Part 3: Development of NCORP Concepts, Protocols, and Amendments

NCI/DCP and NCI/DCCPS Staff Responsibilities

NCI/DCP and DCCPS staff are closely involved, programmatically, in the development of NCORP studies and will communicate with NCORP Research Bases during all stages of study development. As appropriate, NCI NCORP staff will assist the Research Bases in clinical trial or cancer care delivery research design to develop a mutually acceptable protocol compatible with the research interests, capabilities, and needs of the Research Base, its affiliates, and NCI.

NCI/DCP and DCCPS staff are responsible for conducting the review process for concepts, protocols, and amendments. Review from NCI’s Scientific Steering Committees (SSCs) is provided only during the concept review process.

NCORP Research Base Rights and Responsibilities

These procedures apply to cancer prevention, control and screening/post-treatment surveillance clinical trials as well as cancer care delivery research studies except as specifically noted.

The Research Base shall designate Study Chair(s) for each proposed concept/protocol. The Study Chair will have the appropriate experience and training to guide the study. The Research Base is responsible for assuring the Study Chair meets Federal and local regulatory guidelines and accordingly, can fulfill the requirements of a Study Chair. The Research Base is responsible for establishing policies and procedures for the development and submission of NCORP Research Base study concepts and protocols through the NCI DCP Protocol Information Office (PIO) for review and approval. The Research Base is also responsible for assembling appropriate study teams, protocol development and oversight and conduct of approved studies.

I. Concept and Protocol Efficiency

Study concepts and protocols should be developed, submitted, and implemented in accordance with NCORP policies. Research Base SOPs should include timelines for the development of concepts and protocols from initial submission of the concept to NCI through study activation. The SOPs should also include mechanisms for monitoring the performance of the Research Base, its committees and investigators in adhering to these timelines, as well as corrective action plans outlining steps to be taken when these timelines are not met. Data concerning a Research Base’s performance in meeting these timelines for concept/protocol development should be provided in its Annual Progress Report and should meet the NCORP requirements described below.

NCORP Concept/Protocol Efficiency Timelines are as follows (effective 8/1/18):

<table>
<thead>
<tr>
<th>Task</th>
<th>Target Timeline</th>
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<tbody>
<tr>
<td>Initial concept receipt in PIO to approval letter being sent</td>
<td>120 days</td>
</tr>
<tr>
<td>Protocol authoring at Research Base</td>
<td>90 days</td>
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</tbody>
</table>
Protocol receipt to final DCP approval (includes CIRB approval) | 175 days
---|---
Protocol approval to activation | 90 days

Category 1 = Studies with concepts: Time from concept receipt to protocol activation
- Target = 475 days
- Absolute deadline = 525 days*

Category 2 = Studies without concepts: Time from protocol receipt to protocol activation
- Target = 265 days
- Absolute deadline= 315 days*

* Absolute deadline includes an extra 50 days to accommodate one additional revision.

Sixty days prior to the absolute deadline (category 1 and 2) DCP PIO will send a letter informing the Research Base they have 60 days to activate the study or the study will be terminated. Should the Research Base feel they are not able to activate the protocol by the absolute date, they must submit a written extension request to DCP PIO containing the following information:
- Justification for the delay
- Describe what is being done to mitigate/resolve the issue
- Date when protocol is expected to activate

NCI NCORP staff will review and approve or disapprove the extension request.

Studies that do not request and receive an extension at 60 days will receive a second notice 30 days prior to the absolute deadline. This letter will inform the Research Base they have 30 days to activate the study or it will be terminated. The Research Base may request an extension, as per the process outlined above, for review and consideration. All requests for extension must be received in writing by DCP PIO a minimum of 14 days prior to the absolute deadline.

Protocols that have reached the absolute deadline (category 1 or 2) without an extension request approved by the NCI, will be automatically terminated. The Research Base will receive written notification from DCP PIO after the study has been terminated.

II. Process to Utilize the NCORP Network for Externally Funded Research Grants

In order to promote the efficient and equitable use of resources in the initiation, implementation, and completion of research studies, the following guidelines outline the process for submitting externally funded research grant applications that propose to use the NCORP network for study implementation.

Research conducted using NCORP must undergo federal scientific peer review through one of the following three mechanisms:

1. NCI Scientific Steering Committee (SCC) review of a concept proposing research in NCORP that will be supported solely through NCORP funds or through non-federal funding sources.
2. Center for Scientific Review (CSR) Study Section review of grant applications proposing research in NCORP that will in part or entirely be supported by federal funding.

3. If NCI has not established a SCC with purview over a concept, the NCORP Concept Review Committee (CRC) will conduct the review using scientific expertise with NCI and NIH, as required.

A proposed study must be submitted through one of these mechanisms, with the peer review results considered binding for the proposed study. That is, a disapproved concept cannot be submitted as a federal grant to be conducted in NCORP nor can an unfunded federal grant application be submitted as a concept. If NCI Program Staff determine that a substantially similar study has been submitted as both a concept and a federal grant application, the concept will be returned without review. The study will move forward in NCORP only if federal funding is awarded.

NCI program staff will consider the following in assessing whether two proposed studies are substantially similar or different: conceptual foundation; specific aims; study population; primary endpoint; and intervention approach (if any). Investigators with questions about whether one study is substantially similar to or different from another study should consult their NCI Program Director(s).

**Federally Funded Studies (e.g., NIH, AHRQ, DOD)**

The following process is used to request use of the NCORP network to implement studies supported by federal research grant applications (e.g. R series, P01s). These guidelines describe the required process for coordinating communication between NCORP Research Bases and their respective NCI NCORP Program Directors, as well as the review and approval requirements for conducting research in the NCORP network.

