DCP CONSORTIA CHEMOPREVENTION 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 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.

1. Each protocol submission consists of four parts:
	1. DCP Consortia 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 is available at <http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia>.
	2. Main Body and Appendices of the protocol: This document provides standard language plus instructions and prompts for information required in each DCP protocol. The current protocol template is attached to these instructions, and is available at <https://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia>. Please ensure the current version of the template always is used for protocol development.
	3. Additional Study-Related Documents: These documents include the Recruitment and Retention Plan, the Pharmacokinetic and Biomarker Methods Development Report, the Case Report Forms (CRFs) and attachments, the Data Management Plan (DMP), the Multi-Institutional Monitoring Plan (MIMP), and the Data and Safety Monitoring Plan (DSMP).

The Recruitment and Retention Plan, Pharmacokinetic and Biomarker Methods Development Report, CRFs and attachments, and protocol-specific addenda to the DMP, MIMP and DSMP are submitted with the initial protocol. These documents are not considered an integral part of the protocol. Unless required by local practices, these documents do not need to be submitted to the local Institutional Review Board (IRB) and should not be referenced in the protocol.

The DMP, MIMP, and DSMP have been standardized and approved for each consortium. Submit supplemental information or addenda to these plans (*e.g*., a protocol-specific addendum to the DMP) only as required.

* 1. Protocol budget
1. An “administratively complete” protocol submission must include the following components:
	1. First submission
		1. DCP Consortia Protocol Submission Worksheet
		2. Protocol including the informed consent document
			1. A protocol document version number and date must be on the cover page.
			2. All pages of the protocol must include a header that identifies the protocol by DCP protocol number, protocol document version date and version number. Pagination must be complete.
			3. The Table of Contents (TOC) sections and page numbers must match the protocol.
		3. All appendices (correct header and pagination)
		4. All Additional Study-Related Documents (Recruitment and Retention Plan, Pharmacokinetic and Biomarker Methods Development Report, CRFs and attachments, supplemental information or addenda to the standardized DCP-approved documents (DMP, MIMP, and DSMP).
		5. Protocol budget
	2. All subsequent submissions (protocol revisions and amendments) must include:
		1. Cover letter with a point-by-point response to DCP reviewer required and recommended changes with references to the changed document section.
		2. An updated PSW
		3. Amended protocol budget, if applicable, or a statement indicating that the proposed revision or amendment will not result in a change to the budget.
		4. “Tracked changes” or highlighted version of the protocol with informed consent and study-related documents, as appropriate, indicating changes from previous version
		5. Clean copy of all documents with highlights removed
		6. Any changes to the CRFs or other study-related documents resulting from a protocol revision or amendment must be included with the submission for review and approval.
		7. Standard font indicates suggested language that should be retained in the document.
		8. **Bold font** indicates language that must be retained in the document.
		9. Blank space or \_\_\_\_\_\_\_\_ indicates that you should fill in the appropriate information.

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

1. All sections in the Protocol Template should be retained within the body of the document. If not appropriate for a given study, please insert “Not Applicable” after the section number and delete the corresponding text.
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; see image below).



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.**

1. To update the TOC in your protocol document:

 2007–2013 MS Word:

a. On the **References** tab, in the **Table of Contents** group, click **Update Table**.



b. Click **Update entire table**.

2003 MS Word:

a. Click the table of contents.

b. Press F9.

**Please do not edit the TOC manually**.

1. DCP terminology for changes to protocol:
	1. Changes made prior to the initial DCP study approval are “Revisions”
	2. Changes made after DCP approval are “Amendments”
2. Indicate changes using the ‘tracked changes’ function, highlighting, or underlining new or modified text in protocol revisions or amendments to facilitate the review process.
3. All document submissions must be sent electronically to Head, DCP Protocol Information Office (NCI\_DCP\_PIO@mail.nih.gov). Documents submitted elsewhere will not be accepted for review.
4. DCP Consortia forms are available at <http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia>.

