**National Institutes of Health**

**National Cancer Institute**

**Division of Cancer Prevention**

**US-Latin American-Caribbean HIV/HPV Cancer Prevention Clinical Trials Network (ULACNet)**

**PROTOCOL TEMPLATE**

INSTRUCTIONS

The protocol template is a tool to facilitate rapid protocol development. It is not intended to supersede the role of the Protocol Principal Investigator in the authoring and scientific development of the protocol. It contains the language required in protocols submitted to the National Cancer Institute (NCI) Division of Cancer Prevention (DCP). Please modify all sections as necessary to meet the scientific aims of the study and development of the protocol. For ULACNet, a **Partnership Center** is a collaboration between a research institution in the United States as the **Lead Academic Organization (LAO)** and **Affiliate Organizations (AOs)** in the US and low- and middle-income countries (LMICs) in the Latin American and Caribbean (LAC) region.

1. An “administratively complete” initial protocol submission must include the following components:
	1. **ULACNet Protocol Submission Worksheet (PSW):** This document contains prompts for required administrative information. The PSW is required for all protocol submissions including the original protocol, revisions, and amendments. It must match the version and date of the other documents submitted.
	2. **Protocol:** The template document attached to these instructions provides standard language plus instructions and prompts for information required in each ULACNet protocol. Please ensure the current version of the template always is used for protocol development.
	3. **Informed Consent/Assent Form(s):** Please use the informed consent (IC) or informed assent (IA) templates provided as a guideline and include any other sections required by your institution. Only the English version of IC/IA is required. Note: The IC (and IA if applicable) and Protocol must have the same date and version number.
	4. **IRB/Ethics Board Approval:** This may be pending during first protocol submission, but the award prohibits expending human subject funds before IRB approval. IRB approval must be received from the US-based institution and one international site for the trial to be “open to accrual”. All other international site IRB/ethics board approvals must be submitted as received.
	5. **Recruitment Materials:** Collection is for recruitment repository only. They will not be translated. NCI review will not occur.
	6. **Any other study related documents as applicable.**
2. All subsequent submissions (protocol revisions and amendments) must include:
3. **Protocol Submission Worksheet (PSW)**
4. **Cover Letter:** The cover letter must include a point-by-point response to each item listed in the concurrence review or requested amendments.
5. **Tracked Changes Version of Protocol/IC/IA if applicable**
6. **Clean Copy Version of Protocol/IC/IA if applicable**
7. **Updated Additional Study-Related Documents:** Include changes resulting from a protocol revision or amendment.

“Administratively Incomplete” submissions will be returned to the Partnership Center for completion. The review process will begin following receipt of an administratively complete submission.

1. Formatting
2. *All Protocol Template instructions and prompts are in italics*. *Italicized information should be deleted prior to submitting the protocol to DCP.*
3. Please note that the Protocol Template has built-in styles for headings levels 1–4 (Level 1 Heading – Level 4 Heading). These heading styles will automatically update the Table of Contents (TOC) and convert to Bookmarks in a final PDF protocol document. **Please retain the heading styles and do not edit the TOC manually.**
4. Indicate changes using the ‘tracked changes’ function, highlighting, or underlining new or modified text in protocol revisions or amendments to facilitate the review process.
5. Wherever possible, please use the date format: day month year and write out the month (e.g., 05 June 2020).
6. Please update the header of this template document before submission with the protocol number and protocol version number and date. Please delete the footer (ULACNet protocol Template version and date) but please retain the page numbers.
7. DCP terminology for changes to protocol:
	1. Changes made prior to the initial DCP study approval are “**Revisions**”. Each submission of the protocol prior to DCP approval is documented with a whole number for the version number (i.e., 1.0, 2.0, 3.0).
	2. Changes made after DCP approval are “**Amendments**”. Each amendment is documented with a decimal number with the base version number that was approved (i.e., 3.1, 3.2, 3.3).
8. Submission:

All document submissions must be sent electronically ***both*** to the DCP Protocol Information Office mailbox (NCI\_DCP\_PIO@mail.nih.gov) ***and*** the ULACNet mailbox (ULACNet@mail.nih.gov). Documents submitted elsewhere will not be accepted for review.

**Questions:** Contact ULACNet at (240) 276-7532 or e-mail ULACNet@mail.nih.gov

# COVER PAGE

**DCP Protocol #:** *This number will be assigned by DCP according to the ULACNet protocol naming convention described in the ULACNet Program Guidelines. The DCP protocol number must appear on all protocol document versions and all communication to DCP. (ULACNet-XXX)*

**Local Protocol #:** *Insert your local protocol # for this study. If a local protocol number has not been assigned, indicate ‘pending’. DEFINITION: The local protocol number is assigned by the Partnership Center according to local institutional conventions.*