**Prior to submission of a research grant application**

Interested investigators are required to contact NCI (NCORP) Program Directors and the Research Bases to determine if the proposed research is within the research scope of the program. Investigators contacting the NCORP Program Directors in either the Division of Cancer Prevention or the Division of Cancer Control and Population Sciences will be directed to Research Base contacts, so the investigator can determine the Research Base best suited to support the proposed research. When an investigator makes contact with an NCORP Research Base, the Research Base is required to notify their assigned NCORP Program Director of an investigator’s intent to submit a research grant application to a federally funding agency at least four weeks prior to submission. Note: This notification process applies to all federal grant applications, including resubmissions (e.g. R01 A1 applications).

In advance of submitting the grant application, it is expected that the study chair, NCORP Research Base and NCORP Program Director have discussed: 1) the study aim(s), 2) study population, 3) rationale for and feasibility of conducting the study within the network, 4) potential scientific overlap with existing/planned studies, 5) confirmation that the study fits within the cancer control/prevention, symptom management, care delivery or disparities NCORP research scope, and 6) timeline and relevant administrative requirements/budgetary considerations. It is also expected that the study chair and Research Base have communicated with NCORP sites regarding interest and participation in the study. NCI Program Staff may decline to approve use of NCORP in a federal application if the proposed study is deemed infeasible or overlaps with other research being conducted in NCORP.
Because NIH Institutes and NCI Divisions differ in their approach to handling applications and funded grants, there are some variations in process as follows:

- **Cancer Control (including Symptom Science) Prevention & Screening**: The Program Directors in the NCI Division of Cancer Prevention (DCP), Community Oncology and Prevention Trials Research Group, are responsible for the scientific oversight for cancer control/symptom science applications and funded grants using the NCORP network. Some grants outside of NCI are monitored in conjunction with Scientific Program Directors in other NIH Institutes. At the time of submission, applicant(s) may request assignment of their grant application to the NCI and to a specific NCI NCORP Program Director. (For more information go to: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-008.html). By doing so, the application can be more easily/directly/quickly brought to the attention of the interested/involved NCI Program Director after it has been received, logged-in, and assigned to the NCI.

- **Cancer Care Delivery Research**: The primary Scientific Program Director for all cancer care delivery research applications and funded grants will be the person with the most relevant scientific expertise within any NCI Division, NIH Institute, or other federal agency. NIH applicants are encouraged to request assignment of their application to the Scientific Program Director they feel will be the most relevant. NCI Cancer Care Delivery staff will serve as a resource and monitor progress on these grants. Applicants, Research Bases and NCI staff should work together well in advance of submission to establish the appropriate relationships. (For more information go to: (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-008.html)

**NOTE:** Studies included in federal grant applications that were submitted without following the above procedures will not be allowed to use NCORP.

**Post study section review and award**

Federally funded studies (e.g. R01) are not required to undergo Steering Committee concept review because they have already undergone federal scientific peer review. If the grant is funded the study will be submitted as a protocol to NCI DCP Protocol Information Office (PIO) via a Research Base **within 90 days of receipt of the Notice of Award or start of Project Period (as indicated on the Notice of Award); whichever is later.** Therefore, as soon as the Summary Statement is released (usually within 6-8 weeks after completion of the review) the investigator should contact the Scientific Program Director assigned to the grant as well as the NCORP Program Director for the Research Base that will be submitting the protocol to discuss next steps. Communication with the NCORP Program Director and Scientific Program Director is critical during this time, particularly if the grant is supported by a Federal Agency, NIH Institute or Center other than NCI. Inability to meet the 90-day submission time frame may result in forfeiture of access to the NCORP Network.

The full protocol will undergo review by the NCORP Protocol Review Committee. Once the full protocol is approved by the NCORP Protocol Review Committee and NCI Central IRB, the study chair and Research Base may proceed with conducting the federally funded study within NCORP.

Note: The NCI Central IRB (NCI CIRB) does not review grant applications and is not the IRB of record for the research grant. The NCI CIRB is the sole IRB of record for all sites.
conducting clinical trials through the NCORP and NCTN networks and is responsible for study review (initial review, amendments, continuing reviews, recruitment materials, unanticipated problems and serious or continuing noncompliance) and approval of local context considerations.

**Non-Federally Funded NCORP Studies, Applications and Letters of Intent (LOI) - (e.g. PCORI, American Cancer Society, Leukemia and Lymphoma Society)**

The following process is used to request use of the NCORP Network to implement studies supported by non-federal funders. The process supports coordination of communication, review, and approval requirements between NCI and the non-federal funder. The NCI has established communications with some non-federal funding organizations to accommodate their respective review processes.

**Application planning and/or Letter of Intent (LOI)**

Interested investigators are required to contact NCI (NCORP) Program Directors and the Research Bases to determine if the concept is within the research scope of the program. Investigators contacting the NCI Program Directors will be directed to Research Base contacts, so the investigator can determine the Research Base that is best suited for the LOI or concept and provide additional information. When the initial contact is with an NCORP Research Base, the Research Base notifies their assigned NCORP Program Director of an investigator’s intent to submit a research grant application or LOI to a non-federally funding agency or organization at least four weeks prior to submission. NOTE: This notification process applies to all non-federal applications including resubmissions.

The NCORP Research Base or investigator should provide the NCORP Program Director a brief abstract describing the study aim(s), study population and a statement of rationale for use of the NCORP network. The NCORP Program Director will provide feedback regarding: 1) the feasibility of conducting the study within the network, 2) potential scientific overlap with existing/planned studies, and 3) confirmation that the study fits within the cancer control/prevention, symptom management, care delivery or disparities NCORP research scope. NCI Program Staff may decline to approve use of NCORP in a non-federal application if the proposed study is deemed infeasible or overlaps with other research being conducted in NCORP.

