Part 3: Development of Concepts, Protocols, and Amendments for NCORP Cancer Prevention, Control, or Screening/Post-treatment Surveillance Clinical Trials or Cancer Care Delivery Research

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 for protocol development and for overseeing conduct of approved studies. The Research Base PI should contact the DCP Program Director to discuss any DCP NCORP studies that may require cross Network accrual.

Study concepts and protocols should be developed, submitted, and implemented in accordance with DCP 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 and Research Base 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. These timelines should meet the following NCI requirements: 1) revised concept: 30 days; 2) approved concept to protocol development: 90 days; 3) approved protocol to study activation: one year. Exceptions may be requested in writing including justification for the request. If an exception is not received on or before the one-year anniversary of the approved protocol, a new concept will need to be submitted.

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. Studies without a specific hypothesis and robust statistical analysis plan will not be approved. Although optional collection of biospecimens without an approved research plan may be approved for a trial, use of the specimen must be approved by DCP and must be based on studies with specific hypotheses and statistical analysis plans (i.e., biospecimens cannot be "reserved" for future unspecified research without a subsequent study proposal being reviewed and approved).

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

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

Federally funded studies are not required to undergo Steering Committee concept review because they have already undergone peer review. Such studies may come to the attention of NCORP Research Bases and NCI Program Directors without full consideration of feasibility, budget planning, and overlap with open or planned studies. Making necessary adjustments can create delays in study implementation that are inconsistent with the goals of clinical trial stewardship established by the NIH. (http://jamanetwork.com/journals/jama/fullarticle/2553888?guestAccessKey=554e0981-9434-45f2-b122-d0e673cd1182).

Thus, 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 research grant applications (e.g. R series, P01s) that propose to use the NCORP network for study implementation. 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 through the NCORP network.

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. Staff in the NCI Division of Cancer Control and Population Sciences Healthcare Delivery Research Program 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. NIH applicants are encouraged to request assignment of their application to the appropriate Scientific Program Director. (For more information go to: (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-008.html)

Prior to submission of a research grant application

Interested investigators are required to contact NCI (NCORP) Program Directors or the Research Bases to determine if the concept 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 the Research Base that is best suited for the concept and provide contact 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 to a federally funding agency **at least four weeks prior to submission.**

Regardless of the first point of contact, the NCORP Research Base 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 studies, and 3) confirmation that the study fits within the cancer control/prevention, symptom management, care delivery or disparities NCORP research scope. In advance of submitting the grant application, it is expected that the PI and Research Base have communicated with NCORP sites regarding interest and participation in the study.

Post study section review and award

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**. This 90-day requirement will apply to studies that are funded after April 1, 2017. 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 NCI Protocol Review Committee. Once the full protocol is approved by the NCORP Protocol Review Committee and NCI Central IRB, the PI and Research Base may proceed with conducting the federally funded study within NCORP

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 or 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 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.**

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 studies, and 3) confirmation that the study fits within the cancer control/prevention, symptom management, care delivery or disparities NCORP research scope.

When an LOI is selected to be submitted as a full application. The NCORP Program Director will be notified that an application is being submitted and updated on any changes/revisions to study design. All of this must take place at least four weeks before submission of a full application.

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 NCORP Steering Committee or the NCORP Concept Review Committee.
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 NCORP Protocol Review Committee **within 90 days.**

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

II. Cancer Care Delivery Research Concept Preparatory Work

As a Research Base begins to develop a concept, they may embark on preparatory work with a small number (1-2) NCORP sites to design a research concept or to assess the feasibility of conducting a study. Examples could be determining if electronic medical record data can be linked with financial data at sites with a specific medical record system or extracting specific data elements from specific systems. If data are gathered, they may only be used for descriptive analyses in NCORP-related concept and grant applications.

The NCI is asking that prior to starting this work Research Bases provide their CCDR Program Director the following information about these preparatory projects. The purpose of this request is to: manage possible overlap, understand the workload at NCORP sites, facilitate early identification of potential collaborators at other Research Bases and allow for early NCI input. The information you provide will be kept confidential within NCI unless you pre-approve its release. (This information is only needed for preparatory work that Research Bases are doing at NCORP sites, not all concept development work limited to the Base.)

