DIVISION OF CANCER PREVENTION, NATIONAL CANCER INSTITUTE

Cancer Screening Trials Working Group: Implementation Plan

NIH NATIONAL CANCER INSTITUTE

July 29, 2022

Contents

Overview

One of the Division of Cancer Prevention's (DCP) responsibilities is to ensure that DCP-sponsored screening clinical trials accrue successfully to answer the specific research question being addressed by them. This goal requires building on a solid foundation of basic tenets: using realistic expectations of accrual capacity, developing comprehensive recruitment plans with specific attention to the accrual of racial/ethnic minorities and underserved populations, systematically monitoring accrual progress, and applying corrective actions to improve flagging accrual. If sufficient accrual in a timely fashion is not possible, trials should be halted based on the DCP screening trials accrual stopping rules.

The DCP Cancer Screening Trials Working Group (the "Strike Team") presented five recommendations to help DCP achieve this goal:

- Recommendation 1: Participant Recruitment—Planning for Success
- Recommendation 2: Risk-Based Accrual Monitoring
- Recommendation 3: Taking Action—Remediation
- Recommendation 4: Collaborative Infrastructure
- Recommendation 5: Looking Ahead

DCP accepted these recommendations on April 28, 2022. Accordingly, recommendations 1 through 3 will be implemented first and are described in this document. Recommendations 4 and 5 will be implemented subsequently.

Scope and Purpose

The Strike Team recommendations 1-3, following DCP approval, are now documented as "DCP Screening Protocol Requirements" ("DCP Requirements") and are listed in Appendix A. This document provides an Implementation Plan that DCP leadership and staff will follow to ensure these requirements are fulfilled. The new requirements pertain to future DCP-sponsored screening clinical trials (e.g., those trials for which DCP has not reviewed initial protocols). Additionally, specific activities described in this Plan also pertain to the ongoing screening clinical trials.[1]

The DCP programmatic areas and individuals/groups that are responsible for implementing this Plan are:

[1] See Division of Cancer Prevention, National Cancer Institute: Cancer Screening Trials Working Group, Appendix B, Cancer Screening Trials Portfolio

Programmatic Area	Responsible Party
NCI Community Oncology Research Program (NCORP)	Worta McCaskill-Stevens, M.D., M.S. Chief, Community Oncology and Prevention Trials Research Group
HPV Studies (ULACNet, Last Mile SHIP)	Vikrant Sahasrabuddhe, M.B.B.S., M.P.H., Dr.P.H. Deputy Chief and Program Director, Breast and Gynecologic Cancer Research Group
Investigator-Initiated Cancer Screening Grants	Claire Zhu, Ph.D. Program Director, Early Detection Research Group DCP POST group
Cancer Screening Research Network (CSRN)	Lori Minasian, M.D., F.A.C.P. DCP Deputy Director Paul Pinsky, Ph.D. Chief, Early Detection Research Group Elyse LeeVan, M.D. Early Detection Research Group

Implementation Plan

This Implementation Plan consists of four phases. The purpose, actions, and expected outcomes for each phase are described below.

Phase 1: Initial Document/ Process Review	Phase 2: DCP Director Reivew	Phase 3: DCP Monitoring	Phase 4: Evaluation
· One-time assessment · Revise documents and processes to comply with new requirements · Guidelines, templates · Protocol review process	· Prior to DCP approval, Director reviews: · New screening protocols · Significant amendments to ongoing screening protocols	· CTWG conducts quarterly review · Monitor accrual progress of ongoing screening trials · Ensure warning letters are issued, if needed. · Implement stopping rules per DCP requirements	· Process evaluation · Outcome evaluation

Phase 1: Initial Document/Process Review

Purpose:

Ensure that relevant program documents and processes are updated to comply with the DCP Screening Protocol Requirements.

The new DCP Requirements impact how protocols are written by the Research Bases/grantees and how the protocols are reviewed within DCP. The Division's programmatic expectations for developing protocols and conducting extramural clinical trials are set forth in program-specific documents (e.g., published Program Guidelines, Funding Opportunity Announcements). These documents now require review, and potentially revision, to align with the new DCP Requirements.

Further, DCP conducts an internal scientific review of the protocol and must approve the protocol before it can begin. This review process is generally similar for NCORP and ULACNet with the DCP Protocol Information Office (PIO) coordinating the process. However, the review of investigator-initiated grants is not coordinated by the PIO, and the review is conducted by the Program Official assigned to the grant. In both cases, the internal protocol review process needs to incorporate the new DCP Requirements. Therefore, the review process and any associated reviewer templates or checklists may need to be revised to ensure that the DCP Requirements are assessed during the DCP protocol review process.

Action:

- Responsible Party (or designee) for each Programmatic Area
  - Identify, assess, and revise the relevant program documents and processes to ensure compliance with the new DCP Screening Protocol Requirements.
  - Develop a plan for implementing required changes and communicating the new requirements.
  - Present assessment findings, planned revisions, timelines, and communication plans to a quarterly meeting of the CTWG (September 1, 2022).
- CTWG
  - The CTWG is tasked with oversight of this process.
  - The CTWG will ensure that, going forward, all new screening protocols adhere to the DCP Requirements.