When an LOI is selected to be submitted as a full application, the NCORP Research Base will notify the NCORP Program Director that an application is being submitted and will provide any changes/revisions to study design. **All of this must take place at least four weeks before submission of a full application.** Studies included in non-federal grant applications that were submitted without following the above procedures will not be allowed to use NCORP.

**Post award**

If the application is approved for funding by the non-federal sponsor, there are two additional steps required to conduct the research within the NCORP infrastructure.

1. The NCORP Research Base shall submit a concept to the NCI DCP Protocol Information Office (PIO) for scientific review by an NCI Steering Committee or the NCI Concept Review Committee within **90 days of notice of award or project start date whichever is later.**
2. **If the concept is approved**, the NCORP Research Base will then submit a full protocol to the NCI DCP Protocol Information Office (PIO) for review by the NCI Protocol Review Committee. **If the concept is disapproved**, the investigator will not move forward with conducting the study in NCORP.

Once the full protocol is approved by the NCI Protocol Review Committee and NCI Central IRB, the Research Base may proceed with conducting the non-federally funded study within NCORP.

Note: The NCI Central IRB (NCI CIRB) does not review grant applications and is not the IRB of record for the research grant. The NCI CIRB is the sole IRB of record for all sites conducting clinical trials through the NCORP and NCTN networks and is responsible for study review (initial review, amendments, continuing reviews, recruitment materials, unanticipated problems and serious or continuing noncompliance) and approval of local context considerations.

### III. Study Concept Development, Review, and Approval

Investigators are encouraged to communicate with the NCORP Program Directors when developing concepts for clinical trials, HRQOL studies or cancer care delivery studies.

A concept should have been reviewed and approved by all necessary components at the Research Base before submission to DCP PIO. Although not a full protocol, the concept should provide sufficient information to establish the scientific rationale for the proposed study; describe the methodology and programmatic relevance, feasibility and appropriateness of the research for use by NCORP Community Sites or in a community setting and adequately address safety/regulatory issues. NCI program staff will return to Research Bases concepts that do not fulfill these criteria together with a letter that explains the reasons for not accepting the concept for review.

Correlative science studies embedded in NCORP clinical trials/studies at the time of initial concept submission should be appropriately designed as integral and/or integrated studies with robust statistical designs and analysis plans that address specific and important scientific hypotheses. Exploratory studies and those without a specific hypothesis and robust statistical analysis plan will not be approved. Although optional collection of biospecimens without an approved research plan may be approved within a trial, future use of the specimen must be approved by DCP and must be based on studies with specific hypotheses and statistical analysis plans.

The final concept document, Document Submission Worksheet (DSW) and any relevant accompanying materials must be submitted to NCI DCP’s Protocol Information Office (PIO) electronically at [NCI_DCPPIO@mail.nih.gov](mailto:NCI_DCPPIO@mail.nih.gov).

a. Concept Content and Format

Although NCORP does not mandate the use of a set template for concepts, it does require specific information to be included in all study concepts. In addition, the Symptom Management and Quality of Life and the Cancer Care Delivery Steering Committees have optional concept templates that outline considerations particular to their topic areas. Specific instructions for submission and the latest versions of forms and templates can be downloaded from [https://www.cancer.gov/about-nci/organization/ccct/steering-](https://www.cancer.gov/about-nci/organization/ccct/steering-).
committees/concept-submission-guidelines. Concepts do not need to include consent forms or case report forms, although they should include (as appendices) all of the questionnaires or measurement instruments to be used for the primary endpoint. Concepts may be no longer than 10 pages in length, excluding the title pages, references, and appendices.

The required information includes:

i. Document Submission Worksheet

All new and pending concepts must be accompanied by the Document Submission Worksheet (DSW). Select the correct DSW for the type of study you are submitting. Cancer care delivery protocols must be accompanied by the CCDR DSW. All relevant sections of the DSW must be completed. The latest versions of the DSWs as well as other PIO protocol-related forms can be downloaded from: https://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools.

iii. Title Page

This is the primary source of identifying information for DCP PIO. Each concept must have a title page that contains:

1. Date of document
2. Local concept number (i.e., institution or group number)
3. Title of study
4. Clear identification as a cancer control/prevention or cancer care delivery research study
5. Identified study personnel responsible for the study, including name, institution, address, phone and fax numbers, and email address
   a. single study chair
   b. co-chair(s)
   c. related committee chairs
   d. primary statistician
6. Full name of Research Base submitting the study
7. For agents requested from DCP, a listing of each agent by name and Cancer Chemotherapy National Service Center number (NSC Number)
iii. Background

This is the most important section of the concept, as it provides reviewers the rationale and scientific justification for conducting the study. It should contain:

1. A detailed rationale for the study:
   a. What is the current state of knowledge or clinical/care delivery practice? Include preclinical, clinical and/or pilot data that support conducting the study
   b. What research gap is being addressed?
   c. What is the clinical relevance/significance of the problem under study?
   d. How is the study intervention novel?
   e. For randomized, symptom intervention studies, what priority research area identified by the Steering Committee and Research Base does the study address? If not a priority research area, what is the justification for the area of research proposed?
   f. What will this study contribute to cancer prevention, control, or screening/post treatment surveillance or care delivery? Although other contributions are important and should be included, this section should explain how information from the study would affect care of patients or impact the delivery of cancer care.
   g. How will this study contribute to an enhanced understanding or the reduction of cancer disparities?
   h. Why is the study design the best way to make this contribution?
   i. Include information about the study population and intervention; the study populations could include patients, clinicians and/or organizations.
   j. How will this research affect subsequent research?
   k. How will the research inform patient care/improve patient outcomes?
   l. Why were the endpoints chosen?
2. A literature review (a focused review of relevant literature with citations), which should cover:
   
a. Current knowledge
b. Other studies that have contributed information applicable to the study
c. Information on drugs, procedures and measurement instruments to be used
d. Other information justifying the research and its methodology

