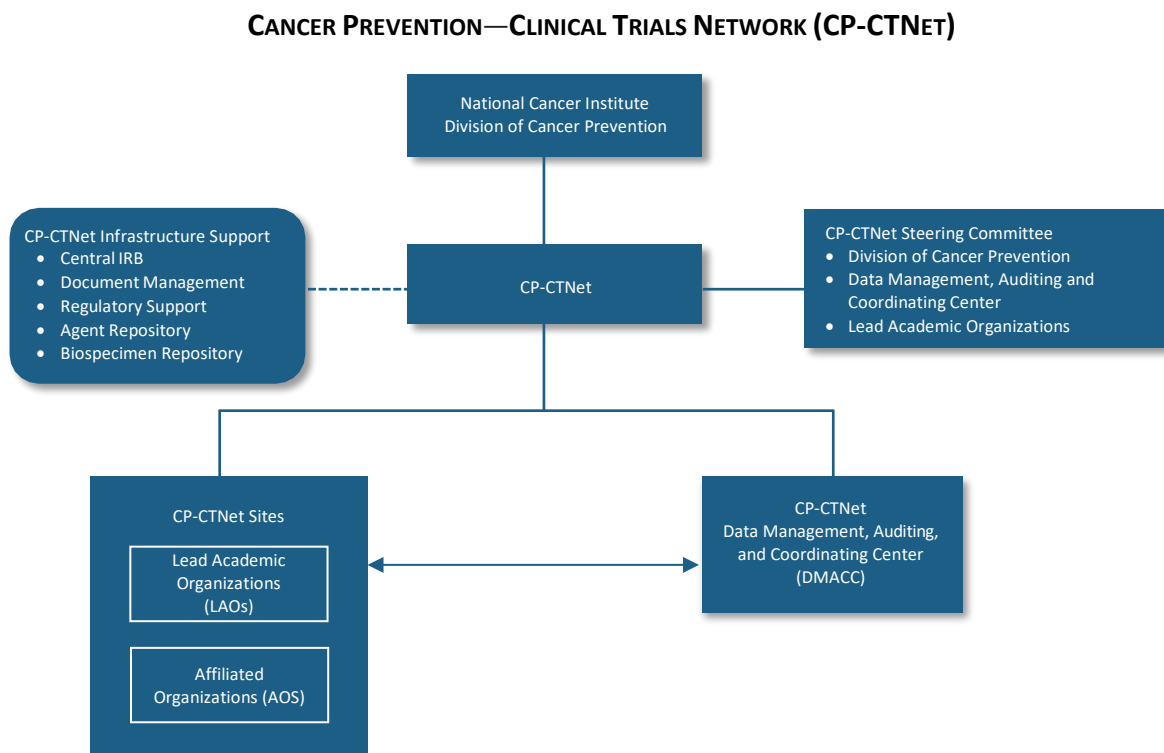
**iii. Objectives**

The objectives of the CP-CTNet include the following:

- To efficiently design and conduct early-phase clinical trials to assess the safety, tolerability, and cancer preventive potential of a variety of agents or interventions. Emphasis is on novel agents and interventions that target relevant pathways important in carcinogenesis
- To characterize the effects of these agents and interventions on their molecular targets, as well as on other biological events associated with cancer development (such as cell proliferation, apoptosis, growth factor expression, oncogene expression, immune response) and correlate these effects with clinical endpoints
- To develop further scientific insights into the mechanism of cancer prevention by the agent or intervention examined, and to continue to develop novel potential markers as determinants of response

## II. Organizational Structure

### a. Organizational Chart



### b. CP-CTNet Grantees

The key components of CP-CTNet are the CP-CTNet Sites and the CP-CTNet Data Management, Auditing, and Coordinating Center (DMACC)

#### i. CP-CTNet Sites

CP-CTNet Sites in collaboration with NCI/DCP will provide scientific leadership for the development and conduct of early-phase cancer prevention clinical trials as well as oversee the management and analysis of the clinical trial data.

Each CP-CTNet Site will consist of a Lead Academic Organization (LAO) and Affiliated Organizations (AOs) that will work together to perform clinical trials. Each CP-CTNet LAO will serve as the research hub for its group. Each LAO will constitute a multi-institutional clinical trial group and provide the infrastructure to develop, implement, analyze, and report the results of early-phase (Phases 0–II) cancer prevention clinical trials. The clinical trials will be performed either by the LAO and/or AOs within each CP-CTNet Site or across CP-CTNet Sites (network-wide trials). An LAO may include other LAOs to act as an AO and accrue to a specific trial.

**1. LAOs will:**

- Provide administrative support, including fiscal management
- Provide oversight of clinical trial performance across their member AOs
- Develop and perform clinical trials within their own institutions
- Manage all aspects of trial operations while adhering to all applicable rules and regulations for the conduct of clinical trials
- Provide statistical support including statistical analysis/analytic results
- Perform trial randomization
- Collaborate with the DMACC regarding data management activities
- Perform site initiation visits
- Report serious adverse events (SAEs) to NCI/DCP
- Ensure timely and accurate data entry
- Participate in one investigator meeting per year

**2. AOs will:**

- Develop clinical trials in collaboration with LAOs
- Accrue to multi-institutional trials
- Ensure timely and accurate data entry
- Report SAEs to NCI/DCP and LAO
- Participate in trials arising within their CP-CTNet Site as well as within other CP-CTNet Sites

Each CP-CTNet Site will perform a variety of early-phase cancer prevention trials in appropriately high-risk populations, ranging from Phase 0 to Phase IIb trials. Agents under study will include those developed by the pharmaceutical industry and provided to NCI for collaborative development, commercially available agents, agents developed by the grantees, and agents developed by NCI.