**US-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network (ULACNet)**

**Protocol Title: *Title of Protocol***

**ULACNet Partnership Center Name: *Name of ULACNet Partnership Center***

**Lead Academic Organization (LAO):** *Name of Organization (add CTEP code)*

**Contact Principal Investigator:** *Name of Contact Principal Investigator of the Partnership Center*

*Division/Department*

 *Address*

 *Address*

 *Telephone (+country code – area code – phone number)*

 *E-mail address*

**US/LAC Affiliate Organization (AO):** *Name of Organization (select US or LAC) (add CTEP code)*

**Protocol Principal Investigator:** *Name of Protocol Principal Investigator*

 *Division/Department*

 *Address*

 *Address*

 *Telephone (+country code – area code – phone number)*

 *E-mail address*

**US/LAC Affiliate Organization (AO):** *Name of Organization (select US or LAC) (add CTEP code)*

**Investigator:** *Name of Investigator*

 *Division/Department*

 *Address*

 *Address*

 *Telephone (+country code – area code – phone number)*

 *E-mail address*

**US/LAC Affiliate Organization (AO):** *Name of Organization (select US or LAC) (add CTEP code)*

**Investigator:** *Name of Investigator*

 *Division/Department*

 *Address*

 *Address*

 *Telephone (+country code – area code – phone number)*

 *E-mail address*

**US/LAC Affiliate Organization (AO):** *Name of Organization (select US or LAC) (add CTEP code)*

**Statistician:** *Name of Statistician*

 *Division/Department*

 *Address*

 *Address*

 *Telephone (+country code – area code – phone number)*

 *E-mail address*

**Funding Sponsor Organization:**National Cancer Institute

**Program Scientist:**  Vikrant Sahasrabuddhe, MBBS, MPH, DrPH

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 ULACNet@mail.nih.gov

***NOTE: If this is a multi-institution study:***

1. ***The protocol title page(s) must include the name and address of the LAO and all AOs participating in the study.***
2. ***The protocol title page(s) must include the names of all co-investigators, the division/department at their institution, and their address, telephone number, and e-mail address.***
3. ***Indicate non-accruing sites (LAO/AO) with an asterisk and an associated footnote (e.g., “No participant accrual occurs at this site”).***

**Investigational Agent(s):** *Investigational Agent(s) Name(s) or N/A if not applicable*

**Supplier**: *Supplier Name or N/A if not applicable*

**IND/IDE Sponsor:** *IND/IDE Sponsor or N/A if not applicable*

**IND/IDE Number:**  *IND/IDE Number* *or N/A if not applicable*

**NIH Grant Number:** U54CAXXXXXX

**Protocol Version and Date:** Version X, dated DD-Month-20YY

**Version Change Log (for Amendments, after initial NCI DCP Approval)**

**Summary of Substantive Changes from Previous Version:**

|  |  |  |
| --- | --- | --- |
| Version Number | Version Date | Summary of Substantive Changes |
|  |  |  |
|  |  |  |

# SCHEMA

*Please provide a schema for the study.*

*The schema diagram provides a quick “snapshot” of the study and ideally be limited to 1 page, with adequate level of detail needed to convey an overview of the study design.*

**Protocol Title: *Title***

**Screening Visit:** *Describe the study population, Obtain informed consent. Screen potential participants by inclusion and exclusion criteria. Specify target sample size.*

**Enrollment visit:** *List major data points to be collected including any clinical assessments, specimens to be collected, examinations/imaging/assays to be performed, questionnaires to be completed, etc. at baseline*

**Randomization:** *Briefly list the process for randomization (if applicable)*

**Investigational Agent(s) or Screening/Diagnostic Tests:** *Describe the investigational agent(s) or the screening/diagnostic tests (as appropriate) to be administered in the protocol*

**Follow-up Visits**: *Indicate visit frequency, timepoints, and follow-up assessments/specimens to be collected, examinations/imaging/assays to be performed, questionnaires to be completed*

**Endpoints:** *List the major endpoints*

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 *1. Select the TOC by highlighting it.*

 *2. Right-click on the highlighted TOC. You will see a dialogue box asking if you want to update the whole table or just the page numbers.*

 *3. Choose update page numbers.*

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# 1. OBJECTIVES

*Study objectives are concise statements of the primary and secondary clinical and statistical questions that the study is designed to answer. Each objective should be stated as specifically and succinctly as possible. Both primary and secondary hypotheses must relate to the hypotheses presented in the rationale (section 2.3) and should be consistent with the objectives described in the statistical section (section 13). Clearly differentiate between primary and secondary objectives. Number the objectives in order of priority.*

1.1 Primary Objectives – *Insert primary protocol objective.*

1.2 Secondary Objectives – *Insert secondary protocol objectives, if pertinent.*

# 2. BACKGROUND

## 2.1 Study Disease

*Please provide background information on the study disease. (May not be applicable in phase 1 trials).*

## 2.2 Study Agent

*Please provide background information on the study agent, if applicable, including information to support safety issues and the rationale for the study dose and duration of exposure.*

## 2.3 Rationale

*Please provide the background rationale for evaluating this agent/intervention/screening method in this cohort/target organ/anatomic site. Present possible mechanisms and/or theoretical framework for conducting the study. Include relevant literature review and pertinent preclinical, pilot, and preliminary and/or unpublished data to support conduct of the trial. Clearly state the hypotheses for the primary and secondary objectives. Justify selection of target population, agent, endpoints and choice of techniques for endpoint assessment, measurement of drugs, metabolites and drug effects. Describe the contributions that the proposed study will make to the current knowledge base.*

# 3. SUMMARY OF STUDY PLAN

*For the convenience of the reader, this section should provide a brief synopsis of the following points:*

* *Study design*
* *Number of participants to be enrolled (total number and number per arm)*

*Example: A maximum of 25 participants will be accrued into each of four intervention arms. Three additional participants are anticipated to accrue per arm to account for an anticipated dropout rate of 10%. Assuming a screening rate of approximately 25 participants per month and an accrual rate of approximately 8–10 participants per month, we expect the study to be complete within 18–24 months.*

* *Brief description of the study population*
* *Intervention plan, including doses, dose groups, and duration of exposure to the study agent.*

*Example: Participants will be given two 30 gram tubes of study agent at the baseline visit and at months 3, 6, 9, and 12. Participants will take study agent for 54 ± 2 weeks (minimum) to 102 ± 2 weeks (maximum). Duration of administration will depend on when a participant is randomized in relationship to when the final participant is randomized. The study will be terminated when all participants have…*

* *Description of run-in period, if applicable.*
* *Time points for performing study assessments*
* *Description of measurements taken to meet study objectives*
* *Description of clinical procedures, lab tests or other measurements taken to monitor effects of study agent on human safety and to minimize risks*
* *Duration of study*

# PARTICIPANT SELECTION

## 4.1 Inclusion Criteria

4.1.1 *Please insert specific health risk or disease requirements. State methods for assessing risk or disease requirements, e.g., risk assessment tools, clinical evaluation, pathology review criteria, etc. For populations with cancer or precancer, include requirements for histological confirmation of diagnosis, time from diagnosis, and disease status at entry.*

4.1.2  *State allowable type and amount of prior therapy, if applicable. Include separate definitions for duration as needed. Include site/total dose for prior radiation exposure as needed.*

4.1.3 *State the age range and reason for age restriction.*

4.1.4 *State any clinical performance eligibility indicators (e.g., ECOG performance status, Karnofsky, normal organ and marrow functions, etc.)*

4.1.5 *Insert other appropriate inclusion criteria relevant to the methodology of the study.*

4.1.6 *Please use or modify the following paragraph as appropriate:*

The effects of  *Study Agent*  on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because  *Agent Class*  are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.1.7 Ability to understand and the willingness to sign a written informed consent document.

*If the study involves participants who are deemed to be minors (for example under 18 years of age):* Ability to understand and the willingness to sign a written informed consent document by the legal representative(s) of the participant and an informed assent form by the participant if age appropriate.

## 4.2 Exclusion Criteria

4.2.1 *List contraindications to participation based on agent pharmacology and metabolism, toxicology, clinical and methodology considerations.*

4.2.2 *Absence of acute medical conditions that would exclude from participation in the opinion of the supervising physician.*

4.2.3 Potential participants receiving any other investigational agents may be excluded in the opinion of the supervising physician.

4.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to  *Study Agent.*

4.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.6 *The investigator(s) must state a medical or scientific reason if pregnant or nursing participants will be excluded from the study. Suggested text is provided below:*

Pregnant women are excluded from this study because  *Study Agent is a/an Agent Class* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with *Study Agent,* Breastfeeding should be discontinued if the mother is treated with *Study Agent.*

## 4.3 Inclusion of Women and Minorities

Both men and women (as applicable) and members of all races and ethnic groups are eligible for this trial.

*Women and members of minority groups and their subpopulations must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. NIH requires accrual estimates by gender/race/ethnicity.*

## 4.4 Recruitment and Retention Plan

*Recruitment and retention efforts should be evaluated routinely by the study staff and modified as necessary to promote rapid accrual and to assure 100% retention of participants. In this section the study staff should describe the following:*

* Recruitment and referral sources: include the number of potentially available participants per proposed site annually.
* Enrollment rate (e.g., number of participants meeting eligibility criteria for enrollment per month) and timeline/milestone plans for accrual.
* Discussion of potential recruitment delays or challenges and alternative strategies that can be implemented if there are enrollment delays or shortfalls.
* Procedures to monitor enrollment and track/retain participants for follow-up assessments.
* Evidence to support the feasibility of enrollment, including prior experience and yield from research efforts using similar referral sources and/or strategies.
* Strategies to ensure the study population has scientifically appropriate diversity and representativeness.
* Decision points for terminating the trial.

## 4.5 Accrual and Feasibility

*Specify the planned sample size and accrual rate (*e.g*., participants/month). Total sample size (including gender and minority considerations) and sampling strategy are described and justified for testing the primary and secondary hypotheses.*

*If the accrual targets do not resemble the prevalence distribution of the study cohort in the population, please provide justification*

***Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable). The total provided for Ethnicity must match the total given for Race.***

**Planned Accrual:**

(*Please* *provide tables for each international country separately and together. Puerto Rico is considered Domestic in this network.)*

**Domestic (including Puerto Rican participants) Planned Enrollment Report**

| **Racial Categories** | Not Hispanic or Latino:Female | Not Hispanic or Latino:Male | Hispanic or Latino:Female | Hispanic or Latino:Male | Total |
| --- | --- | --- | --- | --- | --- |
| American Indian/Alaska Native |  |  |  |  |  |
| Asian |  |  |  |  |  |
| Native Hawaiian or Other Pacific Islander |  |  |  |  |  |
| Black or African American |  |  |  |  |  |
| White  |  |  |  |  |  |
| More Than One Race |  |  |  |  |  |
| Total |  |  |  |  |  |

**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**

| **Racial Categories** | Not Hispanic or Latino:Female | Not Hispanic or Latino:Male | Hispanic or Latino:Female | Hispanic or Latino:Male | Total |
| --- | --- | --- | --- | --- | --- |
| American Indian/Alaska Native |  |  |  |  |  |
| Asian |  |  |  |  |  |
| Native Hawaiian or Other Pacific Islander |  |  |  |  |  |
| Black or African American |  |  |  |  |  |
| White  |  |  |  |  |  |
| More Than One Race |  |  |  |  |  |
| Total |  |  |  |  |  |

# REGISTRATION PROCEDURES

## NCI Registration and Credential Repository (RCR)

Partnership Centers will be collecting regulatory documents and per institutional standards and NIH requirements. All persons participating in any NCI-sponsored clinical trial are required to register and renew their registration annually: <https://ctep.cancer.gov/investigatorResources/default.htm>

*See* [*ClinRegs*](https://www.niaid.nih.gov/grants-contracts/turn-clinregs-info-foreign-clinical-research-requirements)*, a public resource for country-specific clinical research regulatory information at* [*https://clinregs.niaid.nih.gov*](https://clinregs.niaid.nih.gov/)*.*

## ClinicalTrials.gov

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

The Partnership Center is required to register each clinical trial in ClincalTrials.gov within 21 days of enrollment of the first participant. Protocols must be submitted to the NCI Clinical Trials Reporting Office no later than 12 months after the primary completion date. The Partnership Center will post the most recent IRB-approved model consent form to ClinicalTrials.gov within 60 days of the study status changing to “Closed to Accrual and Treatment.” Clinical trials result information must be submitted no later than 12 months after the trial’s primary completion date.

# INSTITUTIONAL REVIEW BOARD

Prior to initiating the study, the Investigators at the Lead Academic Organization and the Affiliate Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Any protocol amendments will be submitted to the DCP PIO/ULACNet. The DCP-approved amended protocol must be approved by the IRB prior to implementation. International sites should submit Research Ethics Board (REB) approval to DCP following country-specific regulations.

*Please list all the IRBs of Record for this study. Complete the following table.*

|  |  |  |
| --- | --- | --- |
| Institution  | IRB Assurance Number | Federalwide Assurance (FWA) |
|  |  |  |

# 7. STUDY INTERVENTION INFORMATION

*Please select (and label this section as) either the ‘INVESTIGATIONAL AGENT INFORMATION’ or ‘SCREENING AND DIAGNOSTIC TEST INFORMATION’ sections below depending on the type of the study design (intervention trials vs. screening trials)*

* **INVESTIGATIONAL AGENT INFORMATION**
* **sCREENING AND DIAGNOSTIC TEST INFORMATION**

# 7A. INVESTIGATIONAL AGENT INFORMATION

## 7.1 Dose Regimen and Dose Groups

*Please describe the regimen and dose groups. State any special precautions or warnings relevant for study agent administration. Each dose group should specify:*

* *Agent(s)*
* *Daily dose(s) and regimen(s) for each agent (e.g., two capsules bid)*
* *Duration (days/weeks/months) for each agent.*

## 7.2 (*Study Agent*)Administration

* *Indicate who will administer the agent,*
* *How much agent (*e.g.*, number of pills) should be administered at how many times/day (be specific; for example: 20 mg capsules, 100 capsules/bottle, 2 bottles distributed at the baseline visit and at months 3, 6, 9,* etc*.),*
* *Time of day dose is to be taken,*
* *Special instructions for taking the agent (*e.g.*, with morning meal).*

## 7.3 Contraindications

*Indicate any restrictions that participants should follow when using the agent (e.g., limit sun exposure, dietary restrictions, etc.).*

## 7.4 Concomitant Medications

*Indicate any limitations on medications, herbs, and vitamin and mineral supplements (other than study agents) while participating in the study. Include time period for the limitation, if applicable.*

## 7.5 Dose Modification

*Explicitly identify when dose modifications are appropriate. Modifications and the factors predicating dose modification should be explicit and clear. If dose modifications are anticipated, please provide a dose de-escalation schema with modifications expressed as a specific dose or amount rather than as a percentage of the starting or previous dose. Also indicate if the agent supply may be used for dose modifications or will an additional supply (smaller doses) be needed to achieve dose modification. If applicable, describe procedures for increasing dose following a toxicity-required dose reduction.*

## 7.6 Adherence/Compliance

*7.6.1 Provide* *a definition of compliance that will be used to describe when participants are considered evaluable for statistical analysis.*

*7.6.2 Describe* *the method(s) used to monitor each* *participant’s agent compliance. Methods. may include diaries, pill counts, drug/metabolite plasma levels, and/or drug effect biomarkers.*

## 7.7 Confidential pharmaceutical information for IND studies (IND #, IND Sponsor)

*Confidential pharmaceutical information for investigational study agents supplied by IND sponsor should be inserted here, specifically:*

* *Formulation to be used in this study*
* *Justification for this formulation if other formulations are available,*
* *Physical description of agent*
* *List of excipients*

## 7.8 Reported Adverse Events and Potential Risks

*The list of “Reported Adverse Events and Potential Risks” should be inserted here. Describe the toxicity profile and related data for the agent at the selected doses and schedule.*

## 7.9 Agent Availability

*Example: Agent XXX and matching placebo will be manufactured and supplied by XXX. Agent XXX and matching placebo will be packaged in bottles containing 100 capsules.*

## 7.10 Agent Distribution

*Indicate the manufacturer, supplier and mechanism for distribution.*

## 7.11 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents. The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility has been delegated to \_\_\_\_ [*insert responsible party] \_\_\_.*

## 7.12 Agent Packaging and Labeling

\_\_\_[*Agent]\_\_* will be packaged by \_\_[*manufacturer]\_\_\_.*

*Describe in detail how the agent will be packaged and distributed, including container, amount of agent per container, container label information, and if blinded, how the label will be constructed to maintain the blind. Label information should include dose, number of doses per day, time of day for dosing, with or without food, and any other specific instructions.*

*Example: Each bottle will be labeled with a one-part label identifying study specific information, such as Study title, DCP protocol number, dosing instructions, recommended storage conditions, the name and address of the distributor, randomization number, and a caution statement indicating that the agent is limited by United States law to investigational use only and the agent should be kept out of reach of children.*

## 7.13 Storage

*Provide instructions regarding proper storage of the agent at the study site(s). Storage temperatures should be expressed as a range, not a specific number. For example, room temperature should be specified (e.g., between 59°F and 86°F).*

## 7.14 Registration/Randomization

*Give specific details on how a participant will be registered in a trial. For randomized trials, describe the procedure for randomizing a participant to a dose group. (May refer to §13.2).*

## 7.15 Blinding and Unblinding Methods

*For blinded studies, describe blinding and unblinding methods. Address the following points:*

* *Procedure for retaining the blind (including specific procedures for protecting the blind should data collected in the study offer evidence of a participant’s assignment to a particular study arm)*
* *Individual authorized to break the blind*
* *Circumstances for breaking the blind*
* *Procedure for breaking the blind*

*The NCI Program Scientist must be notified within 24 hours (with cc: to the ULACNet mailbox at* *ULACNet@mail.nih.gov**) if the blind has been broken.*

## 7.16 Agent Destruction/Disposal

*Provide the following procedure for handling the unused drug: method of disposal, documentation of disposal, and any other relevant standard operating procedures.*

# 7B. SCREENING AND DIAGNOSTIC TEST INFORMATION

## 7.1 Screening and Diagnostic Test Information

*Please describe the attributes and biological basis for the choice of the screening test(s) being evaluated and the appropriate diagnostic (reference) investigation. State details about the screening test performance characteristics (preliminary data), clinical procedures, risks, benefits, and precautions or warnings relevant for the test(s) and investigation(s).*

## 7.2 Conduct of the Screening and Diagnostic Test

* *Indicate who will conduct the study,*
* *Frequency and sequence of study procedures*
* *Clinical protocol of sample collection, handling, transport, and storage*
* *Special instructions for preparing for the investigation (if any)*

## 7.3 Contraindications

*Indicate any restrictions that participants should follow before undergoing the test.*

## 7.4 Concomitant Medications

*Indicate any limitations on medications, herbs, and vitamin and mineral supplements (other than study agents) while participating in the study. Include time period for the limitation, if applicable. Indicate other concomitant clinical procedures that should be avoided prior to or after the study.*

## 7.5 Screening and Diagnostic Protocol Modifications

*Explicitly identify the variations in the screening and diagnostic protocols, and the procedures and precautions, as appropriate*

## 7.6 Adherence/Compliance

*7.6.1 Provide* *a definition of compliance that will be used to describe when participants are considered evaluable for statistical analysis.*

*7.6.2 Describe* *the method(s) used to monitor each* *participant’s compliance to the screening and diagnostic procedures.*

## 7.7 Confidential pharmaceutical information for Investigational Device Exemption (IDE) studies (IDE#, IDE Sponsor), if any

*Confidential information for investigational device exemption (IDE) study protocols should be inserted here, as appropriate.*

## 7.8 Reported Adverse Events and Potential Risks

*The list of “Reported Adverse Events and Potential Risks” for the procedures during the conduct of the Screening and Diagnostic tests should be inserted here.*

## 7.9 Availability of the Screening Test(s) and Diagnostic Investigations

*Example: Assays for Screening Test XX will be supplied by XXX.*

## 7.10 Distribution of the Screening Test(s) and Diagnostic Investigations

*Indicate the manufacturer, supplier and mechanism for distribution.*

## 7.11 Accountability of the Screening Test(s) and Diagnostic Investigations

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all materials required for the conduct of the Screening Test(s) and Diagnostic Investigations. The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility has been delegated to \_\_\_\_ [*insert responsible party] \_\_\_.*

## 7.12 Screening Test(s) and Diagnostic Investigations

\_\_\_[ Screening Test(s) and Diagnostic Investigations*]\_\_* will be packaged by \_\_[*manufacturer]\_\_\_.*

*Describe in detail how the Screening Test(s) and Diagnostic Investigations will be packaged and distributed.*

## 7.13 Storage

*Provide instructions regarding proper storage of any relevant material used for the Screening Test(s) and Diagnostic Investigations at the study site(s). Storage temperatures should be expressed as a range, not a specific number. For example, room temperature should be specified (e.g., between 59°F and 86°F).*

## 7.14 Registration/Randomization

*Give specific details on how a participant will be registered in a trial. For randomized trials, describe the procedure for randomizing a participant to a dose group. (May refer to §13.2).*

## 7.15 Blinding and Unblinding Methods

*For blinded studies, describe blinding and unblinding methods. Address the following points:*

* *Procedure for retaining the blind (including specific procedures for protecting the blind should data collected in the study offer evidence of a participant’s assignment to a particular study arm)*
* *Individual authorized to break the blind*
* *Circumstances for breaking the blind*
* *Procedure for breaking the blind*

*The NCI Program Scientist must be notified within 24 hours (with cc: to the ULACNet mailbox at* *ULACNet@mail.nih.gov**) if the blind has been broken.*

## 7.16 Agent Destruction/Disposal

*Provide the following procedure for handling the unused drug: method of disposal, documentation of disposal, and any other relevant standard operating procedures.*

# 8. CLINICAL EVALUATIONS AND PROCEDURES

## 8.1 Schedule of Events

*A table that lists baseline testing/pre-study evaluation, agent administration/Screening Test(s) and Diagnostic Investigations, study assessments, procedures and case report forms should be included. A sample schedule of events is provided on the following page. The protocol should state the expected duration of participation in the study and the sequence and duration of all study periods, including follow-up, if any.*

## 8.2 Baseline Testing/Pre-Study Evaluation

*Describe all procedures (including registration and randomization) that must be completed for a participant before the study intervention may begin. Note any time restrictions for testing (e.g., pre-study labs must be done within 14 days of registration).*

## 8.3 Evaluation During Study Intervention

*Indicate the procedures to be performed during the study intervention phase.*

## 8.4 Evaluation at Completion of Study Intervention

*Specify the evaluations that must be performed upon discontinuation of study agent/completion of the Screening Test(s) and Diagnostic Investigations. Ensure that these evaluations are consistent with the endpoints described in the objectives and statistical analysis sections of the protocol.*

## 8.5 Post-intervention Follow-up Period

*If a defined post-intervention follow-up period is required, specify observations or tests to be performed. Define the length and purpose of the follow-up period.*

## 8.6 Methods for Clinical Procedures

*If applicable, document any special processes, instructions or methodology for clinical procedures required by the protocol, such as invasive procedures and imaging. Include special instructions for procedure prep (*e.g.*, NPO after midnight) and scheduling instructions for tests that may be available only at certain locations or times.*

**SCHEDULE OF EVENTS**

| **Evaluation/ Procedure** | **Registration** | **Baseline** | **Registration/ Randomization** | **Study visit/Follow-up visits (e.g., Months 1-3)** | **Study visit/Follow-up visits (e.g., Months 4-6)** | **Study visit/Follow-up visits (e.g., Months 7-9)** | **Study Exit visit** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Informed Consent | X |  |  |  |  |  |  |
| Assess Eligibility | X | X |  |  |  |  |  |
| Medical History |  | X |  |  |  |  |  |
| Physical Exam |  | X |  |  |  |  |  |
| Vital Signs/ Height and Weight |  | X |  | X |  | X |  |
| Laboratory Tests |  | X |  | X |  | X |  |
| X-Rays |  | X |  |  |  | X |  |
| EKG |  | X |  |  |  | X |  |
| Biopsies |  | X |  |  |  | X |  |
| Biomarkers |  | X |  |  |  | X |  |
| Study Evaluations/ Assessments |  | X |  | X |  | X |  |
| Concomitant Medications |  | X |  | X | X | X | X |
| Dispense Study Agent\* |  |  | X | X |  |  |  |
| Collect Study Agent\* |  |  |  |  |  | X |  |
| Review Agent Diary/Record\* |  |  | X | X |  | X |  |
| Adverse Events |  |  |  | X | X | X | X |
| Telephone Contact |  |  |  |  | X |  |  |

*\*For Interventional studies*

# 9. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

*Delineation of study endpoints, methods for measuring or evaluating, and timing of endpoint ascertainment should be described here.*

## 9.1 Primary Endpoint

## 9.2 Secondary Endpoints

## 9.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, AE or serious adverse event (SAE), inadequate agent supply, noncompliance, concomitant medications, medical contraindication, or *specify other reasons, if applicable*. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. *The protocol should state whether and how subjects are to be replaced, if applicable.*

## 9.4 Off-Study Criteria

Participants may go ‘off-study’ for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility (including screen failure), pregnancy, or *specify other reasons, if applicable.*

This trial will be using the Data and Safety Monitoring Board (DSMB) at \_\_\_\_\_\_\_\_\_. The primary responsibilities of the DSMB will be to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the study.

## 9.5 Study Termination

NCI, DCP as the funding sponsor has the right to discontinue the study at any time.

# 10. SPECIMEN MANAGEMENT

## 10.1 Laboratories

*Identify the laboratory(ies) that will perform each analysis for each specimen. Where appropriate, list individuals who will perform analysis and/or procedures for conducting consensus reviews of specimens.*

## 10.2 Collection and Handling Procedures

*For each type of specimen obtained, please describe the following*

* *Amount to be collected*
* *When specimen should be obtained (*e.g*., fasting, prior to a.m. dose)*
* *Processing of specimen (*e.g*., details of tissue fixation, embedding, processing and sectioning)*
* *Labeling of specimen*
* *Tracking of specimens (*e.g.*, logs or tracking sheets for participants)*
* *Temperature storage requirements*
* *Storage duration*

*Note: If this section is too lengthy, please place this information in an appendix to the protocol.*

## 10.3 Biohazard Containment

Sample language for U.S. sites: Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory pathogens such Mycobacterium tuberculosis (MTB) are transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the Centers for Disease Control and Prevention in the United States, the WHO internationally and the National Institutes of Health.

Mandatory language for protocols requiring the transfer of specimens or infectious substances (U.S. and international sites): All protocol specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

## 10.4 Shipping Instructions

*Include this section only if specimens will be shipped to an off-site laboratory for analysis. For each specimen, describe the following: packaging, carrier requirements, when specimens may be shipped, and name, address, and telephone number of the person to whom the specimens are being sent.*

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

## 10.5 Specimen Repository

*Indicate methods and procedures for storage and archiving of specimens here.*

# 11. REPORTING ADVERSE EVENTS

*DEFINITION: An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not the untoward occurrence is considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.*

*Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician’s assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician’s assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.*

A list of AEs that have occurred or might occur can be found below, as well as in the Investigator Brochure or package insert.

## 11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

*Please outline your plan for routine review of all study adverse events. All AE reports sent to Partnership Center from clinical sites should be forwarded to NCI via ULACNet@mail.nih.gov.*

11.1.2 AE Data Elements

The following data elements are required for AE reporting.

* AE verbatim term
* NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) AE term (MedDRA lowest level term)
* CTCAE (MedDRA) System Organ Class (SOC)
* Event onset date and event ended date
* Treatment assignment at time of AE onset
* Severity grade
* Attribution to study agent (relatedness)
* Whether or not the event was reported as a SAE
* Whether or not the subject dropped due to the event
* Outcome of the event

11.1.3 Severity of AEs

*Identify the AE using the CTCAE version 5.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at* [*http://ctep.cancer.gov/protocolDevelopment/electronic\_applications/ctc.htm*](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0. as stated below.

**CTCAE v5.0 general severity guidelines:**

| Grade | Severity | Description  |
| --- | --- | --- |
| 1 | Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate | Moderate; minimal, local or noninvasive intervention indicated;limiting age-appropriate instrumental activities of daily living (ADL)\*. |
| 3 | Severe | Severe or medically significant but not immediately life-threatening;hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL\*\*. |
| 4 | Life-threatening | Life-threatening consequences; urgent intervention indicated. |
| 5 | Fatal | Death related to AE. |

**ADL**

\*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

\*\*Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

## 11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

• Death

• A life-threatening AE

• Inpatient hospitalization or prolongation of existing hospitalization

• A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions

• A congenital anomaly or birth defect

• Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the Participant and may require intervention to prevent one of the other outcomes.

*Based on FDA’s* Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies*, it is possible to list specific SAEs for routine reporting (not using the SAE Report Form) that are anticipated to occur in the study population at some frequency independent of drug exposure (*e.g*., characteristics of the study population, natural progression of the disease, background event rates, co-morbid conditions, and past experience with similar populations). For example, in a long-term osteoporosis trial in an elderly population, it would be reasonable to list myocardial infarction, but unreasonable to list acute narrow angle glaucoma, an event that can occur in this elderly population, but is relatively rare. A plan for monitoring the frequency of these events in the treatment group* vs*. the concomitant or historical control group should be provided in the protocol. If aggregate analysis indicates a higher frequency in the treatment group, this should be reported as a SAE in a narrative format.*

11.2.2 Reporting SAEs to DCP

*Please outline your plan for routine review of all severe adverse events.*

*All SAE reports sent to the Partnership Center from clinical sites should be forwarded to the NCI Program Scientist (with cc: to the ULACNet mailbox at* *ULACNet@mail.nih.gov**) within 24 hours of receipt at the Partnership Center.*

## 11.3 Social Impact Events

*Sample language from NIAID:*

*Individuals enrolled in this study may experience personal problems resulting from the study participation. Such problems are termed social impact events. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that participants may experience stigmatization or discrimination as a result of being perceived as being HIV- infected or at risk for HIV infection. For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Problems may also occur in circumstances in which study participation is not disclosed, such as impact on employment related to time taken for study visits.*

*In the event that a participant reports a social impact event, every effort will be made by study staff to provide appropriate assistance, and/or referrals to appropriate resources. Social impact events are documented and reviewed on a scheduled basis by the protocol team leadership with the goal of reducing their incidence and enhancing the ability of study staff to mitigate them when possible.*

*Social impact events that are judged by the PI/designee to be serious, unexpected, or more severe or frequent than anticipated, will be reported to the responsible site’s EC/IRB promptly, or otherwise in accordance with the EC/IRB’s requirements.*

# 12. STUDY MONITORING

## 12.1 Source Documents

*The protocol should state what constitutes a source document. Data recorded directly on the CRFs (*i.e*., no prior written or electronic record of data), which will be considered as source data should be identified.*

## 12.2 Data and Safety Monitoring Plan

*NIH and NCI policy requires a Data and Safety Monitoring Plan (DSMP) to document the institution’s procedures to ensure safety of participants, validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trials cannot be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the method and degree of monitoring should be commensurate with risk. The NCI guidelines, essential elements and sample plans are available at:* <http://cancercenters.cancer.gov/GrantsFunding/DSMPRevCriteria>.

*Each ULACNet Site must adhere to their approved Data and Safety Monitoring Plan including Data and Safety Monitoring Board (DSMB) oversight and provide a summary in this section.*

## 12.3 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

## 12.4 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidance, and NCI/DCP requirements, unless the standard at the Lead Academic Organization site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

# 13. STATISTICAL CONSIDERATIONS

## 13.1 Study Design/Description

*A description of the trial design should be consistent with the Summary of Study Plan (section 3) and Protocol Schema and include a statement of the hypothesis, a description of the type/phase/design of the trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, open-label, dose escalation, dose-ranging, adaptive, superiority or non-inferiority design, screening trial), a description of methods to be used to minimize bias, the number of study groups/arms and study intervention duration, single site or multi-site, name of study intervention(s), etc.*

## 13.2 Randomization/Stratification

*This section should contain a description of randomization and blinding procedures (if applicable to the study design). In addition, details regarding the implementation of procedures to minimize bias should be included in this section. DO NOT include details that might compromise these strategies. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported. If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Describe efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible. Measures to prevent unblinding by laboratory measurements, if used, should be described. Include a description of your plans to manage and report inadvertent unblinding. If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained. If blinding is considered desirable but not feasible, the reasons and implications should be discussed. This section should also discuss any planned enrolment stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose).*

## 13.3 Primary Objective, Endpoint(s), Analysis Plan

*The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).*

*The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold. In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit. Briefly explain why the endpoint(s) were chosen.*

## 13.4 Secondary and Tertiary/Exploratory Objectives (if applicable), Endpoints, Analysis Plans

*The secondary objective(s) are goals that will provide further information on the use of the intervention. Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention’s effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases. Briefly explain why the endpoint(s) were chosen.*

*In addition to secondary objectives, tertiary/exploratory objective(s) may be specified. These objectives serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. Exploratory endpoints should be specified. Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses. Endpoints that are not listed in an alpha conserving plan will be considered exploratory. Briefly explain why the endpoint(s) were chosen.*

## 13.5 Reporting and Exclusions

*Definition of compliance is clearly stated. Non-compliance is sufficiently addressed. Particular consideration is given to dropouts, drop-ins, and lost-to-follow up. Handling of missing data or data from non-compliers is described. Any methods used to impute missing data should be described.*

## 13.6 Interim Analysis

*If relevant to the study agent and study design, provide a plan for interim analysis and stopping rules. Include plans for monitoring the progress of the trial to implement early termination.*

## 13.7 Ancillary Studies

*Address the following, as appropriate:*

* *If known, indicate the prevalence of the marker*
* *Specify how any cut points will be determined*
* *Specify the statistical power of the correlative study for the endpoint chosen*
* *If relevant, indicate what corrections will be made for multiple comparisons*
* *If appropriate, indicate relevant clinical endpoint, and a plan for how this endpoint will be correlated with the target(s) or marker(s).*

# 14. REGULATORY And ETHICAL CONSIDERATIONS

## 14.1 Recommended Regulatory Documents

Besides the regulatory documents that will be entered into the Registration and Credential Repository (see section *§*4.1), the following documents are also recommended to be maintained by the Partnership Center:

* + 1. Documentation of Federalwide Assurance (FWA) number for the Lead Academic Organization and all US and LAC Affiliate Organizations.
		2. Signed Investigator’s Brochure/Package Insert acknowledgement form

14.1.3 Delegation of Tasks Log form for the Lead Academic Organization and all US and LAC Affiliate Organizations signed by the Clinical Investigator for each site and initialed by all study personnel listed on the form.

## 14.2 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option should be included within the informed consent document.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP. The informed consent document will be reviewed by the IRB at each accruing site at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP and then submitted to each accruing organization’s IRB for acknowledgement prior to initiation if applicable.

# 15. FINANCING, EXPENSES, AND/OR INSURANCE

*The protocol should describe any expenses incurred by the study participant and/or their insurance carrier. This includes any injuries the participant may have related to their participation in the study.* *This section can also include any description about participant reimbursement for loss of efforts/wages/time due to participation in the study (as covered in the Informed Consent).*

# 16. REFERENCES

*Please provide the citations for all publications referenced in the text.*