3. Information related to feasibility:
   
a. State if NCORP Community Sites and Minority/Underserved Community Sites have been involved in developing and/or reviewing the concept
b. What is level of interest expressed by NCORP sites and how this information was elicited?
c. Note level of anticipated participation and accrual from NCORP sites and other members
d. Provide any additional epidemiological data or information to support the anticipated accrual or participation rate, particularly as it relates to racial/ethnic minorities
e. Specify procedures for recruitment and retention of participants (if applicable) including minority and underserved populations
f. If the study will involve costs in addition to data management (i.e., tests/procedures not covered by insurance), describe them and include a source of funding
g. Describe the time commitment of patients, research staff, physicians or other study participants
h. For cancer care delivery research studies, provide information on the anticipated feasibility of data collection from organizations/practices and non-patient study participants (e.g. physicians, nurses)
iv. Study objective(s)

v. Study design, including:

1. Schema: This one-page diagram provides an overview of the study design. To be most useful, it should include:
   a. Sample size
   b. Study population
   c. Stratification factors
   d. Study design (e.g. randomization, case controlled, observational)
   e. Specific intervention(s) (with dose, timing of data collection, etc.) if applicable

2. Eligibility criteria and characteristics of study population

3. Clear definitions of the primary and secondary endpoints

4. Stratification factors and justification for using them

5. Detailed description of the intervention if applicable (including, for drugs, the provider; for complementary and alternative treatments, information on quality control and content; for behavioral or organizational interventions, the availability of resources in the community setting to provide the intervention, for procedural interventions, the willingness of the study populations to implement; for practitioner/organizational interventions, the availability of participants)
   a. For pharmaceutical agents, including complementary and alternative agents:
      i. Describe how agent will be provided, supported and assessed for quality control
      ii. Document plan to submit protocol to FDA for IND review
   b. For behavioral and organizational interventions:
      i. Describe availability of resources in community setting to provide intervention
      ii. Document plan to train community sites to provide intervention
6. Detailed description of the outcome measure(s) used included reliability and validity for the disease and patient population under study.

7. Detailed methodology and explanation regarding how sub-studies (if applicable) will contribute useful information to the parent trial.

   a. If biomarkers are included, state rationale for use and whether they are validated.

   b. Include funding source for biomarker collection, testing and storage.

vi. Statistical plan analyses:

1. Define stratification factors with justification.

2. Specify procedures to be used for randomizing subjects to treatment (or placebo) arms.

3. Definitions for primary and secondary endpoints; for observational studies, explanatory variables/composites.

4. Define study endpoints, how and when they will be measured.

5. Sample size calculation and planned accrual rate.

   a. Information on the composition of the proposed study population (accrual targets). For studies accruing patients, include information on sex/gender and racial/ethnic group in the format as provided on the Document Submission Worksheet (DSW). Cancer care delivery studies accruing non-patients and/or organizations/practices should complete the appropriate sections of the DSW.

   b. If the protocol is a NIH-defined Phase III trial (a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments), the investigator must address whether he/she expects to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The protocol must include one of the following:
1. Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR

2. Plans to include and analyze sex/gender and or racial/ethnic subgroups when prior studies strongly support NO significant differences in intervention effect between subgroups, OR

3. Plans to conduct valid analyses of the intervention effect in sex/gender and/or race/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups

6. Studies collecting multiple levels of data (e.g. patient, non-patient, organization/practice) including qualitative data (if applicable) must include detailed plans for data analysis, triangulation, and interpretation as appropriate.

7. Full plans for analyzing and interpreting results regarding the primary and secondary endpoints

8. Plan for missing data

9. Plans for addressing data limitations

b. Concept Review

NCI NCORP staff are responsible for facilitating the review process for all proposed studies. For concepts which fall within the purview of an established Scientific Steering Committee (SSC) (e.g. the Symptom Management and Quality of Life Steering Committee, Prevention Steering Committee, or the Cancer Care Delivery Steering Committee), the SSC conducts the review of the concept and determines the outcome of the review (i.e. approval, disapproval, or pending). If NCI has not established a SSC with purview over a concept the NCORP Concept Review Committee (CRC) will conduct the review.

Prior to presentation at a SCC, the NCORP CRC will evaluate all concepts for previously described content criteria (Section III, second paragraph) as well as to ensure there are adequate resources available to NCORP to conduct the study. The NCORP CRC will also review for the existence and nature of concurrent clinical trials/studies in the area of research, including research in other NCI-funded programs that may compete with or complement the proposed study.

Several NCI/DCP and DCCPS staff are full members of specific SSCs relevant to NCORP research. Designated NCI staff are voting members of the SSCs and present the NCORP
CRC review to the committee. NCI staff has special responsibilities on these NCI SSCs, including developing meeting agendas with the SSCs co-Chairs, preparing the Consensus Evaluations for concepts evaluated by the committees, and working with the SSC Co-Chairs on the scientific direction of the committee.