- Name of Research Base:
- Name of Project:
- Purpose or goal of the project:
- Rationale/importance of the topic:
- Selected NCORP Sites:

Provide a brief summary/abstract (maximum one page) of the project including: description of the project, outline of the project plan, estimated duration of the project, estimated time required at site to do the project and how this work will contribute to concept development.

III. Study Concept Development, Review, and Approval

A concept should have been reviewed and approved by all necessary components at the Research Base before submission to DCP. Although not a full protocol, the concept should provide sufficient information to establish the scientific rationale for the proposed study, describe the study methodology, and support the feasibility of conducting a successful study. 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.

a. Concept Content

Although DCP does not mandate the use of a set template for concepts, it does require specific information to be included in all study concepts. This information includes:

i. 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 clinical trial 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)

ii. 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 the delivery of cancer care.

g. Why is the study design the best way to make this contribution?

h. Include information about the study population and intervention; the study populations could include patients, clinicians and/or organizations.

i. How will this research affect subsequent research?

j. How will the research inform patient care/improve patient outcomes?

k. 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 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 data or information to support the anticipated accrual or participation rate

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, 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 availability of organizational, financial and other administrative data

iii. Study objective(s)

iv. 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)

6. Detailed description of the outcome measure(s) used included reliability and validity for the disease and patient population under study

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

    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

8. Detailed methodology and explanation regarding how sub-studies (if applicable) will contribute useful information relevant to specified hypotheses.

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

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

v. Statistical analyses plan, including:

1. Hypothesis
2. Define study endpoints including how and when they will be measured
3. Sample size calculation
4. Estimated effect size
5. Justify choice of effect size and include power analysis
6. Estimate of drop-outs/loss to follow-up
7. Plan for handling missing data
8. Plan for analyzing the primary endpoint

9. Timing of data collection

10. Analysis plan for all sub-studies (if applicable)

11. Plans for addressing data limitations (if applicable)

12. Description of how the statistical significance translates to a significant difference clinically.

b. Concept Submission

Investigators are encouraged to communicate with DCP Program Directors when developing concepts for clinical trials and HRQOL studies and with the DCCPS Program Directors when developing concepts for cancer care delivery studies. However, the final concept document and any relevant accompanying materials must be submitted to NCI DCP's Protocol Information Office (PIO) electronically at NCI_DCP_PIO@mail.nih.gov. All new concepts must be accompanied by a fully completed Document Submission Worksheet (DSW). Specific instructions and the latest version of forms and templates can be found and downloaded from http://prevention.cancer.gov/clinicaltrials/management/pio/instructions. Subsequent submissions for the same concept also require the submission of the DSW.

In some circumstances investigators at Research Bases may wish to utilize the NCORP Network to support a study that has received approval through a peer review process and funding from a governmental or nongovernmental source other than NCORP grant (e.g., an R01, PCORI). These studies may or may not need to be submitted as concepts (see Non-Federally Funded NCORP Study Proposals and Federally Funded NCORP Studies above). All full protocols are subject to DCP review and approval (see Protocol Development, below).

c. Concept Review

NCI/DCP staff is responsible for facilitating the review process for proposed clinical trials and NCI/DCCPS staff is responsible for facilitating the review process for proposed cancer care delivery research 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 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 revise/resubmit). Prior to the review meeting of the SSC, the DCP Concept Review Committee for clinical trials and the DCCPS Concept Review Committee for cancer care delivery research reviews the concept and submits a review to the Chairs of the appropriate SSC. If NCI has not established a SSC with purview over a concept (e.g. a prevention or screening study), the DCP or DCCPS Concept Review Committee will be enhanced with extramural reviewers and will provide the sole review of the concept.

Prior to review by either a SSC or a Concept Review Committee, NCI program staff reviews each submitted concept to determine that the proposed research study is within the scope of NCORP research and that the concept document includes all required components and is not duplicative of existing studies. 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.

The review process is described in detail below under "NCI/DCP and NCI/DCCPS staff Responsibilities".