**Questions:**

**Contact the DCP Protocol Information Office at (240) 276-7130 or e-mail** **NCI\_DCP\_PIO@mail.nih.gov**

# COVER PAGE

**DCP Protocol #:** *This number will be assigned by DCP and may be the same as or different from the local protocol number. The DCP protocol number must appear on all protocol document versions and all communication to DCP.*

**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 Lead Organization according to local institutional conventions or Consortium guidelines.*

 **PROTOCOL TITLE**

**Consortium Name:** *Insert name of Consortium*

**Name of Consortium Principal** *Name & Title of the Principal Investigator of Consortium Lead Organization*

**Investigator:** *Address*

 *Address*

*Telephone*

*Fax*

*E-mail address*

**Organization Name:** *Organization Name*

**Protocol Principal Investigator:** *Protocol Principal Investigator*

 *Investigator’s Specialty*

 *Address*

 *Address*

 *Telephone*

 *Fax*

 *E-mail address*

**Organization:** *Organization Name*

**Investigator:** *Investigator’s Name*

 *Investigator’s Specialty*

 *Address*

 *Address*

 *Telephone*

 *Fax*

 *E-mail address*

**Organization:** *Organization Name*

**Investigator:** *Investigator’s Name*

 *Investigator’s Specialty*

 *Address*

 *Address*

 *Telephone*

 *Fax*

 *E-mail address*

**Organization:** *Organization* *Name*

**Statistician:** *Statistician Name*

 *Address*

 *Address*

 *Telephone*

 *Fax*

 *E-mail address*

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

1. ***The protocol title page(s) must include the name and address of each participating institution and any affiliates participating in the study.***
2. ***The protocol title page(s) must include the names of all investigators at each institution; his/her telephone, Fax, and e-mail address.***
3. ***Indicate the protocol lead investigator responsible for the study at each institution; his/her telephone, Fax, and e-mail address.***
4. ***Indicate administrative (non-accruing) sites with an asterisk and an associated footnote (e.g., “No participant accrual occurs at this site”).***

**IND Sponsor:** *NCI/Division of Cancer Prevention (or another Sponsor)*

 *If other sponsor, please add contact information.*

**IND#** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Agent(s)/Supplier**: *Study Agent(s) /Supplier Name*

**NCI Contract # \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Protocol Version Date:** \_\_\_\_\_ *(Date)* \_\_\_\_\_

**Protocol Revision or**

**Amendment #** *Revision or Amendment #*

# SCHEMA

*Please provide a schema for the study.*

*Protocol Title*

*Study Population*

*Baseline data collection*

*Randomization*

*Intervention*

*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 13.0). 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, 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 in this cohort/target organ. 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.*

*Include the following text as rationale for tobacco and alcohol use questionnaires:*

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline and *(include follow-up timepoint*), to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

# 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*

# 4. 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 *Please 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.*

4.1.3Age ≥18 years. *Please state reason for age restriction. If applicable, the following text can be used*.

Because no dosing or adverse event (AE) data are currently available on the use of  *Study Agent*  in participants <18 years of age, children are excluded from this study but will be eligible for future pediatric trials, if applicable.

4.1.4 *ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix A)*

4.1.5 Participants must have normal organ and marrow function as defined below:

*Insert baseline lab parameters appropriate to agent and cohort, for example:*

Leukocytes ≥3,000/microliter

Absolute neutrophil count ≥1,500/microliter

Platelets ≥100,000/microliter

Total bilirubin within normal institutional limits

AST (SGOT)/ALT (SGPT) ≤1.5 × institutional upper limit of normal (ULN)

Creatinine within normal institutional limits

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

4.1.7 *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.

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

## 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 *Healthy volunteers may be required to demonstrate absence of chronic medical conditions or regular use of certain medications.*

4.2.3 Participants may not be receiving any other investigational agents.

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 or participants who are cancer survivors or those who are HIV-positive will be excluded from the study. Detailed information regarding these special populations is available in the DCP Clinical Trials Resource. 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. This information should be recorded on the DCP PSW. Additional information regarding the NIH policy is available in the Early Phase Prevention Trials Consortia section of the DCP website Resource.*

# 5. AGENT ADMINISTRATION

Intervention will be administered on an *inpatient/outpatient* basis. Reported AEs and potential risks are described in Section 6.2.

## 5.1 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.*

## 5.2 (*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).*

## 5.3 Run-in Procedures

*If the study includes a placebo run-in phase prior to randomization to assess compliance, please describe the procedure, including method of administering placebo, dose, duration, and methods for assessing compliance. Compliance should be clearly defined.*

## 5.4 Contraindications

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

## 5.5 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.*

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g*., biopsy) should also be included.