Any changes in the NCI SSCs related to composition of committee membership, conflict of interest, and evaluation/prioritization procedures for NCORP studies requires review and approval by the NCORP Director, NCI/DCP, and the CCDR Scientific Lead, in conjunction with the NCI Coordinating Center for Clinical Trials which provides oversight of the NCI SCCs, to ensure that procedures are consistent with the intent of NCORP and the Terms and Conditions of Award under the Cooperative Agreements for all key components of NCORP.

a. Scientific Steering Committees (SSCs)

The NCI SSCs most relevant to the work of NCORP are the Symptom Management and Quality of Life Scientific Steering Committee, the Clinical Imaging Scientific Steering Committee, Prevention Steering Committee and the Cancer Care Delivery Research Scientific Steering Committee.

NCORP concept review by a SSC is based on the area of study:

- Concepts related to cancer symptom management or quality of life are evaluated by the NCI Symptom Management and Quality of Life Scientific Steering Committee with ad hoc extramural scientific reviewers as needed. The SSC does not review non-randomized, pediatric and longitudinal studies and studies with sample size less than 100.

- Concepts related to cancer screening, prevention and post-treatment surveillance are evaluated by the Division of Cancer Prevention (DCP) Concept Review Committee (CRC), with ad hoc extramural scientific reviewers, as needed. Depending on the modality under investigation, the Clinical Imaging Steering Committee expertise may be required.

- Concepts related to cancer care delivery are evaluated by the Cancer Care Delivery Research Steering Committee with ad hoc extramural scientific reviewers, as needed.

- Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) applications that are related to cancer prevention and control or cancer care delivery are evaluated by the appropriate NCI SSC or by DCP’s CRC or DCCPS’s CRC with ad hoc extramural scientific reviewers.

b. Review Outcome

The appropriate NCI SSC (or the NCORP CRCs, as described above) discusses the submitted concept at a meeting with assigned reviewers and committee members and makes a decision on the concept from one of the 3 options provided below:

1. **Approved** – The SSC or NCORP CRC approves the concept and does not need to evaluate a revised concept. The Research Base can begin to develop the protocol. The concept review letter can include important
comments and/or recommendations for items to be included in the protocol; the Research Base must respond to these comments and recommendations in a cover letter accompanying the protocol.

2. **Pending** – The SSC or NCORP CRC had concerns regarding the study as explained in the Consensus Evaluation. Given these concerns, the SSC or NCORP CRC did not approve the concept. Instead, the SSC or NCORP CRC gave the concept a status of “pending” to indicate that approval of the concept might be warranted if the investigators can satisfactorily address, within 90 days, the SSC or NCORP CRC’s concerns and suggestions regarding changes to the concept as outlined in the Consensus summary letter. The deadline for resubmission will be included in the Consensus Summary Letter sent to the Research Base/Study Chair. **Only one revision of a concept is allowed.**

3. **Disapproved** – In the judgment of the SSC or NCORP CRC, the concept as written is not feasible and/or lacks adequate scientific merit, and the changes necessary to address these concerns would result in a study that is substantially different from the study proposed. Disapproval can also indicate that preclinical/early phase studies do not exist to support conduct of the proposed phase II or III trial. Research Bases cannot resubmit disapproved concepts, even with revisions. However, concepts for study of the same subject area with a substantially different study design and/or with inclusion of results from necessary preclinical/early phase studies will be considered new concepts for review.

**IV. Protocol Development, Review, and Approval**

After receiving approval for a concept from the Division of Cancer Prevention PIO or external federal grant funding is awarded (i.e., R01, etc.), the Research Base should begin to formulate a protocol to conduct the proposed research.

a. Protocol Content

The protocol must include:

i. Document Submission Worksheet:

   All new protocols must be accompanied by the Document Submission Worksheet (DSW). Select the correct DSW for the type of study you are submitting. Cancer care delivery protocols must be accompanied by the CCDR DSW. All relevant sections of the DSW must be completed. The latest versions of the DSWs as well as other PIO protocol-related forms can be downloaded from: [https://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools](https://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools). Subsequent submissions for the same protocol also require the submission of the DSW.

ii. NCORP Research Base Protocol Funding Sheet:

   A protocol-specific NCORP Research Base Funding Sheet must accompany each new protocol submission. A group-specific NCORP Research Base Protocol Funding Sheet template has been provided to each of the funded NCORP Research Bases. Revisions to the funding sheet templates are distributed to the
relevant Research Base contacts, if and/or when any updates are made.

Each proposed study component (e.g., base intervention, bio-specimen, advanced imaging, patient and/or non-patient incentives, etc.) of the protocol, for which there is site reimbursement regardless of the funding source, must be itemized according to the NCORP Research Base Funding Sheet template. In addition, specific details regarding the type(s) of bio-specimen collection(s), interval(s), etc., must be provided. Study specific notes should be provided if necessary. A contact for question(s) about funding should also be included.

The study components will be reviewed by the NCORP Protocol Review Committee. The review decisions will be communicated to the Research Base in the protocol consensus review letter and/or with a revised funding sheet, should modifications be needed. Please note, the study components approved at the time of protocol review do not infer approval for the associated correlatives science study(s) to be conducted using the bio-specimens, images, etc.

### iii. Cover Letter

The cover letter will include point by point responses to issues (if any) raised in the concept approval letter and will identify places in the protocol that include changes relevant to these issues. The cover letter should also indicate any other significant changes made to the previously approved concept and provide reasons.