IV. Protocol Development, Review, and Approval

After receiving approval for a concept from the Division of Cancer Prevention, the Research Base should begin to formulate a protocol to conduct the proposed research. The protocol is a document that can be used by clinicians, research staff, Research Base, NCI, and others associated with the research to conduct the study. Because most elements of the concept are incorporated into the protocol, there is some redundancy. Because the utility of research and the scientific basis for conducting a study will change over time, concept approval expires on the due date included in the approval letter or within 3 months. If the Research Base intends to submit a protocol that will be received later than the due date, it should contact the DCP PIO for guidance. The Cancer Prevention and Control Protocol Review Committee will assign credit for each study at the time of protocol approval.

In some circumstances investigators may want to utilize the NCORP network for accrual to a study that has received federal funding (e.g. R01) outside of the NCORP UG1 mechanism. These studies are submitted to the DCP PIO as protocols (not concepts) and are reviewed for feasibility of conduct within NCORP and the budget is reviewed for duplication. The protocol is not reviewed scientifically nor reviewed by a SSC. (See Federally Funded NCORP Studies 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/howtomarketyourdevice/investigationaldeviceexemptionide/default.htm

For FDA approved agents or devices, the Principal Investigator (PI) 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 Community Oncology and Prevention Trials Research Group, DCP via email at ncorp@mail.nih.gov or phone 240-276-7050.

a. Protocol Content

The protocol must include:

i. Document Submission Worksheet:

All new protocols must be accompanied by the Document Submission Worksheet (DSW). All relevant sections of the DSW must be completed. The latest version of the DSW as well as other PIO protocol-related forms can be downloaded from: http://prevention.cancer.gov/clinicaltrials/management/pio/instructions. Subsequent submissions for the same concept 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. Each proposed component (e.g., base intervention, bio-specimen, advanced imaging, 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.

Those study components that specify the funding source as "**federal**" will be reviewed by the DCP 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.
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.

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.

iii. *Cover Letter*

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

If the protocol is for a study that will receive Government funding other than that 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.

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 protocol 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. 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, 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

    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)

    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 – require dose, schedule, and duration; other interventions – e.g. behavioral/organizational - require details regarding implementation and any special training, facilities, and equipment). A training or procedure manual may be included as an appendix.

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

   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)

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.

2. Special instructions for the intervention

x. *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 DCP Document Submission Worksheet

    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

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

xi. *Adverse Event Reporting*

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

2. Use current version of the CTC (must indicate the version number in protocol)

xii. *Consent Form*

Information on consent documents and templates are available at: http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm.

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 English only patient reported outcomes documents (e.g., QoL forms)

a. Non-English speaking patients are generally not eligible for these trials and therefore translating the consent document is not appropriate.

2) CCDR studies focused on the provider/clinician or system level

a. Sites requiring translation of these documents 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.

The Research Base submits the protocol documents to the Program and Information Office (PIO) of DCP. Research Bases should submit protocols electronically to NCI_DCP_PIO@mail.nih.gov. Attachments that are difficult to send electronically may be sent by mail:

U.S. Mail Address:

Protocol Information Office
Division of Cancer Prevention
National Cancer Institute
9609 Medical Center Drive, RM 5E526 MSC 9786
Bethesda, MD 20892-9786

Commercial Delivery Address:

Protocol Information Office
Division of Cancer Prevention
National Cancer Institute
9609 Medical Center Drive, RM 5E526 MSC 9786
Rockville, MD 20850

b. Protocol Review

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.

Purpose of the Review

The protocol review will focus on the inclusion in the protocol of all information and procedures necessary for conducting a successful study. Specific attention is paid to responses to concerns of the SSC and/or DCP Protocol 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 eligibility criteria), the Protocol Review Committee will review all aspects of the protocol to determine that the study has scientific validity and is feasible to conduct in the NCORP network. If the changes are of sufficient significance the Protocol Review Committee may also request the investigators to submit a new concept.

c. Review Outcome

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

Protocol review letters can take one of four forms:

1. Protocol Approved

   The Protocol Review Committee (PRC) has determined that the protocol is ready for use in the NCORP network. The approval letter includes the credit assignment for the protocol (not applicable for cancer care delivery research).

2. Protocol 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 DCP will issue a final approval. Examples include need for approval by a Central IRB or approval of plan for drug distribution for agents that will be distributed by NCI.

3. Revise and Resubmit

   The PRC has identified potentially remediable problems that the investigators should review and comment on. These problems usually require revisions to the protocol. DCP/DCCPS will send a review letter that states this decision and includes a list of all issues that require response by investigators.