Expected Outcome:

1. DCP cancer screening protocols and protocol review processes are modified, as necessary, to adhere to the DCP Screening Protocol Requirements.
2. All new cancer screening protocols approved by DCP adhere to the DCP Screening Protocol Requirements.

Phase 2: DCP Director Review

Purpose:

Screening protocols require DCP Director review and approval.

Action:

A new workflow process will be implemented to route (1) all new screening protocols that are undergoing initial DCP review and (2) all significant amendments[2] of ongoing screening protocols to the DCP Director, or designee, for review and comment before DCP approval.

The process, outlined in Appendix B, relies on the programmatic designee to initiate and manage this review process with the DCP Director and to incorporate the Director's review comments into the protocol/amendment review letter to the study chair. The Program Officials for investigator-initiated grants will similarly share new protocols

[2] "Significant amendments" include changes in study design, endpoints, and sample size.

and significant amendments with the DCP Director at the appropriate points in the grant review process.

Expected Outcome:

The DCP Director's review is requested and comments, if any, are incorporated into the DCP review process for new screening protocols and for significant amendments to ongoing cancer screening protocols.

Phase 3: CTWG Monitoring

Purpose:

The CTWG will meet quarterly to review and discuss progress on DCP's screening clinical trials.

The CTWG is tasked with oversight of the systematic monitoring of DCP's screening clinical trials. This oversight process is not intended to replace or duplicate the oversight responsibilities of DCP program staff. It is, however, an opportunity for the DCP Director and the CTWG to monitor overall progress, provide feedback, and address challenges in the screening trials.

Actions:

- Responsible Party (or designee) for each Programmatic Area presents an update on their screening trials at each quarterly meeting of the CTWG. The update includes:
  - Key dates (approved, activated, first enrolled, etc.) and current status
  - Accrual: planned (as documented in the protocol) vs. actual
  - Accrual of minority populations
  - Most recent reviews: DSMB, CIRB
  - Key issues related to accrual (e.g., amendments, recruitment planning)
  - If accrual is not meeting milestones:
    - Issuance and monitoring of corrective action plan
    - Issuance of stopping rules
- CTWG
  - The CTWG members attend the quarterly review meetings, participate in the review process, and provide guidance and feedback.

Expected Outcomes:

1. The CTWG meets quarterly to review the DCP screening portfolio of studies.
2. Overall and minority accrual are assessed and, when appropriate, corrective action plans are implemented and slow accrual stopping rules are invoked.

Phase 4: Evaluation

Purpose:

Process and outcome evaluations will assess whether the DCP Screening Protocol Requirements were implemented as intended and to assess the effectiveness of the CTWG review.

Action:

The Strike Team will develop an Evaluation Plan that will be presented to the DCP Director and the CTWG for approval.

Each DCP Programmatic Area/designee will collaborate with the Strike Team in the evaluation process by answering questionnaires, providing data, and/or participating in a screening trial audit.

Appendix A

DCP Screening Protocol Requirements

These requirements should be included either in the body of the protocol document or as "other protocol documents."

I. Study Design/Study Plan

a. Eligibility criteria are clearly defined and include populations who experience risk for the condition under study.

b. The proposed sample size is justified based on site accrual capability, staff experience, and track record with the cohort in similar trials, feasibility studies, endpoints, etc.

c. The proposed accrual duration is explicitly stated in the protocol document and justified.

II. Recruitment Planning

a. The protocol contains a comprehensive discussion of the recruitment approach and explicitly details the accrual approaches for racial/ethnic minorities and underrepresented populations.

b. The recruitment discussion identifies any differential timeline or expected accrual rates for underrepresented populations, citing data for populations that have been shown to enroll later in trial recruitment.

c. The description addresses any unique structures, relationships, or processes needed to recruit sufficient participants in the proposed timelines.

d. The protocol confirms that a detailed recruitment plan will be ready for implementation prior to randomizing the first participant.

e. The process of site selection is described.

f. The description addresses the inclusion of non-English speakers and how the consent and other patient-facing study materials will be translated into Spanish (at a minimum) and be available before recruitment begins.

g. DCP requires that large screening trials (>10,000 participants) have a Participant Advisory Board (PAB). A description of the PAB addresses the purpose, function, and responsibilities of the PAB.

h. The description discusses the process for systematically evaluating and revising the recruitment plan throughout the enrollment period.

i. A detailed recruitment plan and patient advisory board plan are encouraged and may be included as "Additional Study-Related Documents," thus allowing document updates independent of a protocol amendment.

III. Accrual Milestones

a. The protocol contains milestone dates with the expected overall and minority accrual defined for each milestone.