If the protocol is for a study that will receive federal funding other than that provided in the NCORP grant and has received approval from a peer review panel, the cover letter should provide this information; a copy of the grant application, budget pages, and summary review statement should be included as attachments. The cover letter should indicate any changes made to the protocol from the funded grant application and rationale for the changes.
iv. Title Page

The title page of the protocol is the primary source of identifying information for the NCI DCP Protocol Information Office (PIO), for the agent distribution system, for the IND file at the FDA, and for the listing of the protocol in the Physician Data Query (PDQ) system, as applicable. Each protocol submitted, therefore, must have a title page that contains the following items:

1. Date of document
2. Local protocol number (i.e., institution or group number)
3. Title of study
4. A single study chair who will be responsible for the study, including name, institution, address, phone and fax numbers, and e-mail address
5. List of the following study personnel including name, institution, address, phone and fax numbers and e-mail address:
   a. Single study chair
   b. co-chair(s)
   c. related committee chairs
   d. primary statistician
   e. protocol coordinator
   f. data manager
   g. protocol contacts
6. Full name of Research Base submitting the study
7. List of each participating institution or Research Base (can be summarized as open to all Research Base members)
8. For DCP-supplied agents, a listing of each agent by name and NSC number (not applicable for cancer care delivery research)

v. Background

The background can largely be taken from the background from the approved concept or funded grant application. It provides the reviewers the relevant arguments for conducting the proposed study. The background section should be updated with recent relevant literature, information or discussion requested by the Concept Review Committee (CRC), or as appropriate based on changes to the protocol made after concept approval.

vi. Detailed Schema
vii. Aims/Objectives

viii. Methodology

1. Characteristics of study population:
   a. Eligibility and ineligibility criteria (including non-patients and/or organizations as appropriate)*
   b. Source of study participants
   c. Sampling, recruitment, and retention procedures (include estimates of minority recruitment and plans to increase minority recruitment, including participation of institutions intended to boost minority recruitment). Studies involving non-patients (e.g. clinicians) or organizations should include recruitment plans for these individuals and/or organizations.
   d. Procedures for stratification (include stratification factors with definitions and justification for stratifying by these factors)

2. Plans for intervention:
   a. Detailed description of study design (e.g., randomized, quasi-experimental, case-controlled, observational)
   b. Detailed description of study intervention
   c. Schedule for administration of intervention (Agents – i.e. drugs and herbal/natural products – provide dose, schedule, and duration; other interventions – e.g. behavioral/organizational - provide details regarding implementation and any special training, facilities, and equipment). A training or procedure manual may be included as an appendix. Studies with practice level intervention should outline the training content.
   d. Schedule for adjustments to planned intervention related to side effects (if applicable)

3. Plans for data collection:
   a. Number and timing of contacts with participants including non-patients and organizations.
   b. Data to be collected at each contact
   c. Rules for missed contacts (if applicable)
d. Procedures to maximize response rates (if applicable)

e. Procedures for administration of instruments and follow-up (if applicable)

f. Procedures for collection of multiple levels of data (e.g. patient, non-patient, organization/practice) including qualitative data (if applicable) and a detailed description of how the study aims and its respective data collection activities build on one another.

ix. *Drug Distribution*

1. Plans for obtaining, storing, and distributing drugs and placebos. CAM agents must include information on testing of agent, product consistency etc.

x. Special instructions for the intervention, i.e., timing of administration, contraindications, etc.

xi. Study Calendar or Study Parameters Table outlining the tests and observations to be performed and the timing of them

xii. *Statistics*

1. Define stratification factors with justification

2. Specify procedures to be used for randomizing subjects to treatment (or placebo) arms

3. Definitions for primary and secondary endpoints; for observational studies, explanatory variables/composites.

4. Define study endpoints, how and when they will be measured.

5. Specify procedures to be used for assigning participants to intervention studies/trials. For observational studies describe statistical model and variables/composites used in the analysis.

6. Sample size calculation and planned accrual rate

   a. Information on the composition of the proposed study population (accrual targets). For studies accruing patients, include information on sex/gender and racial/ethnic group in the format as provided on the Document Submission Worksheet (DSW). Cancer care delivery studies accruing non-patients and/or organizations/practices should complete the appropriate sections of the DSW.
b. If the protocol is a NIH-defined Phase III trial (a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments), the investigator must address whether he/she expects to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The protocol must include one of the following:

i. Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR

ii. Plans to include and analyze sex/gender and or racial/ethnic subgroups when prior studies strongly support NO significant differences in intervention effect between subgroups, OR

iii. Plans to conduct valid analyses of the intervention effect in sex/gender and/or race/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups

7. Studies collecting multiple levels of data (e.g. patient, non-patient, organization/practice) including qualitative data (if applicable) must include detailed plans for data analysis, triangulation, and interpretation as appropriate.

8. Full plans for analyzing and interpreting results regarding the primary and secondary endpoints

9. Plan for missing data

10. Plans for addressing data limitations

xii. Adverse Event Reporting

a. Procedures to be used to report adverse events to the Research Base, NCI, and/or FDA

b. Use current version of the NCI Common Toxicity Criteria (CTC) (must indicate the version number in protocol)
xiii. Consent Form, Additional Supporting Documents, PRO Documents, and Recruitment Materials

Information on consent documents and templates are available at: http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm. When preparing informed consent documents for cancer care delivery protocols, investigators should consider whether the study includes non-patient participants and if it does, provide informed consent documents or request waivers of documentation of informed consent for these participants as appropriate. - See OHRP FAQs https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html

Items listed as part of the protocol (i.e. specified in the Table of Contents (TOC)) and attached as appendices must be resubmitted at each amendment and as a result will have the same version date as the protocol document. Additional supporting documents such as questionnaires, email invites, screening logs, although required to be submitted and reviewed at NCI during the initial protocol review, are not considered part of the protocol and should not be listed in the protocol’s TOC. Rather these additional documents should be submitted as supporting documents and be referred to by name in the protocol (e.g. questionnaire, survey, communications tools). Referencing the materials as supporting documents will minimize future amendments and reduce version date discrepancies. It is possible for additional supporting documents to have different version dates from the protocol. Different version dates would occur when there is either an update to the protocol or the supporting documents.