**Each CP-CTNet Site will be responsible for the following activities:**

- Design and conduct early-phase cancer prevention trials using a single agent, combinations of agents, or other modalities
- Emphasize novel agents or interventions that target relevant pathways important in carcinogenesis, such as those involved in proliferation, apoptosis, differentiation, and cell signaling
- Develop one to three new clinical trials per year, with expected accrual of at least 10 participants in year 1 and at least 40 participants in the subsequent years at each CP-CTNet Site
- Conduct prevention clinical trials in participants at high risk for cancers arising in one of at least three different target organs (at least one of which is breast, colon, prostate, or lung and at least one of which is not one of those four target organs). CP-CTNet should have access to populations at high risk for the development of cancer in these organs



- Develop statistically appropriate clinical trial designs, including novel designs using “omic” technologies, to rapidly obtain evidence of preliminary efficacy. A variety of clinical trial models, including Phase 0 micro-dosing trials, Phase I pharmacokinetic and pharmacodynamic (PK/PD) trials, window-of-opportunity trials performed prior to definitive treatment for premalignant lesions or cancer, and Phase IIa or IIb cancer prevention clinical trials, will be used
- Evaluate translational endpoints in biospecimens obtained from participants 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)
- Assess PK/PD of the studied agents and establish relationships between the dose, schedule, exposure, and effect
- Obtain mechanistic proof-of-principle data for new agents or approaches directed at novel molecular targets important in carcinogenesis
- Collect, process, and store biospecimens from trial participants for biomarker analysis
- Evaluate novel technologies (e.g., imaging, blood based) for assessing the effects of interventions

## ii. CP-CTNet DMACC

The DMACC is expected to collaborate with and advise the CP-CTNet sites with respect to trial design and protocol development. The DMACC will support the CP-CTNet Sites and coordinate trans-network activities across three key functional areas:

- Centralized data management and data reporting
- Clinical trials auditing
- Administrative and logistical coordination across CP-CTNet Sites

**Each area will have a Functional Area Director. The Director(s) will have the primary responsibility for:**

- Protecting the confidentiality of CP-CTNet clinical trial data and the information shared with CP-CTNet organizations, including, without limitation, unpublished data, protocols, data analysis, and other confidential information received by CP-CTNet personnel
- Developing and supporting the trial data collection and reporting requirements
- Participating in the collective management of the CP-CTNet, including the internal evaluation of the CP-CTNet program

## 1. Centralized Data Management and Reporting:

- Provide centralized data management for CP-CTNet clinical trials using NCI-designated Clinical Data Management System, currently Medidata Rave®
- Coordinate with and leverage, where feasible, technology from related NCI-sponsored informatics initiatives; for example, NCI Informatics Technology for Cancer Research program and NCI Cancer Research Data Commons <https://datascience.cancer.gov/data-commons>  
Additional information regarding this can be found at <http://prevention.cancer.gov/CP-CTNet>
- Create and enforce data management policies, formulate management techniques for quality data collection to ensure adequacy, integrity, and legitimacy of data, and devise and implement secure procedures for data management and analysis with attention to all technical and regulatory aspects.
- Develop web services (e.g., Representational State Transfer (REST) and application programming interface [API]) for system-to-system data exchange. The DMACC is expected to develop web services using industry best practices to exchange clinical trial data to CP-CTNet Sites and to NCI/DCP. Support routine and ad hoc reporting of clinical trials data to CP-CTNet Sites and to NCI/DCP. The DMACC is expected to develop reports using pre-designed and custom formats that utilize real-time, historical, auditing, and/or analytical information.

## 2. Clinical Trials Auditing:

Auditing is a systematic and independent examination of trial-related activities and documents to determine whether the trial-related activities are conducted, and the data submitted via Medidata Rave and/or NCI/DCP are recorded, analyzed, and accurately reported according to the protocol, CP-CTNet standard operating procedures (SOPs), good clinical practice (GCP), and the applicable federal regulatory requirements. Auditing can be done remotely or on-site. The DMACC will be responsible for:

- Conducting independent auditing of clinical trials data and processes at all CP-CTNet LAOs and AOs to ensure that all relevant GCP guidelines, protocol requirements, applicable regulatory requirements, federal regulations, and NIH/NCI/DCP policies are followed
- Interacting with CP-CTNet Sites and NCI/DCP staff to identify areas for systemic and policy-level improvements in order to increase both efficiency and compliance, ensure the protection of human subjects, and enhance the quality and integrity of CP-CTNet clinical trials

### **3. Administrative and Logistical Coordination:**

- Provide support for administrative and logistical coordination across CP-CTNet operations. The DMACC will establish and maintain a unified and coordinated operational structure, including processes and documentation that appropriately support and integrate the logistical and administrative requirements of CP-CTNet
- Will serve as a resource for ad hoc statistical support
- Establish project timelines in coordination with NCI/DCP to ensure all required DMACC activities are adequate
- Develop a Manual of Operations (MOP) and SOPs in support of CP-CTNet operations and management
- Provide support for the development, presentation, and dissemination of educational materials and other capacity-building resources for CP-CTNet activities. Trial-specific materials will be the responsibilities of the CP-CTNet Sites
- Develop, manage, and maintain a virtual biospecimen data inventory system that will permit real-time remote access to the status of biospecimens and related data from CP-CTNet clinical trials. The virtual inventory system should include standard clinical and specimen annotations and trial-specific information and should have remote (web-based) real-time access functionality. The virtual repository will interface with CP-CTNet Sites and the NCI/DCP Biorepository Program
- Schedule and facilitate network-wide meetings for NCI/DCP and CP-CTNet staff

To achieve the goals of the three functional areas, the DMACC will provide appropriate multi-disciplinary expertise and skills as well as established infrastructure for all the applicable areas of activities, including:

- Information technology
- Clinical research informatics
- Clinical trials auditing
- Clinical trials methodology and biostatistics
- Operations management to support CP-CTNet activities

## **III. Governance**

### **a. CP-CTNet Steering Committee**

The representatives of CP-CTNet grantees, with the participation of NCI/DCP, will form a steering committee. The CP-CTNet Steering Committee will act as the governing body of the CP-CTNet Sites and the DMACC. The Steering Committee will integrate the efforts of all CP-CTNet grantees and provide oversight of collaborative activities.

**Steering Committee structure will include the following:**

- Steering Committee Chair
  - The Committee will be chaired by a CP-CTNet PD/Principal Investigator (PI) elected by Steering Committee voting members
- Steering Committee Members
  - Two representatives from each CP-CTNet LAO and two representatives from the DMACC (one of whom must be the PD/PI)
    - Each LAO will have one vote
    - The DMACC will have one vote
  - CP-CTNet Director
    - NCI Project Scientist(s) will collectively have one vote for NCI
  - The NCI/DCP Program Official will be a non-voting member
  - Additional non-voting members may be added ad hoc, and membership will be approved by the voting members

**The Steering Committee will be responsible for the following activities:**

- Holding quarterly meetings
- Developing operating policies for the Steering Committee and working in conjunction with the DMACC to develop Network SOPs. The DMACC will work with NCI staff to make SOPs available for public access when applicable
- Approving the DMACC Manual of Operations developed by the DMACC
- Reviewing and approving the trials that will use Rapid Response Restricted Funds (described in the Project Management section below)
- Co-organizing with the NCI/DCP the annual in-person site coordinator/investigator meeting to be held at NCI/DCP <https://prevention.cancer.gov/news-and-events/meetings-and-events/2018>
- Addressing other programmatic responsibilities jointly, as needed, by the CP-CTNet Sites and the NCI/DCP staff

**b. Subcommittees**

Subcommittees may be established for specific purposes (e.g., for joint development of clinical trial protocols by CP-CTNet grantees and NCI/DCP staff members).

**c. NCI Oversight**

**i. NCI/DCP Roles and Responsibilities**

The role of the NCI/DCP staff is to assist, facilitate, and ensure optimal coordination of CP-CTNet activities. NCI/DCP program staff members will serve in one or more of the following roles:

**1. NCI/DCP CP-CTNet Director (Overall Project Scientist)**

An NCI/DCP program staff member will be designated as an overall Project Scientist and will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards. Responsibilities include, but are not limited to, the following:

- Routine scientific and programmatic stewardship of all the awards for CP-CTNet
- Primary contact for scientific inquiries, including information concerning the content of specific protocols or concept reviews, and feedback on general scientific direction of CP-CTNet Site
- Routine programmatic administration is the responsibility of CP-CTNet Director, who ensures uniformity of implementation of the program across the various key components
- Serve as NCI/DCP voting member on the Steering Committee

## 2. **NCI/DCP Program Official**

An NCI/DCP Program Official will be responsible for the normal scientific and programmatic stewardship of each award and will be named in the award notice. Responsibilities include the following:

- Address and approve non-competitive award (Type 5) budget requests and any supplemental budget requests
- Serve as point of contact for NCI OGA
- Work closely with the CP-CTNet Director and CP-CTNet Project Scientists
- Review administrative materials supporting LAO requests, performing budget analyses, and facilitating the completion of action items involving coordination between NCI/DCP, NCI OGA, and the awardees under the program
- Exchange information with the LAO Directors of Operations for the key components of CP-CTNet and OGA staff on administrative changes and priorities

## 3. **NCI/DCP Scientific Program Staff: Medical Monitors, Scientific Leads, and Nurse Consultants**

Medical Monitors, Scientific Leads, and Nurse Consultants will have substantial involvement in specific trials. Responsibilities include, but are not are limited to, the following:

- Develop draft clinical trial solicitations
- Ensure that clinical trials proposed are within the research scope of CP-CTNet
- Evaluate and approve clinical trial concepts, protocols, and amendments of all CP-CTNet trials
- Serve as a resource for scientific information on trial design
- Work with CP-CTNet awardees to collaboratively manage issues associated with their participating in the conduct of clinical trials across the network

- Inform the PDs/PIs of scientific opportunities resulting from NCI-supported clinical research programs and facilitate collaborations between the CP-CTNet and other NCI-sponsored programs
- Facilitate formal aspects of collaborations with outside organizations including review of any memoranda of understanding and data/material transfer agreements for compliance with NIH/NCI and federal policies
- Review accrual and overall performance of CP-CTNet clinical trials by the site
- Review compliance with applicable US Department of Health and Human Services (HHS), Food and Drug Administration (FDA), Office for Human Research Protections, NIH, and NCI regulations for clinical research involving human research subjects
- Monitor the progress and performance of the key components of CP-CTNet
- Ensure that plans for data management, data reporting, auditing, and coordination of clinical trials are within the research scope of CP-CTNet and relevant to the state-of-the-science, NIH/NCI priorities, resources, and availability of funding
- Serve as a resource for best practices for data management, data reporting, clinical trials auditing, recruitment, and retention
- Oversee and participate as necessary in clinical trials, audits, and quality assurance site visits (on-site and remote) and review of audit reports
- Sponsor strategy sessions, when indicated, to discuss specific research initiatives
- Final review and approval of requests for use of any biospecimens collected per the approved protocol for CP-CTNet trials

Within NCI/DCP, major scientific policy and programmatic decisions concerning CP-CTNet are made only after appropriate consultation with and involvement by the NCI/DCP CP-CTNet Official, the CP-CTNet Scientific Lead, the Program Officials, and NCI/DCP Group Chiefs that are involved in the program and NCI/DCP leadership will be engaged as necessary and appropriate

CP-CTNet Sites, the DMACC, the Steering Committee, NCI/DCP staff, and NCI/DCP support contract programs will interact closely to meet the goals of the network.

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. NCI may also review all records related to awardees' performance for appropriate collection, review, and distribution of biospecimens collected in association with CP-CTNet trials.

**ii. NCI Office of Grants Administration**

The Grants Management Specialist for NCI OGA is responsible for the fiscal and administrative aspects of each application and award.

The Grants Management Specialist for OGA works closely with the CP-CTNet Program Official and the CP-CTNet Overall Project Scientist to assure that appropriate science is funded in accordance with applicable laws, regulations, policies, and peer review recommendations to the extent that the budget allows and NCI priorities dictate.

**d. Joint Responsibilities of NCI/DCP and CP-CTNet Grantees**

CP-CTNet grantees will be expected to participate as active team members and work closely with NCI/DCP on the development of appropriate clinical trial protocols.

These joint activities will include (but will not be limited to) the following:

- i.** General aspects of collaboration on trial development and conduct, especially with respect to compliance with federal regulations for clinical trial research, accrual, and participation in activities related to the collective management of the CP-CTNet, as appropriate
- ii.** Development of concepts for new clinical trials, either in response to specific concept solicitations from NCI or as unsolicited concepts developed by the LAOs or AOs
- iii.** Meeting as frequently as needed to ensure optimal trial performance and to review trials performed under the CP-CTNet awards

The awardee shall, with NCI/DCP assistance, develop appropriate early-phase prevention clinical trial protocols. PIs of the CP-CTNet awards, the NCI CP-CTNet Director, the NCI/DCP Program Official, and NCI/DCP Scientific Program staff will be members of the CP-CTNet.

CP-CTNet Sites will be expected to participate as active team members. They will meet at least quarterly or as frequently as needed to ensure optimal study performance and to review studies performed under the award and drug development plans. Areas of joint responsibility include:

- General aspects of collaboration on study development and conduct, especially with respect to compliance with federal regulations for clinical trial research, accrual and participating in activities related to the collective management of the CP-CTNet, as appropriate

Other programmatic responsibilities will be addressed jointly, as needed, by the CP-CTNet awardees and NCI staff.

#### **IV. CP-CTNet Infrastructure Support**

The CP-CTNet Sites are expected to interact as appropriate with other NCI/DCP support programs, such as NCI/DCP Regulatory Support, NCI/DCP Agent Repository, NCI/DCP Protocol Information Office, as well as other NIH/NCI programs that play an important role in carrying out CP-CTNet research objectives.

**a. NCI Central Institutional Review Board (CIRB)**

The CIRB uses a centralized approach to human subject protection through a process that streamlines local Institutional Review Board (IRB) review of selected NCI-sponsored trials for institutions across the country by relying on national experts to ensure trials are reviewed efficiently and with the highest ethical and quality standards <https://www.ncicirb.org/> The NIH policy on the Use of a Single Institutional Review Board for Multi-Site Research <https://grants.nih.gov/grants/guide/notice-files/not-od-16-094.html> became effective on January 25, 2018. In compliance with this policy, [NCI Central IRB](#) (NCI CIRB) is the sole IRB of record for all sites conducting clinical trials through the CP-CTNet, and is responsible for trial review (initial review, amendments, continuing reviews, recruitment materials, unanticipated problems, and serious or continuing noncompliance) and approval of local context considerations.

For international sites, protocol approval is required from the International Ethics Committee only. The exception is for sites in US territories (e.g., Puerto Rico), which are overseen by the CIRB.

**To comply with the NIH policy:**

- All US AOs must be members of the NCI CIRB and use the NCI CIRB for all CP-CTNet clinical trials
- All CP-CTNET Sites must be enrolled in the CIRB as of the date of their award
- All CP-CTNet protocols will be approved by the CIRB
- All CP-CTNet Sites will comply with the conditions of their Federal-Wide Agreement (FWA) and the [CIRB Standard Operating Procedures](#)
- To help ensure the safety of participants enrolled in NIH-funded trials, the awardee must provide NIH copies of documents related to all major changes in the status of ongoing protocols

**b. NCI DCP Document Management**

The Protocol Information Office (PIO) is the central clearinghouse for clinical trials management within DCP.

The PIO will be responsible for receiving, processing, reviewing, tracking, and obtaining approval of all protocol-related information, including concepts, revisions, protocols, amendments, and changes in protocol status.

**c. NCI DCP Regulatory Support**

LAOs and AOs are required to prepare, submit, and maintain regulatory documents according to all applicable regulations and requirements throughout the duration of each trial.

**The regulatory contractor will provide support for the following:**

- Investigational New Drug (IND) application preparation and annual reporting
- Development of the Investigator's Brochure
- FDA reporting



- Maintenance of files for agreement documents including Cooperative Research and Development Agreements (CRADAs), Clinical Trial Agreements (CTAs), Confidential Disclosure Agreements (CDAs), and Material Transfer Agreements (MTAs).
- SAE reporting
- Regulatory document collection, review, and maintenance through all phases of the trial. Regulatory documents that will be collected include Form 1572, Financial Disclosure Form, Biosketch/CV, and GCP training

**d. NCI DCP Agent Repository**

The drug repository maintains a centralized source of agents and development services necessary to support cancer prevention studies for effective medical interventions in the prevention or reduction of cancer. The repository provides important logistic organization for acquisition, tracking, storage, maintenance, testing, and quality control. The repository provides repackaging and distribution of investigational agents and placebo formulation.

**e. NCI Biospecimen Repository**

Development of effective interventions, based on comprehensive analysis of critical pathways of cancer initiation and progression, requires access to biological specimens from patients treated in prospective studies. High-quality biological specimen banks containing uniformly collected specimens from such studies, along with validated clinical and outcome data, are essential for development and delivery of new diagnostic and predictive tools to guide the use of targeted therapies.

The NCI Biospecimen Repository will be used for storage of carefully collected and controlled high-quality biospecimens, annotated with clinical data and properly consented for investigational use.

**V. Solicitations**

Agents to be developed will be announced twice yearly via NCI solicitations for concepts for clinical trials. Agents may be developed for specific indications by individual CP-CTNet Sites or jointly by more than one site. CP-CTNet Sites are also expected to propose unsolicited concepts using agents or interventions available to their investigators. CP-CTNet can submit unsolicited concepts or revised concepts four times each year. A disapproved concept can be resubmitted one time with NCI/DCP agreement.

**VI. Protocol Operations**

**a. Qualified Investigators—Registration Credential Repository (RCR)**

FDA regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually.

The RCR was created to meet the FDA and NCI regulatory requirements. The RCR is a self-service online registration application used for the electronic submission of NCI registration documents by clinical research personnel participating on NCI-sponsored clinical trials. Electronic submission of NCI registration documents includes FDA Form 1572, NCI Biosketch, Financial Disclosure Form and GCP training, and agent shipment form, if applicable.

Each CP-CTNet Site is responsible for ensuring that institutional investigators enrolling participants on CP-CTNet trials are NCI registered investigators (i.e., completed NCI [RCR] processes). In addition, non-physician investigators and Associate Plus staff will be required to register annually via the [NCI Registration and Credential Repository \(RCR\) system](#).

Prior to registration in the RCR, investigators will need to create an IAM account by clicking on the following link: <https://ctepcore.nci.nih.gov/iam/index.jsp>.

**i. Registration types**

There are five registration types, including the following:

- **Investigator (IVR)**—MD, DO, or international equivalent
- **Non-Physician Investigator (NPIVR)**—advanced practice providers (e.g., NP or PA) or graduate-level researchers (e.g., PhD)
- **Associate Plus (AP)**—clinical site staff (e.g., RN, CRA or statistician) with data entry access (e.g., OPEN, RAVE, TRIAD)
- **Associate (A)**—other clinical site staff involved in the conduct of NCI-sponsored trials
- **Associate Basic (AB)**—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems

LAOs and AOs are also responsible for submitting specific regulatory documents to the Division of Cancer Prevention (NCI/DCP) Regulatory Contractor via the RCR.

**b. Conflict of Interest Policy**

CP-CTNet sites receiving NIH funding from a grant or cooperative agreement must establish a Conflict of Interest Policy that is in compliance with all of the Department of Health and Human Services (HHS) regulatory requirements for conflict of interest as outlined by NIH grants policy available at <http://grants.nih.gov/grants/policy/coi>. This policy should ensure that there is no reasonable expectation that any investigator or staff member of the CP-CTNet site or that any of its member institutions/sites involved in the design, conduct, or reporting of research will be biased by any conflict of interest (using the definition of “investigator” provided in the NIH grants policy). A management plan is also required for situations in which conflicts of interest are identified.

### c. Protocol Management

#### i. Concept, Protocol, and Amendment Submission and Approval

CP-CTNet LAO shall submit a concept for review and approval prior to protocol development. Concepts shall be submitted in response to an NCI/DCP solicitation and are **only accepted** during an open solicitation period. If the concept is approved, the CP-CTNet LAO is responsible for the preparation, development, and submission of protocols to the NCI/DCP Protocol Information Office (PIO) for NCI/DCP review and approval in accordance with CP-CTNet policies. A Recruitment and Retention Plan and a Biomarker Development Methods Report will be required at the time of protocol submission.

The CP-CTNet LAO is responsible for communicating the results of NCI/DCP's review to relevant CP-CTNet AOs. The CP-CTNet LAO is responsible for ensuring receipt of NCI/DCP's approval prior to trial activation.

The CP-CTNet LAO shall not expend NCI funds to conduct any trial disapproved by NCI/DCP.

Final approvals of protocols and amendments must be obtained from NCI/DCP prior to activation.

#### ii. Protocol Efficiency Timelines

The CP-CTNet LAO internal SOPs should include timelines for the development of concepts and protocols from initial submission of the concept to NCI through trial activation. The SOPs should also include mechanisms for monitoring the performance of the CP-CTNet Site in adhering to these timelines as well as corrective action plans outlining steps to be taken when these timelines are not met.

These timelines should meet the following CP-CTNet Program requirement of a target deadline of **390** days from Concept Receipt to Protocol Activation:

1. Concept Receipt to Concept Approval: **30 days**
2. Concept Approval to Protocol Receipt: **60 days**
3. Protocol Review and Approval (including CIRB approval): **210 days**
4. Protocol Approval to Activation (first participant on study): **90 days**

To accommodate for unknown delays, an extra **150** days has been added to the timeline to equal **540** days. Prior to the **540**-day absolute deadline, requests for an extension with justification should be submitted in writing to the NCI/DCP PIO.

If an exception is not granted prior to the 540-day deadline, the concept or protocol will be terminated.

All concepts and protocols that have not submitted an exception request and have not met the absolute deadline will be automatically terminated.

### iii. Trial Reporting Requirements

#### 1. Clinical Trials Accrual (Recruitment and Retention)

Clinical trials accrual will be informed by a comprehensive quality improvement program that consists of systematic planning and ongoing evaluation with responsive actions for continuous improvement. The purpose of this program is for NCI/DCP and the sites to evaluate the effectiveness of recruitment strategies, the need for accrual/recruitment strategy or protocol changes, as well as feasibility of trial completion and the advisability of potentially stopping the trial due to accrual issues. The program will allow integration with the accrual data from NCI/DCP's prior early-phase cancer prevention trials (<http://www.dcpaquip.com/>).

LAOs/AOs will be responsible for entering the data into a DMACC managed system. The DMACC will provide reports and ad hoc analyses to NCI/DCP and the LAOs/AOs.

#### 2. Minimum Data Set (MDS)

The MDS is a collection of specified administrative, participant demographic, and adverse event data that serves as an important source of information about NCI/DCP CP-CTNet clinical trials.

The DMACC will submit MDS reports monthly to NCI/DCP. Files should be successfully submitted by the 10th of each month. The LAOs/AOs will be responsible for reviewing the data and answering queries.

#### 3. Serious Adverse Events

Investigators, co-investigators, site coordinators, and designees at LAOs and AOs are responsible for properly reporting all SAEs that occur during the conduct of a study to NCI/DCP, the NCI/DCP regulatory contractor, and the appropriate IRB.

Investigators, co-investigators, site coordinators, and/or designees at each enrolling site will report SAEs to the assigned NCI/DCP Medical Monitor, DCP's Regulatory Contractor the study PI and the LAO (if the SAE occurred at an AO) by email within 24 hours of knowledge of an SAE. When applicable, complete follow-up reports as soon as additional information is available.

Sites must establish a system for expediting the reporting of all SAEs to ensure that potential patient safety issues can be identified and addressed quickly. Adverse events should be reported using the most recent version of Common Terminology Criteria for Adverse Events (CTCAE) and other applicable adverse event reporting tools.

For any study using agents under an NCI/DCP-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 NCI/DCP before any action is taken. For CP-CTNet studies that are not being conducted under an NCI/DCP IND, any major patient safety issues (e.g., study closure/suspension for adverse events, inappropriate randomization of patients to treatment arms) also require immediate notification to NCI/DCP before any action is taken.

In general, for studies with these types of immediate safety issues that are under monitoring by a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), immediate notification should be made to the DSMB/DMC Chair and the CP-CTNet Director.

#### **4. Protocol Deviations**

A protocol deviation is any noncompliance with the study design and/or procedures of an NCI/DCP and IRB/CIRB-approved protocol. Protocol deviations may result from the actions of the study participant, the investigators, or the clinical staff conducting the study.

Investigators, site coordinators, and designees at the LAOs and AOs are responsible for recording and reporting protocol deviations to NCI/DCP and the DMACC as soon as they are identified.

NCI/DCP does not allow any protocol waivers or exceptions for the enrollment of a participant in violation of protocol inclusion/exclusion criteria.

Investigators, site coordinators, and designees at each enrolling site will report protocol deviations using the electronic, fillable form (handwritten forms will not be accepted).

If the incident is a potential or unanticipated problem, or a potentially serious or continuing noncompliance issue, the PI or designee will be required to report to the appropriate IRB(s).

#### **d. Early Trial Closure**

Requests to close a trial early may be made by either the LAO or NCI/DCP.

The CP-CTNet will establish policies and procedures for early closure of studies.

Outlined below are NCI/DCP early stopping guidelines for slowly accruing trials. If accrual is behind expectations for a specific study, the LAO should involve the appropriate NCI/DCP staff in discussions about possible ways to enhance accrual in order to avoid study closure. Some excluded may apply. NCI/DCP may request that a study be closed to accrual for reasons including the following:

- Insufficient accrual rate
- Poor protocol performance
- Protection of patient safety
- Study results that are already conclusive

- Emergence of new information that diminishes the scientific importance of the study question
- Unavailability of study agent

**e. Clinical Trial Reporting Program (CTRP) and ClinicalTrials.gov Registration and Result Reporting**

In an effort to make information about clinical trials widely available to the public, the US Department of Health and Human Services issued The Final Rule (42 CFR Part 11) that clarifies and expands the regulatory requirements and procedures for submitting registration and results information for certain trials to ClinicalTrials.gov, in accordance with FDAAA 801. In addition, NIH has issued a complementary policy for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded clinical trials, including those not subject to the final rule. The sponsor is responsible for ensuring adherence to these policies.

**i. Trial Registration**

To be compliant with the FDA Amendments Act (FDAAA) Final Rule Section 801 and NIH policies, the LAO is required to register each clinical trial in ClinicalTrials.gov within 21 days of enrollment of the first participant.

**ii. Posting Clinical Trial Protocols**

NCI/DCP PIO is responsible for providing NCI’s Clinical Trials Reporting Office (CTRO) with the most recently approved protocol version (with redaction as needed), including the informed consent, for posting to the public ClinicalTrials.gov website.

- Protocols must be submitted to CTRO no later than 12 months after the primary completion date.

NCI/DCP Scientific Program staff will be responsible for working with pharmaceutical partners, as appropriate, to determine if any proprietary information needs to be redacted prior to sending it to PIO for public posting.

**iii. Posting Informed Consent Document**

All NCI/DCP-supported studies must post the most recent CIRB-approved model consent form to ClinicalTrials.gov within 60 days of the study status changing to “Closed to Accrual and Treatment.”

**For studies in which NCI/DCP is the IND sponsor,** NCI will post the most recent CIRB-approved model consent form to ClinicalTrials.gov within 60 days of the study status changing to “Closed to Accrual and Treatment.”

- LAO must ensure that the study status is promptly updated in NCI/DCP systems to “Closed to Accrual and Treatment” at the appropriate time by emailing the NCI/DCP PIO with the study status change as soon as study treatment ends. This is necessary so that NCI/DCP can ensure compliance with this requirement

- When the study status changes to “Closed to Accrual and Treatment,” NCI/DCP will provide all industry partners with the most recent CIRB-approved model consent form and allow 30 days for them to request redactions before finalizing the consent form for posting

**For studies in which NCI/DCP is not the IND sponsor and for studies that are IND-exempt,** the LAO will post the most recent CIRB-approved model consent form to ClinicalTrials.gov within 60 days of the study status changing to “Closed to Accrual and Treatment.”

**iv. Clinical Trial Results Reporting**

The LAO must submit clinical trial results via the ClinicalTrials.gov Protocol Registration and Results System Information Website (<https://register.clinicaltrials.gov>) (CTRP) in accordance with network policies and procedures. The standard submission deadline for results information is no later than 12 months after the trial’s primary completion date.

NIH expects registration of all trials whether required under the law or not. For more information, see [http://grants.nih.gov/ClinicalTrials\\_fdaaa/](http://grants.nih.gov/ClinicalTrials_fdaaa/).

**f. Resource Sharing Plans**

**i. Data Sharing Policy**

The CP-CTNet will develop a plan for sharing research data. Information on the NIH policy regarding sharing research data can be found on the NIH website at [http://grants.nih.gov/grants/policy/data\\_sharing](http://grants.nih.gov/grants/policy/data_sharing). The LAO’s policy for data sharing must be submitted to and approved by the CP-CTNet Director. Per this policy, requests for data will only be considered once the primary study analyses have been published.

Requests for data from clinical trials conducted under a binding collaborative agreement between NCI/DCP and a pharmaceutical/biotechnology company that 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/DCP (i.e., the CP-CTNet Director). Release of data may also be subject to the terms of any contracts the LAO has with other entities that cover any of the requested data.

**ii. Biospecimen Sharing Policy**

LAOs are required to follow NCI/DCP policy regarding review of requests for use of banked biospecimens collected in association with CP-CTNet trials that it leads, which requires approval by a designated review committee.

LAOs should also have plans in place regarding the following types of resources, as appropriate for the clinical research it conducts: Sharing Model Organisms and Genomic Data Sharing.

**g. Data Rights**

NCI will have access to all data generated under this cooperative agreement and may periodically review the data. The awardee will retain custody and primary rights to the data consistent with current HHS, Public Health Service (PHS), and NIH policies. Pharmaceutical and biotechnology companies will have access to all data generated under NCI/DCP collaborative agreements.

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 HHS, 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 CP-CTNet trials/studies.

## **VII. Roster Management**

The LAO is responsible for establishing, maintaining, and monitoring all its members that participate in CP-CTNet trials/studies. The LAO must have a “real-time,” comprehensive, consolidated roster of all its members with their relevant Cancer Therapy Evaluation Program (CTEP) institution codes, associated investigators, and research staff. This roster information is used for determining compliance with monitoring requirements.

The LAO’s organizational rosters will be managed by the Consortia-Sys website (<https://applications.prevention.cancer.gov/consortia-sys>). Requests to add memberships to a roster will be done via this website. All requests require that the following documents be uploaded:

- Consortium Letter of Commitment
- Site Letter of Commitment
- CV/NIH Biosketch

All site coordinators will be notified when an action is required or when a decision is made on a membership request. Consortia-Sys automates the current request/review process that is occurring through email.

Approvals for new membership will be determined by the CP-CTNet Director or, as needed, by a designee of the Director.

## **VIII. Data and Safety Monitoring Requirements**

The NIH policy for data and safety monitoring requires oversight and monitoring of all NIH-conducted or NIH-supported clinical trials to ensure the safety of participants and the validity and integrity of the data. Further information concerning these requirements is found at [http://grants.nih.gov/grants/policy/hs/data\\_safety.htm](http://grants.nih.gov/grants/policy/hs/data_safety.htm).

The data and safety monitoring functions and clinical trial oversight are distinct from the CIRB trial review and approval requirements. A Data Safety Monitoring Plan will be submitted to NCI/DCP for each CP-CTNet Site.



## IX. Clinical Trial Monitoring

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and applicable regulatory requirements.

## X. Protocol Funding

### a. Terms of Award

- 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 being involved 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
- Awardees are allowed to accept funds from non-governmental sources to support CP-CTNet research that is not supported in part or in full by NCI. These funds are considered “program income” (e.g., additional per case data management funding supplementing NCI/DCP data management funding, support for correlative science studies that use biospecimen, or image collections funded by NCI/DCP for trials under the CP-CTNet) and must be reported under the Terms and Conditions of Award for the CP-CTNet 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\\_2011/nihgps\\_ch8.htm#\\_Program\\_Income](https://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income)
- All key components of the CP-CTNet must report these funds to NCI on an annual basis (in the non-competitive Type 5 application—the annual progress report) and must indicate the clinical trial that the funds are being used to support (or other functional component if the funds are not provided to support specific trials). The Terms and Conditions of Award for all the cooperative agreements under the CP-CTNet 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
- Individual trials will not be funded separately. The trial conduct, participant care, as well as primary and major secondary endpoints should all be done within the allotted budget. The cross-network trials will be funded from the budgets from the participating LAO CP-CTNet Sites. Rapid Restricted Funds may be utilized to support participant accrual to cross-network trials. Additional outside funds, such as those from institutional, foundation, or other grant programs, may be utilized
- NCI reserves the right to reduce the budget or withhold an award in the event of substantial awardee underperformance (e.g., vastly insufficient participant accrual per the protocol specified) or other substantial failure to comply with the terms of award

**b. Rapid Response Restricted Fund**

The Rapid Response Restricted Fund is part of the total budget (in years 2–5 only). An amount of \$100,000 per year (direct costs) should be entered as “Rapid Response Restricted Fund” under the “Other Expenses” category in the budget form for years 2–5.

This fund is intended for participant accrual to cross-network trials and/or novel biomarker development and analysis. Specific projects to use this fund will be proposed post-award and will be subject to Steering Committee approval.

**c. Additional Non-Governmental Funds**

Awardees are allowed to accept funds from non-governmental sources to support CP-CTNet research that is not supported in part or in full by NCI. These funds are considered “program income” (e.g., additional per case data management funding supplementing NCI/DCP data management funding, support for correlative science studies that use biospecimen or image collections funded by NCI/DCP for trials under the CP-CTNet) and must be reported under the Terms and Conditions of Award for the CP-CTNet 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\\_2011/nihgps\\_ch8.htm# Program Income](https://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm# Program Income).

**XI. 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, in which a Dispute Resolution Panel will be convened. The panel will have three members: a designee of the CP-CTNet group representatives chosen from the CP-CTNet 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. 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, a specific appeal process will be in place for decisions regarding approval of CP-CTNet study proposals and the types of studies supported by CP-CTNet.

## Key Definitions for these Guidelines

- **Accrued Participant:** an individual who has completed the informed consent process, has been deemed eligible through all levels of the screening process, and has started the trial intervention (e.g., actually received the agent and/or intervention to be tested)
- **AO (Affiliated Organization):** any institution collaborating with the LAO on clinical trials under sub-contractual/consortium arrangements
- **“Clinical Research” and “Clinical Trial”** in this FOA follow the NIH definitions. <https://grants.nih.gov/policy/clinical-trials.htm>
- **CP-CTNet Site:** the Lead Academic Organization and its Affiliated Organizations.
- **LAO (Lead Academic Organization):** the research and administrative hub for the CP-CTNet Site.
- **NCI Central Institutional Review Board (CIRB):** a centralized approach to human subject protection through a process that streamlines local IRB review of selected NCI-sponsored trials for institutions across the country by relying on national experts to ensure trials are reviewed efficiently and with the highest ethical and quality standards (<https://www.ncicirb.org/about-cirb/>)
- **Principle Investigator:** the person in charge of a CP-CTNet Site
- **Screened Participant:** an individual who has signed consent to proceed with evaluation for eligibility for a trial after preliminary eligibility has been determined
- **Study chair:** the investigator who leads a given clinical trial
- **Target organ:** organ of focus for a given clinical trial

## Important Abbreviations

ABBREVIATION	FULL TERM
CDE	Common Data Elements
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board at NCI
CoC	Certificate of Confidentiality
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
CSA	Clinical Supply Agreement
CSR	Center for Scientific Research (at NIH)
CTA	Clinical Trial Agreement
CTAC	Clinical Trials and Translational Research Advisory Committee
CTCAE	Common Toxicity Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program (in DCTD)
CTRP	Clinical Trials Reporting Program
CTRO	Clinical Trials Reporting Office
DAR	Drug Accountability Record
DCP	Division of Cancer Prevention
DEA	Division of Extramural Activities
DMC	Data Monitoring Committee (also known as Data and Safety Monitoring Board)
DSMB	Data and Safety Monitoring Board (also known as Data Monitoring Committee)
FOA	Funding Opportunity Announcement
FDA	Food and Drug Administration
FWA	Federal Wide Assurance (for OHRP)
GCP	Good Clinical Practice
GMS	Grants Management Specialist

ABBREVIATION	FULL TERM
HHS	US Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protection
IDE	Investigational Device Exception
IND	Investigational New Drug Application
IRB	Institutional Review Board
LOI	Letter of Intent
NCAB	National Cancer Advisory Board
NCI	National Cancer Institute
NIH	National Institutes of Health
OD	Office of the Director at the NCI
OER	Office of Extramural Research, NIH
OGA	Office of Grants Administration
OHRP	Office for Human Research Protections
PA	Program Announcement
PHS	Public Health Service
PI	Principal Investigator
PIO	Protocol and Information Office
SOP	Standard Operating Procedure
URL	Uniform Resource Locator (internet address of resource)