4. Protocol Disapproved

   NOTE: Protocol disapproval is not common because approval of the concept indicated NCI's support for the proposed research. However, the Cancer Prevention and Control Protocol Review Committee and/or the DCCPS Cancer Care Delivery Research Protocol Review Committee reserve the right to disapprove a protocol, particularly when the protocol differs significantly from the approved concept.

   If DCP disapproves a protocol, it will send a review letter that states this decision and provides reasons for the decision.

   All study protocols require approval by the NCI CIRB prior to final approval of the study protocol document by NCI/DCP. (NCI CIRB approval does not apply to cancer care delivery studies.)

d. After Approval

Research Bases must submit the activation date to PIO when the study opens.

The Research Base is responsible for communicating the results of the NCI/DCP review/evaluation process to relevant Research Base committees and members.

All Cancer Prevention and Control study protocols require approval by the NCI CIRB prior to final approval of the study protocol document by NCI/DCP. There is no CIRB for Cancer Care Delivery Research. All Cancer Care Delivery Research study protocols must be reviewed at the local level, Research Bases and NCORP sites are responsible for obtaining local IRB/human subjects clearance.

V. Protocol Amendment Development, Review, and Approval

a. Types of Amendments

1. Scientific Amendments

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

ii. Change in eligibility criteria

iii. Change in sample size

iv. Change in study evaluation, design, or analysis

v. Change in drug information

vi. Change in study chair or PI

vii. Change in the informed consent

viii. Any change to protocol conducted under a DCP-sponsored Investigational New Drug Application IND.

2. 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:

i. Editorial changes only (that do not affect the design or conduct of the study and are not associated with safety of subjects)

ii. Addition or deletion of participating organization(s) unless this is a 'limited institution' protocol

iii. Change in name or contact information of study personnel (other than the study chair or principal investigator)

3. Activation Amendments

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

b. Amendment Content

i. 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.

ii. 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.

iii. 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.

iv. A marked copy of the revised protocol and consent document, clearly indicating newly added text (e.g. redlined) and deleted text (e.g. strikeout), must be attached

v. A clean copy of the revised protocol with consent document

vi. Title page of protocol indicates the date of the protocol amendment; if multiple dates are listed, one date must be clearly labeled NCI Version Date.

vii. Document Submission Worksheet (DSW)

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: http://prevention.cancer.gov/clinicaltrials/management/pio/instructions.

iii. Attachments that are difficult to send electronically may be sent by mail:

U.S. Mail Address:

Protocol Information Office
Division of Cancer Prevention
National Cancer Institute
9609 Medical Center Drive, RM 5E512
Bethesda, MD 20892-9786

Commercial Delivery Address:

Protocol Information Office
Division of Cancer Prevention

National Cancer Institute
9609 Medical Center Drive, RM 5E512 MSC 9786
Rockville, MD 20850

Questions regarding amendment submission procedures may be directed to the PIO at (240) 276-7130 or NCI_DCP_PIO@mail.nih.gov .

d. Amendment Review

All scientific amendments must receive approval from DCP prior to implementation.

e. Review Outcome

The PRC will determine one of two outcomes for each submitted amendment: approval or disapproval. All changes requested require approval for the amendment to receive approval.

The response letter will include reasons for disapproval for all disapproved amendments. The Research Base can revise disapproved amendments in response to PRC's comments and resubmit as new amendments.

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: http://ctep.cancer.gov/protocolDevelopment//policies_deviations.htm .

NCI/DCP and NCI/DCCPS Staff Responsibilities

NCI/DCP and DCCPS staff will be closely involved in the development of NCORP studies. NCI/DCP and DCCPS staff will communicate with NCORP Research Bases during all stages of study development. All concepts for cancer prevention, control, and care delivery studies must be submitted to the NCI DCP Protocol Information Office (PIO) at: NCI_DCP_PIO@mail.nih.gov .

The general process for receiving approval of proposed studies is as follows:

- A concept is submitted for review to the NCI DCP Protocol Information Office (PIO);
- If the concept is approved, a protocol document with an informed consent document is submitted for review to the DCP PIO.

NCI/DCP and DCCPS staff is responsible for conducting the review process for concepts, protocols, and amendments as described herein. Review from NCI's SSCs is provided only

during the concept review process. Protocol reviews occur within 4-6 weeks after receipt of protocol. This allows time to schedule reviewers and also gives reviewers adequate time to review the protocol.

I. Concept Review

NCI program staff reviews each submitted concept to determine that the proposed research is relevant to cancer prevention, control, and/or care delivery and that the concept includes all required components. 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.

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, and the Cancer Care Delivery Research Scientific Steering Committee. The Symptom Management and Quality of Life Steering Committee evaluates symptom management intervention clinical trial concepts conducted through NCORP for scientific merit. The Clinical Imaging Steering Committee evaluates large primary advanced imaging studies for scientific merit. The Cancer Care Delivery Research Scientific Steering Committee will evaluate cancer care delivery research studies for scientific merit.

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. The SCC does not review non-randomized, pediatric and longitudinal studies.

- Concepts related to cancer screening and prevention are evaluated by the Division of Cancer Prevention (DCP) Concept Review Committee (CRC), with ad hoc extramural scientific reviewers, as needed.

- Concepts related to cancer surveillance are evaluated and prioritized by the Clinical Imaging Steering Committee or by the Division of Cancer Prevention (DCP) Concept Review Committee (CRC), with ad hoc extramural scientific reviewers, depending on the modality under investigation.

- Concepts related to cancer care delivery are evaluated by the DCCPS CRC, with assistance from external reviewers 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.

This triage process for review and prioritization of proposed concepts is subject to change (i.e., NCI may choose in the future to institute specific SSCs for cancer screening and prevention studies.

Prior to presentation at a SSC, the DCP CRC or DCCPS CRC evaluates all NCORP concepts for the scientific rationale, programmatic relevance; potential impact on cancer prevention, control and care delivery; priority; design; statistical requirements; plans for conducting the proposed study; the feasibility and appropriateness of the research for use by NCORP Community Sites or in a community setting; 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; and, where applicable, the availability of investigational agents.

The DCP CRC or DCCPS CRC submits a review of the concept to the Chairs of the SCC. This review is one of several reviews considered by the SSC.

Several NCI/DCP and DCCPS staff are full members of specific SSCs relevant to cancer control and cancer care delivery research. Designated NCI staff are voting members of the SSCs. 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 change in the policies and procedures of 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 Associate Director, NCI/DCCPS 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.

b. Review Outcome

The appropriate NCI SSC (or the DCP/DCCPS 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 as written or with recommendations*** – The SSC, DCP CRC OR DCCPS 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; NCORP Research Base must respond to these comments and recommendations in a cover letter accompanying the protocol.

2. ***Revise and Resubmit*** – The SSC, DCP CRC OR DCCPS CRC has determined that the concept requires additional information or has design issues that can be addressed within 60 days and requires the investigators to address the itemized concerns in a cover letter that accompanies a

revised concept. This option can also indicate that the SSC or DCP CRC has determined that the concept as written lacks adequate scientific justification or is not feasible to conduct, but that relatively modest changes to the study design might address these concerns. The deadline for resubmission will be included in the Consensus Evaluation letter sent to the Research Base and the Study PI(s). Only one revision of a concept is allowed.

3. ***Disapproved*** – In the judgment of the SSC, DCP CRC OR DCCPS 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.

   All concepts that are prioritized for further development by SSCs must undergo expedited review by DCP or DCCPS before final approval is given in order to ensure significant safety, feasibility, and regulatory issues are adequately addressed, including ensuring that there are adequate resources available to NCORP to conduct the study, and to prevent duplication.

II. Protocol Review

DCP/COPTRG will assist the Research Bases in clinical trial design to develop a mutually acceptable protocol compatible with the research interests, capabilities, and needs of the Research Base, its affiliates, and NCI.

DCP conducts the only review of clinical trial protocols. All input from NCI's SSCs occurs during the concept review process. Protocol reviews occur within 4-6 weeks after receipt of protocol. This allows time to schedule reviewers and also gives reviewers adequate time to review the protocol.

DCCPS will assist the Research Bases in study design to develop a mutually acceptable protocol compatible with the research interests, capabilities, and needs of the Research Base, its affiliates, and NCI.

DCCPS will conduct the only review of cancer care delivery protocols. All input from NCI's SSCs occurs during the concept review process. Protocol reviews occur within 4-6 weeks after receipt of protocol. This allows time to schedule reviewers and also gives reviewers adequate time to review the protocol.

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 external HRQOL experts.

a. Review Group

The standing Cancer Prevention and Control Protocol Review Committee will be augmented as needed by invited reviewers inside and/or outside the NCI. The reviewers for the protocol often include the same reviewers as those for the concept, but this is not always the case. The chair of the Cancer Prevention and Control Protocol Review Committee conducts the reviews and is the principal contact with investigators regarding protocols under review.

The standing DCCPS Cancer Care Delivery Protocol Review Committee will be augmented as needed by invited reviewers inside and/or outside the NCI. The reviewers for the protocol often include the same reviewers as those for the concept, but this is not always the case. The chair of the DCCPS Cancer Care Delivery Protocol Review Committee conducts the reviews and is the principal contact with investigators regarding protocols under review.

b. Review Purpose

The protocol review will focus on the inclusion in the protocol of all information and procedures necessary for conducting a successful study. Specific attention is paid to responses to concerns of the SSC and/or DCP/DCCPS conveyed to the Research Base at the time of concept approval. Since the rationale for the study and the broad study design have already received, these are not generally the focus of a protocol review. However, if the protocol differs from the concept in significant ways (e.g. change in endpoint, change in participant eligibility criteria), the Protocol Review Committee (PRC) will review all aspects of the protocol to determine that the study has scientific validity and is feasible to conduct in NCORP network. If the changes are of sufficient significance the Protocol Review Committee may also request the investigators to submit a new concept.

If the protocol is for a study that will receive government or non-government funding other than that in NCORP grant and has received approval from a peer review panel, the Division of Cancer Prevention considers the earlier peer review as a concept approval. Protocol review for these studies is similar to reviews for other NCORP protocols, but the Protocol Review Committee will also evaluate feasibility and appropriateness of the study for use in the NCORP network.

c. Review Outcome

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

Protocol review letters can take one of four forms:

1. **Protocol Approved**
   The PRC has determined that the protocol is ready for use in the NCORP network.

The approval letter includes the credit assignment for the protocol, when applicable.

2. **Protocol Approval on Hold**
   The 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 DCP will issue a final approval. Examples include need for approval by a Central IRB or approval of plan for drug distribution for agents that will be distributed by NCI.

3. **Revise and Resubmit**
   The PRC has identified potentially remediable problems that the investigators should review and comment on. These problems usually require revisions to the protocol. DCP/DCCPS will send a review letter that states this decision and includes a list of all issues that require response by investigators.

   Investigator should respond to all the PRC's comments, change the protocol where necessary, and resubmit to the NCI DCP Protocol Information Office as a revised protocol for further review. The review letter includes a date by which the revised protocol is due to DCP.

4. **Protocol Disapproved**
   NOTE: Protocol disapproval is not common because approval of the concept indicated NCI's support for the proposed research. However, the Cancer Prevention and Control Protocol Review Committee and/or the DCCPS Cancer Care Delivery Research Protocol Review Committee reserve the right to disapprove a protocol, particularly when the protocol differs significantly from the approved concept.

   If DCP disapproves a protocol, it will send a review letter that states this decision and provides reasons for the decision.

   All study protocols require approval by the NCI CIRB **prior** to final approval of the study protocol document by NCI/DCP. (NCI CIRB approval does not apply to cancer care delivery studies.)

III. Amendment Review

Any change to the protocol document subsequent to its approval by DCP 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. Additional information on the procedures for protocol amendment can be found in Section IV above under Research Base Responsibilities and in the Investigator's Handbook.

The Cancer Prevention and Control Protocol Review Committee and for cancer care delivery research, the DCCPS Cancer Care Delivery Research Protocol Review Committee, will review all amendments within 2 weeks of receipt in DCP PIO. Research Bases will receive a response within 2 weeks after review.

The PRC will determine one of two outcomes for each submitted amendment: **approval** or **disapproval**. All changes requested require approval for the amendment to receive approval. It 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 PRC's comments and resubmit as new amendments.