Translated copies of NCI CIRB-approved documents such as consent forms or recruitment materials, may be submitted by the Study Chair or Principal Investigator to the NCI CIRB. All NCI CIRB approved model consent documents will be translated into Spanish via the CTSU, approved by the CIRB and then posted with the trial documents on the CTSU website with the exception of the following:

1) Trials utilizing PRO documents (e.g., QoL forms)
   a. If the PRO element is mandatory and is only available in English, the eligibility criteria should specifically exclude non-English speaking patients. If the PRO is optional, completion of the PRO must be optional for all study participants.
   b. For validated instruments that are available in languages other than English, the CIRB’s approval of the English instrument as part of its review of a study is considered to extend to the validated translated versions. The protocol should indicate the languages in which the instrument is available, reference for the validation of the translated instrument, and provide investigators with information on how to obtain the translated instrument.

2) Recruitment materials
a. Sites requiring translation of recruitment materials will need to have them translated at the local level and submit them to the NCI CIRB for approval via the Study Specific Worksheet. Documents submitted to the NCI CIRB need to include the protocol version date (PVD) or version number that corresponds to the approved English version and a statement of accuracy referencing the PVD/version number.

b. Sites may obtain the CIRB-approved Spanish consent form from the CIRB tab on the CTSU website. In order to use the CIRB-approved Spanish consent form, the site must have its CIRB-approved consent form boilerplate language translated into Spanish and approved as part of the Signatory Institution Worksheet about Local context. PI’s and their research staff may develop materials specific to their site such as recruitment materials or additional information sheets. These materials are submitted to the CIRB for review and approval according to the description in 2a above.

IND/IDE Policy:

The following policy is for cancer prevention and control trials, supported and/or sponsored by NCI Community Oncology Research Program (including symptom management, prevention, comparative effectiveness, and others). Investigators are to follow the current Food and Drug Administration (FDA) guidance related to INDs (Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND and for IDEs (Device Advice: Investigational Device Exemption (IDE):

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf and

http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdvice/investigationaldeviceexemptionide/default.htm

For FDA approved agents or devices, the Study Chair must provide compelling information or data, in sufficient detail in a paragraph entitled IND Status within the protocol, to support the fact that the risks associated with the drug or device are not significantly increased in the study population and, therefore, an IND or IDE is not required. In addition to addressing the criteria that is listed in the FDA guidance documents, investigators should include references and discuss the evidence and any other information obtained in securing an agent for DCP studies in support of an exemption. Lacking sufficient safety information, DCP reserves the right to require that the investigator seek an IND/IDE exemption from the FDA. If the FDA determines that an IND/IDE is necessary to conduct a trial and requires changes to the protocol to obtain the IND, DCP will not approve the submitted protocol until the group/PI makes the required changes and obtains an IND/IDE or exemption status.

The FDA can review the protocol ONLY when it is ready for submission. Concepts or partially-completed protocols will not be reviewed by the FDA. Applications for IND/IDE status can be submitted to the FDA at the same time the new protocol is sent to DCP. The FDA has stated that IND/IDE status determination will be made in
30 days, with an email letter informing the sponsor or group/PI of the number or exempt status. The PI is responsible for providing the IND status to NCI DCP’s Protocol Information Office (PIO) to obtain approval to open a new protocol. The FDA’s letter of notification can then be submitted to the PIO for an approved protocol on hold or it can be incorporated into the appendix of a revised protocol if revisions are required by the DCP’s review committee.

For all IND-related questions, please contact the NCI DCP Community Oncology and Prevention Trials Research Group via email at ncorp@mail.nih.gov or phone 240-276-7050.

b. Protocol Review

NCI NCORP staff conduct reviews of all control/prevention and care delivery protocols. All input from NCI’s SSCs occurs during the concept review process.

The standing NCORP Protocol Review Committee (PRC) will be augmented as needed by invited reviewers inside and/or outside the NCI. The PRC chair conducts the reviews and is the principal contact with investigators regarding protocols under review.

Treatment and imaging clinical trials with embedded health related quality of life (HRQOL)/patient reported outcomes are reviewed at the protocol level by DCP and Division of Cancer Treatment and Diagnosis (DCTD) staff.

The protocol review will focus on the inclusion in the protocol of all information and procedures necessary for Sites to conduct a successful study. Specific attention is paid to responses to concerns of the SSC and/or NCORP Concept Review Committee conveyed to the Research Base at the time of concept approval. If the protocol differs from the concept in significant ways (e.g., change in endpoint, change in trial design, change patient population), the Protocol Review Committee may request the investigators submit a new concept.

Protocols using grant funding should include a cover letter outlining ways in which the protocol differs from the grant application (if applicable).

Since public funds are used to support Research Base studies sponsored under NCORP Cooperative Agreement, no Research Base study using funds supplied under the Cooperative Agreement can be opened without prior approval from the NCI/DCP as communicated in approval letters sent to the Research Base Chair directly from the NCI DCP Protocol Information Office. The Research Base also is not allowed to expend any NCI funds under this Cooperative Agreement to support any study disapproved by the NCI/DCP.

c. Review Outcome

DCP PIO will send all correspondence regarding protocol reviews by email to: 1) Principal Investigator of the Research Base, 2) Study Chair, and 3) one additional person designated by each Research Base to receive copies of correspondence related to all concepts and protocols under review at NCORP.
DCP PIO sends consensus summaries of protocol reviews within four weeks of the review meeting.