## 5.6 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.*

## 5.7 Adherence/Compliance

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

5.7.2 *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.*

# 6. PHARMACEUTICAL INFORMATION

## 6.1 *Study Agent* (*IND #, IND Sponsor*)

*Confidential pharmaceutical information for investigational study agents supplied by NCI, DCP will be provided as an attachment to the Task Order Technical Proposal Submission form approval letter and should be inserted here.*

*Non-DCP supplied agents: insert appropriate agent information here. Specify:*

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

## 6.2 Reported Adverse Events and Potential Risks

*The list of “Reported Adverse Events and Potential Risks” included in the Task Order Technical Proposal Submission form approval letter should be inserted here.*

*Non-DCP supplied agents: describe the toxicity profile and related data for the agent at the selected doses and schedule.*

## 6.3 Availability

*Study Agent* is an investigational agent supplied to investigators by the Division of Cancer Prevention (DCP), NCI*.*

*Example: Agent A and Agent B are investigational agents for chemoprevention studies provided by NCI/DCP. Agent C will be supplied to NCI/DCP by XXX (20 mg capsules, 30 capsules/bottle). Agent D and matching placebo D will be supplied to NCI/DCP by XXX (50 mg capsules, 30 capsules/bottle).*

*Non-DCP supplied agents: delete the above statement and specify source and availability of supply.*

*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.*

*If the study agent is provided by NCI under a Cooperative Research and Development Agreement (CRADA) or Clinical Trials Agreement (CTA with the manufacturer, the appropriate text below must be included in the protocol and the* ***incorrect text deleted****. Information on the study agent’s CRADA/CTA status will be provided in Task Order Technical Proposal Submission form approval letter.*

*Study Agent i*s provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between *Agent Manufacturer*  and the DCP, NCI (see §12.7)*.*

*Study Agent* is provided to the NCI under a Clinical Trials Agreement (CTA) between *Agent Manufacturer*  and the DCP, NCI (see §12.7)*.*

## 6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each Organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham

MRIGlobal

DCP Repository

1222 Ozark Street

North Kansas City, MO 64116

Phone: (816) 360-3805

FAX: (816) 753-5359

Emergency Telephone: (816) 360-3800

*For non-DCP supplied agents indicate the manufacturer, supplier and mechanism for distribution. DCP procedures for agent distribution and the required forms are available on the DCP website.*

## 6.5 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 received from DCP using the NCI Drug Accountability Record Form (DARF). 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] \_\_\_.* Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

*DCP requirements for agent accountability and the required forms are available on the DCP website.*

## 6.6 Packaging and Labeling

\_\_\_[Agent]\_\_ will be packaged by \_\_[manufacturer or NCI, DCP]\_\_\_.

*DCP will package, label and distribute agent for all DCP-supplied agents. Occasionally, a pharmaceutical collaborator or the site performs one or more of these activities. DCP will send a draft label to the Principal Investigator and the DCP regulatory support contractor for review and approval. Final labels are printed and attached to the bottle prior to shipping to the site. DCP will provide information regarding packaging (container, amount of agent per container) and labeling in the Task Order approval letter. The information provided by DCP should be inserted into this section of the protocol.*

*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.*

*Protocols using non-DCP supplied agents: 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.*

**6.7 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).  Refer to the Pharmacy Manual for the Temperature Excursion policy and procedure(s).  The Pharmaceutical partner (if required), Consortia Lead Organization, the DCP agent repository contractor, DCP Medical Monitor and Nurse Consultant should be notified in the event of a Temperature Excursion.*

## 6.8 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 §13.3).*

## 6.9 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 Medical Monitor must be notified that the blind has been broken.*

*Provide DCP Medical Monitor Name and title (see Task Order Technical Proposal Submission* *Decision Letter)*

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*Insert the full contact information including address, telephone number, FAX number, and email of the DCP Medical Monitor*

## 6.10 Agent Destruction/Disposal

DCP-supplied agents: at the completion of investigation, all unused study agent will be returned to NCI, DCP Repository according to the DCP “Guidelines for AGENT RETURNS” and using the DCP form “Return Drug List”.

*The Guidelines and form are available on the DCP website.*

*Non-DCP agents, provide the following procedure for handling the unused drug: method of disposal, documentation of disposal, and any other relevant standard operating procedures.*

# 7. CLINICAL EVALUATIONS AND PROCEDURES

## 7.1 Schedule of Events

*A table that lists baseline testing/pre-study evaluation, agent administration, study assessments, procedures and case report forms should be included. Tobacco and alcohol use assessments should be included at baseline and end of treatment or follow-up, as appropriate. 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 trial periods, including follow-up, if any.*

## 7.2 Baseline Testing/Prestudy 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). Include tobacco and alcohol use assessment, using the Baseline questionnaires.*

*Specify the amount of study agent that will be distributed to the participant at each visit. Also describe how the participant will return study agent for example: Day 0, participants will be randomized to receive either study agent or placebo and will be given a supply of study agent (3 bottles for a total of 90 capsules); day 60, participants will return any unused study agent and will be given a supply of study agent (3 bottles for a total of 90 capsules).*

*Refer to §5.3, Run-In Procedures, if applicable.*

## 7.3 Evaluation During Study Intervention

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

## 7.4 Evaluation at Completion of Study Intervention

*Specify the evaluations that must be performed at the discontinuation of study agent. Ensure that these evaluations are consistent with the endpoints described in the objectives and statistical analysis sections of the protocol. Include tobacco and alcohol use assessments, using the Follow-up questionnaires.*

**7.5 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.*

## 7.6 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** | **Randomization** | **Months 1–3** | **Months 4–5** | **Month 6 or Early Termination** | **Follow-Up 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 |  |
| Tobacco and Alcohol Use Assessment |  | 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 |  | X |

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# 8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

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

## 8.1 Primary Endpoint

*Depending on the study hypotheses and design, the primary endpoint may be an incidence of invasive or preinvasive disease (*e.g*., polyp incidence), clinical response (*e.g*., change in number and severity of leukoplakia by physical exam), histologic or cytologic response (*e.g*., change in severity of dysplasia in biopsy materials), and/or modulation of surrogate endpoint biomarkers (SEBs). Define endpoints clearly and briefly describe methods and intervals for assessment. A detailed description of methods should be included in the Pharmacokinetic and Biomarker Method Development Report document (part of the Additional Study-Related Documents that are submitted with the protocol) as appropriate. Do not reference the Pharmacokinetic and Biomarker Method Development Report here since it is not an actual part of the protocol.*

## 8.2 Secondary Endpoints

*As appropriate, secondary endpoints (serum/plasma/tissue agent/metabolite levels, other agent effect biomarkers) should be defined clearly and prioritized. Methods for assessment should be referenced in this section with detailed descriptions of laboratory and computer modeling procedures provided in the required “Pharmacokinetic and Biomarker Method Development Report” document (part of the additional Study-Related Documents).*

## 8.3 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.*

## 8.4 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.*

## 8.5 Study Termination

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

# 9. CORRELATIVE/SPECIAL STUDIES

## 9.1 Rationale for Methodology Selection

*Provide the rationale for selecting the assay methodology, particularly in cases where various assays are available that may assess different qualities of the marker (example: mutation analysis* vs*. IHC for p53; gene expression vs. protein expression). Methodology should be included, as appropriate, in the Pharmacokinetic and Biomarker Methods Development Report.*

## 9.2 Comparable Methods

*Discuss the comparability of the methods proposed to those previously used and the likelihood that the resulting data will be able to be compared to existing data.*

# 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 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.

## 10.4 Tissue Banking

*Indicate methods and procedures for tissue banking here.*

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI’s expense.

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# 11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not 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 in §6.2 Reported Adverse Events and Potential Risks, as well as 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.

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 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
* CTCAE (MedDRA) System Organ Class (SOC)
* Event onset date and event ended date
* Treatment assignment code (TAC) 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

11.1.3.1 Identify the AE using the CTCAE version 4.0. 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>

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 v4.0. as stated below.

**CTCAE v4.0 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 patient 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

* + - 1. The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found at <http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia>.
			2. Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

*Provide DCP Medical Monitor Name and title (see Task Order Technical Proposal Submission form Decision Letter)*

NCI/Division of Cancer Prevention

*Insert the full contact information including address, telephone number, FAX number, and email of the DCP Medical Monitor*

Include the following information when calling the Medical Monitor:

* + - * Date and time of the SAE
			* Date and time of the SAE report
			* Name of reporter
			* Call back phone number
			* Affiliation/Institution conducting the study
			* DCP protocol number
			* Title of protocol
			* Description of the SAE, including attribution to drug
			1. The Lead Organization and all Participating Organizations will email written SAE reports to DCP’s Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com within 48 hours of learning of the event using the fillable PDF SAE Report Form.

* + - 1. The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.
			2. The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. *The protocol should state the length of time for follow-up of an SAE.*

# 12. STUDY MONITORING

## 12.1 Data Management

*An approved Master Data Management Plan that is applicable to all studies within the Consortium will be on file at DCP. If there are any changes required to the Master DMP that are specific to this protocol only, then DMP Attachment #1 should be submitted with the protocol as part of the set of “Additional Study-Related Documents”. Any changes or updates to the Master Data Management Plan following DCP approval should be submitted separately to the DCP Protocol Information Office for approval.*

## 12.2 Case Report Forms

*The site may use DCP Chemoprevention CRF Templates from the DCP website to develop study-specific CRFs. The DCP templates contain NCI Common Data Elements (CDEs); use of these standardized terms facilitates data collection and analysis across studies. The standard template set may require modification to capture the unique data elements (*i.e*., biomarkers) of each protocol. NCI CDEs, where available, shall be used for all CRF modifications. The site may also use their own institutional CRFs however, they must use NCI Common Data Elements (CDEs).*

*The CRFs and attachments will be submitted with the protocol for DCP PSRC review as part of the set of “Additional Study-Related Documents”. DCP must approve the final CRFs prior to study initiation. CRFs may require changes throughout the conduct of the clinical trial. The need for change may result from protocol amendments or other reasons. Amended CRFs and attachments should be submitted to the DCP Protocol Information Office for review and approval.*

## 12.3 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.*

## 12.4 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 guidelines, essential elements and sample plans are available at:* <http://cancercenters.cancer.gov/GrantsFunding/DSMPRevCriteria>. *Please note that the requirements differ depending on whether a trial is conducted under an IND.*

*An approved Master DSMP applicable to all studies within a Consortium will be on file at DCP. If there are any changes required to the Master DSMP that are specific to this protocol only, then DSMP Attachment #1 should be submitted with the protocol as part of the set of “Additional Study-Related Documents”.*

*Please provide a brief summary of the Master DSMP in this section.*

##

## 12.5 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.

Please refer to the monitoring section (Step 3) of the Early Phase Prevention Trials area of the DCP website for information regarding DCP site visit procedures and requirements at <http://prevention.cancer.gov/clinical-trials/clinical-trials-management/2012-consortia-early-phase>.

## 12.6 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.), as well as IRB records 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 guidances, and NCI/DCP requirements, unless the standard at the 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.

## 12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

*If the study agent is provided by DCP under a CRADA or CTA with the manufacturer, this section must be included in the protocol, but the inappropriate text (CTA* or *CRADA)* *should be deleted. Information on the study agent’s CRADA/CTA status will be provided in the approved Task Order Technical Proposal Submission form response. If neither a CRADA nor CTA applies to the study agent, this section should be marked “N/A” and the text below deleted.*

The agent(s) supplied by DCP, NCI, used in this protocol, is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Prevention. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator@ contained within the terms of award, apply to the use of Agent(s) in this study:

12.7.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a patient participating on the study or participant’s family member requests a copy of this protocol, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from the DCP website.

12.7.2 For a clinical protocol where there is an Investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-party Data”).

12.7.3 NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

12.7.4 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

12.7.5 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

12.7.6 Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

12.7.7 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators of Collaborator's wish to contact them.

12.7.8 Any manuscripts reporting the results of this clinical trial must be provided to DCP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days (or as specified in the CTA) from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to the Protocol Information Office at NCI\_DCP\_PIO@mail.nih.gov.

The Protocol Information Office will forward manuscripts to the DCP Project Officer for distribution to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator’s confidential/proprietary information.

# 13. STATISTICAL CONSIDERATIONS

## 13.1 Study Design/Description

*Indicate the type of study (*e.g*., phase I, phase II, observational) as applicable. Include justification for the selection of the particular study design. If a randomized study, indicate whether blinding is used and the methodology to ensure the blinding. Indicate whether or not the study employs intent to treat principles. If applicable indicate both the range of true values of the primary endpoint sufficiently promising to justify further testing of the agent (*e.g*.,* ***true*** *response rate of at least 20%) and a range of values sufficiently discouraging to justify no further testing of the agent (*e.g*.,* ***true*** *response rate no greater than 5%). Consider early testing for sufficiently discouraging results (*e.g*., interim analysis). Indicate the decision rule for declaring the agent promising based on the* ***observed value*** *of the primary endpoint. Provide the probability of a positive result, given that the true value falls within the promising range, and the probability of a negative result (along with the probability of early negative termination), given that the true value falls within the discouraging range.*

## 13.2 Randomization/Stratification

*Methods for randomization and stratification are described and justified. Blocking and/or other techniques used to balance intervention assignments are described completely. Indicate whether interim analysis and efficacy determination will be done for each stratum individually.*

## 13.3Accrual 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 U.S. population, please provide justification*

 **Ethnic Categories: Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

#### **Not Hispanic or Latino**

**Racial Categories: American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

**Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam

**Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

**Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

***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:**

**Domestic 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 |  |  |  |  |  |

13.4 Primary Objective, Endpoint(s), Analysis Plan

*Describe the primary objective of the study. Define the primary endpoints and indicate how the analysis plan will satisfy the primary objective of the study. Definition of the primary endpoint(s) should indicate time-points considered in computing the primary endpoint from the data observed. The analysis plan should consider the appropriateness for the particular type of endpoint (for example continuous, binary, time-dependent). Analysis plans should indicate the planned statistical test used to evaluate the objectives of the study along with power calculations and sample size requirements. When known, provide pilot or historical data to support power calculations. Clearly state all assumptions for the power calculations and indicate whether significance levels are one- or two-sided values. Consideration should be given to handling missing data if applicable.*

## 13.5 Secondary Objectives, Endpoints, Analysis Plans

*Describe the secondary objectives of the study. Define the secondary endpoints and indicate how the analysis plan will satisfy the secondary objectives of the study. Definition of the secondary endpoint(s) should indicate time-points considered in computing the secondary endpoint from the data observed. The analysis plan should consider the appropriateness for the particular type of endpoint (for example continuous, binary, time-dependent). Analysis plans should indicate the planned statistical test used to evaluate the secondary objectives of the study. Clearly indicate whether significance levels are one- or two-sided values. Consideration should be given to handling missing data if applicable.*

## 13.6 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.*

## 13.7 Evaluation of Toxicity

*All participants will be evaluable for toxicity from the time of their first dose of [Study Agent] .*

## 13.8 Evaluation of Response

*All participants included in the study must be assessed for response to intervention, even if there are major protocol deviations or if they are ineligible.*

*All of the participants who met the eligibility criteria (with the possible exception of those who did not receive study agent) will be included in the main analysis. All conclusions regarding efficacy will be based on all eligible participants.*

*Subanalyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (*e.g*., early death due to other reasons, early discontinuation of intervention, major protocol violations,* etc*.). However, subanalyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported. For all measurements of response, the 95% confidence intervals should also be provided.*

## 13.9 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.*

## 13.10 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. ETHICAL AND REGULATORY CONSIDERATIONS

## 14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

## 14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations. CVs or biosketches do not need to be updated for participating study staff after drug shipment authorization (DSA).

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

* + 1. Lab certification (*e.g*., CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.
		2. Documentation of Good Clinical Practice training for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.
		3. Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.
		4. Signed Investigator’s Brochure/Package Insert acknowledgement form
		5. Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form
		6. Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

## 14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

## 14.4 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 may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization’s IRB, and then submitted to each organization’s IRB for approval prior to initiation.

## 14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP’s Regulatory Contractor:

 Paper Document/CD-ROM Submissions:

 Regulatory Affairs Department

 CCS Associates, Inc.

 1923 Landings Drive

 Mountain View, CA 94043

 Phone: 650-691-4400

 Fax: 650-691-4410

 E-mail Submissions:

 regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP’s Regulatory Contractor.

## 14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

# 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.*

# REFERENCES

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

# APPENDIX A

**Performance Status Criteria**

**ECOG Performance Status Scale**

| **Grade** | **Descriptions** |
| --- | --- |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
|
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g*., light housework, office work). |
|
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
|
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
|
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
|
| 5 | Dead. |

**Karnofsky Performance Scale**

| **Percent** | **Description** |
| --- | --- |
| 100 | Normal, no complaints, no evidence of disease. |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 80 | Normal activity with effort; some signs or symptoms of disease. |
| 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| 50 | Requires considerable assistance and frequent medical care. |
| 40 | Disabled, requires special care and assistance. |
| 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 20 | Very sick, hospitalization indicated. Death not imminent. |
| 10 | Moribund, fatal processes progressing rapidly. |
| 0 | Dead. |