IV. Accrual Monitoring

a. The protocol describes the process for monitoring overall and racial/ethnic minority accrual. The monitoring section of the protocol addresses:

   i. Roles and responsibilities for implementing the monitoring plan

   ii. Frequency and method of monitoring and accrual reporting

   iii. Roles and responsibilities for addressing and reporting accrual that does not meet the milestone

   iv. Communication and coordination between stakeholders for addressing slow accrual

Appendix B

DCP Director Review of Screening Protocols

Programmatic Area		New Screening Protocols		Ongoing Screening Protocols: "Significant" Amendments*		
	Responsible Party	*Required Action*	*Timing*	*Responsible Party*	*Required Action*	*Timing*
NCORP	Chair of the Protocol Review Committee	▪ Send protocol to DCP Director ▪ Receive/discuss Director comments ▪ Incorporate Director comments into the Consensus Review Document/Review letter	First/initial protocol review	Program Director/Project Scientist	▪ Determine if "significant" amendment ▪ Send protocol to DCP Director ▪ Receive/discuss Director comments ▪ Incorporate Director comments into review letter	Incorporate into the existing amendment review process
HPV protocols (ULACNet, Last Mile, Cascade)	Project Scientist	Same as above	Incorporate into the Clinical Trials Oversight Committee review of the protocol	Project Scientist	Same as above	Same as above
Investigator-initiated screening protocols	Program Official	▪ Send protocol to Director ▪ Receive/discuss Director comments ▪ PO will obtain response to any Director questions	Occurs after the initial peer review and if the score is within the fundable range or within the zone of consideration. PO requests additional info if DCP-requirements aren't met.	Director review applies only to new grants.		

*Significant amendments include changes in the study design, sample size, endpoints.

Appendix C

Slow Accrual Stopping Rules

Background

- DCP's goal is to systematically apply the new DCP Requirements to ensure that screening protocols contain realistic accrual goals and that potential accrual concerns are addressed before DCP approval of the protocol.
- DCP acknowledges that accrual that does not meet expectations may occur for a variety of reasons.

Stopping Rules

- DCP collected and analyzed accrual data from its ongoing and past screening protocols and large prevention trials (n = 12). The small number of trials is not sufficient to establish a definitive set of stopping rules but identifies a preliminary set of stopping rules to be used and refined over time. DCP will continue to collect accrual data for ongoing and future screening trials, and when sufficient data exists, the preliminary stopping rules will be modified.
- The preliminary approach is to evaluate the actual accrual of a trial based upon the protocol's expected accrual time frame.
  - If the actual accrual does not meet the expected accrual at a specified time point, a warning letter will be issued.
  - If the accrual improves and meets the next projected period goals, it continues and is monitored closely.
  - If the trial accrual does not meet the next projected period goals, then it is terminated for inability to accrue.
  - Accrual evaluation timepoints ("breakpoints") are expressed as a percentage of expected accrual at a percentage of the projected accrual time period.
    - First breakpoint: 10% of expected accrual at 25% of projected accrual period
    - Second breakpoint: 25% of expected accrual at 50% of projected accrual period
    - Third breakpoint: 50% of expected accrual at 75% of projected accrual period
    - Fourth breakpoint: 65% of expected accrual at 85% of projected accrual period
    - Fifth breakpoint: 90% of expected accrual at 100% of accrual period

Implementation

- These preliminary stopping rules apply to all new screening trials.
- Study monitoring by network groups, DSMBs, study teams, and program staff will continue.
- In addition, the DCP CTWG will meet quarterly to systematically monitor progress in overall and minority accrual.

- Program Officials will request a Corrective Action Plan if a study does not meet the defined breakpoint. Program Officials will provide the CTWG with status updates, and the CTWG will discuss next steps.

Appendix D

Presentations to the CTWG

Implementation Phase I: Initial Document/Process Review

The following elements will be compiled into a PowerPoint presentation template that the program designee will use to present their findings to the CTWG on September 1, 2022.

- Programmatic Area (e.g., NCORP, ULACNet, investigator-initiated grants)
- Documents and processes reviewed
- Assessment of adherence to DCP Screening Protocol Requirements
- Planned revisions to documents and processes
- Timeline for completing changes
- Stakeholder communication plan

Implementation Phase 3: CTWG Monitoring/ Quarterly Protocol Status Review

The following elements will be compiled into a PowerPoint presentation template that the program designee will use to present a quarterly status update to the CTWG (December, March, June, September)

- Programmatic Area
- List of screening trials
- Information for each trial
  - Key dates (approved, activated, first enrolled, etc.) and current status
  - Results of the DCP Director' review
  - Accrual: planned (as documented in the protocol) vs. actual; overall and minority. Assessment of accrual against the preliminary stopping rule breakpoints.
  - Most recent reviews: DSMB, CIRB
  - Key issues related to accrual (e.g., amendments, recruitment planning)
  - If accrual is not meeting milestones:
    - Request Corrective Action Plan and monitor progress
    - Reassess accrual at next breakpoint