Protocol consensus summaries can take one of three forms:

1. **Approval on Hold**

   PRC has determined that the protocol is suitable for conducting a study in the NCORP network and that no further changes are required to the protocol at the present time. However, further reviews and/or approvals by other components of NCI are required before NCORP will issue a final approval. All NCORP protocols require approval by the NCI CIRB prior to final approval, consequently all initial decisions will be approval on hold to CIRB. Other examples include approval of plan for drug distribution for agents that will be distributed by NCI.

2. **Pending**

   The PRC had concerns regarding the study as explained in a consensus evaluation letter. Given these concerns, the protocol was not approved. Instead, the PRC gave the protocol a status of "pending" to indicate that approval of the protocol might be warranted if the investigators can satisfactorily address, within 60 days, the PRC's concerns and suggestions regarding changes to the protocol as outlined in the consensus evaluation. The deadline for resubmission will be included in the Consensus Evaluation Letter sent to the Research Base/Study PI.

3. **Disapproved**

   The PRC reserves the right to disapprove a protocol, particularly when the protocol differs significantly from the approved concept.

   If the PRC disapproves a protocol, the Research Base will receive a letter that states this decision and reasons for the decision.

   d. **After Approval**

   Research Bases must submit the activation date to PIO when the study opens. See page 1 for timelines and absolute dates which must be adhered to.

   The Research Base is responsible for communicating the results of the NCI/NCORP review/evaluation process to relevant Research Base committees and members.
The Cancer Prevention and Control PRC will assign credit for each control/prevention study at the time of protocol approval. Cancer care delivery protocols are not assigned credits.

V. Protocol Amendment Development, Review, and Approval

a. Types of Amendments

i. Scientific Amendments

Scientific amendments are those affecting the design or conduct of the study or those associated with safety of subjects. Examples of scientific changes include:

1. Change in eligibility criteria
2. Change in sample size
3. Change in study evaluation, design, or analysis
4. Change in drug information
5. Change in study chair
6. Change in the informed consent
7. Any change to protocol conducted under a DCP-sponsored Investigational New Drug Application IND.

ii. Administrative Amendments

Administrative amendments are those not affecting the design or conduct of the study or affecting safety of subjects. The following are examples of administrative changes:

1. Editorial changes only (that do not affect the design or conduct of the study and are not associated with safety of subjects)
2. Addition or deletion of participating organization(s) unless this is a ‘limited institution’ protocol
3. Change in name or contact information of study personnel (other than the study chair or principal investigator)

iii. Activation Amendments

Activation amendments are all amendments with changes in the protocol that occur between NCORP approval and activation. They can be either scientific or administrative. They can incorporate changes
requested or recommended in the NCORP protocol approval letter in addition to other changes the investigators want to make.

b. Amendment Content

i. A completed Document Submission Worksheet (DSW).

ii. A cover letter must provide the rationale and scientific justification for each scientific change and an assessment of how that change will affect the conduct, outcome, and interpretation of the study.

iii. All changes (scientific and administrative) must be described with justification in a point-by-point format (Change from/Change to) and the changed protocol page(s) and section number(s) should be referenced.

iv. If an amendment will include both scientific and administrative changes, separate them within the amendment. Alternatively, submit separate amendments composed entirely of administrative changes or scientific changes.

v. A new version date on the title page of protocol. The version date must be current and different from any previous version of the protocol. The version date of the protocol, informed consent form and items listed as part of the protocol (i.e. specified in the Table of Contents (TOC)) and attached as appendices must match. If multiple dates are listed, one date must be clearly labeled NCI Version Date.

vi. A tracked change copy of the revised protocol, consent document, and items listed as part of the protocol clearly indicating newly added text (e.g. redlined) and deleted text (e.g. strikeout), must be attached.

vii. A clean copy of the revised protocol with consent document and items listed as part of the protocol.

viii. Any additional supporting documents not listed in the TOC that have been revised/amended should be submitted with clean and track change versions as well as updated version dates on the documents. NOTE: These documents do not have to be submitted unless they have been revised/amended.

c. Amendment Submission

i. All documents must be submitted electronically to the NCI DCP Protocol Information Office (NCI_DCP_PIO@mail.nih.gov).

ii. The Document Submission Worksheet must accompany every amendment and are available on the DCP PIO web page at:
d. Amendment Review

Any change to the protocol document subsequent to its approval by NCI NCORP staff must be submitted to NCI DCP’s Protocol Information Office (PIO) in writing for review and approval by DCP prior to implementation of the change.

The NCI NCORP staff will review all amendments within 2 weeks of receipt in DCP PIO.

e. Review Outcome

The NCI NCORP staff will determine one of two outcomes for each submitted amendment: approval or disapproval. No partial approvals are allowed. All changes requested require approval for the amendment to receive approval.

PIO will convey the results of the review to the Research Base chair and the Study Chair in a response letter within 2 weeks of review. The response letter will include reasons for disapproval for all disapproved amendments. The Research Base can revise disapproved amendments in response to NCI NCORP comments and resubmit as new amendments.

All study amendments require approval by the NCI CIRB prior to final approval of the amended study protocol document by NCI NCORP staff.

NOTE: Research Bases must submit an Activation Notice for protocols that are activated as approved.

NOTE: In concordance with NCI CTEP guidelines, NCI DCP and DCCPS will not issue or approve any waivers for protocol deviations. If a change to an NCI DCP or DCCPS-approved protocol is necessary, the Study Chair may submit an amendment to the protocol. Please see the following URL for further information: