NOTE - When finalizing your protocol please:

1. **Delete** any instructions that may appear in this template (including this box).
2. **Keep** the standard template language that is included here.
3. **Insert** your text at the highlighted sections (your text should not be highlighted).
4. **Delete** statements that begin with (If applicable), if statement is not needed, but if information is needed then delete the direction "(If applicable)".
5. **Delete sections** that are not applicable for your protocol.
6. **Please do not adjust the margins,** particularly please keep a minimum left margin of 1" and bottom margin of no less than 0.5" to accommodate the footer).

<<INSERT - Protocol Title>>

Protocol Number:	<<INSERT – Protocol Number>>
National Clinical Trial (NCT) Number:	<<INSERT – NCT #>>
Principal Investigator:	<<INSERT - Principal Investigator's Name (as listed on Medical License, especially if FDA sponsored study)>> <<INSERT (especially if FDA regulated study) - PI's mailing address, best contact phone number and fax number>>
(If applicable) **IND/IDE Sponsor:**	<< INSERT – IND/IDE Holder)>>
(If applicable) **Coordinating Center and Lead Principal Investigator:**	<< INSERT Lead Institution & Lead PI's Name)>>
(If applicable) **Funded by:**	<< INSERT – Funding Sponsor>>

PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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STATEMENT OF COMPLIANCE

<<FOR SINGLE SITE STUDY>> This is an investigator-initiated study. The principal investigator (PI), <<INSERT PI Name>>, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), as applicable.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

<<FOR MULTI-SITE STUDY>>

Site Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

LIST OF ABBREVIATIONS

PARTICIPATING SITES

<<For studies where the PI is the IND holder or where IRB review has been ceded to COMIRB from other institution, list all participating sites here:>>

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:	*<<INSERT - Full Protocol Title>>*
Population:	***<<INSERT – Study Population>>***
Phase:	*<<INSERT - I, II or III>>*
Participating Sites:	*<<INSERT – Names of Sites >>*
Description of Study Intervention:	*<<INSERT – Name of Study Drug>>*
Study Duration:	*<<INSERT – Total duration of study, including analysis>>*
Participant Duration:	*<<INSERT – Total duration of subject participation, including follow-up >>*

1.2 STUDY SCHEMA

<<INSERT - Diagram>>

1.3 SCHEDULE OF EVENTS

<<INSERT - Table>>

2 INTRODUCTION

2.1 STUDY RATIONALE

<<INSERT – text>>

2.2 BACKGROUND

<<INSERT – text>>

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

<<INSERT – text>>

2.3.2 KNOWN POTENTIAL BENEFITS

<<INSERT – text>>

2.3.3 ASSESSMENT OF POTENTIAL BENEFITS

<<INSERT – text>>

REQUIRED TEXT:
The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: <<INSERT – text>>
- To Society: <<INSERT – text >>
- Justify the importance of the knowledge gained: <<INSERT - text>>

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Secondary	

Tertiary/Exploratory	

4 STUDY DESIGN

4.1 OVERALL DESIGN

<<INSERT - Text>>

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

<<INSERT - Text>>

4.3 JUSTIFICATION FOR DOSE

<<INSERT - Text>>

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

REQUIRED TEXT:

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Be a <<INSERT – gender(s)>> aged <<INSERT – age range>>.
4. For persons of reproductive potential, use of highly effective method(s) of contraception.

<<INSERT - Text>>

5.2 EXCLUSION CRITERIA

REQUIRED TEXT:

An individual who meets any of the following criteria will be excluded from participation in this study:

1. <<INSERT - Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>>.
2. <<INSERT - Specify use of disallowed concomitant medications>>.

<<INSERT - Text>>

5.3 LIFESTYLE CONSIDERATIONS

<<INSERT – text>>

5.4 SCREEN FAILURES

<<INSERT – text>>

<<If applicable, include>> Subject may be re-screened for eligibility with documented approval from the PI.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

<<INSERT – text>>

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

<<INSERT – text>>

6.1.2 DOSING AND ADMINISTRATION

<<INSERT – text>>

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

<<INSERT – text>>

6.2.1 ACQUISITION AND ACCOUNTABILITY

<<INSERT – text>>

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

<<INSERT – text>>

6.2.3 PRODUCT STORAGE AND STABILITY

<<INSERT – text>>

6.2.4 PREPARATION

<<INSERT – text>>

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

<<INSERT – text>>

6.4 STUDY INTERVENTION COMPLIANCE

<<INSERT – text>>

6.5 PROHIBITED THERAPY

<<INSERT – text>>

6.6 CONCOMITANT THERAPY

<<INSERT – text>>

6.6.1 RESCUE MEDICINE

<<INSERT – text>>

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION (STOPPING RULES)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

<<INSERT – text>>

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

REQUIRED TEXT:

Participants are free to withdraw from participation in the study at any time upon request.
In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- Sponsor-Investigator determines it is in the best interest of the patient

- Patient non-compliance

Patients must discontinue study treatment if they experience any of the following:
<<INSERT – text>>

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study or study drug discontinuation should be documented on the appropriate eCRF.

7.3 LOST TO FOLLOW-UP

REQUIRED TEXT:

A subject will be considered lost to follow-up if he or she fails to return for <<INSERT – text>> <specify number of visits> scheduled visits and is unable to be contacted by the study staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- Site will attempt to contact the subject and reschedule the missed visit and advise subject on importance of maintaining assigned visit schedule;
- Before a subject is deemed lost to follow-up, the investigator will make every effort to regain contact with the subject. These contact attempts must be documented in the subject's medical record or study file;
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

<<INSERT – text>>

8.2 SAFETY AND OTHER ASSESSMENTS

<<INSERT – text>>

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

REQUIRED TEXT:

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

REQUIRED TEXT:

Serious adverse event or **serious suspected adverse reaction**. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/ birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Adverse events of special interest (AESIs) are a subset of adverse events of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Sponsor-Investigator and <<INSERT – text>> is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor-Investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

AESIs for this study are as follows: <<INSERT – text>>

8.3.4 CLASSIFICATION OF AN ADVERSE EVENT

8.3.4.1 SEVERITY OF EVENT

REQUIRED TEXT:

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

OR

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The following table will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE (v5.0).

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events. Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

8.3.4.2 RELATIONSHIP TO STUDY INTERVENTION

REQUIRED TEXT:

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to the study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

OR

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease

provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.4.3 EXPECTEDNESS

REQUIRED TEXT:

Expectedness will only be documented for SAEs. <<INSERT – Role (not name) of individual>> will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

REQUIRED TEXT:

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study treatment or until initiation of new treatment,

whichever comes first. SAEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit.

8.3.6 ADVERSE EVENT REPORTING

REQUIRED TEXT:
The investigator must record non-serious adverse events and report to Datra and IRB according to timetable for reporting specified in section 10.1.5.
<< If applicable, INSERT – Text from funder/drug manufacturer re: reporting timelines>>

8.3.7 SERIOUS ADVERSE EVENT REPORTING

REQUIRED TEXT FOR STUDIES WHERE PI HOLDS IND:
The investigator must record all serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.5. Per institutional policy, all serious adverse events occurring at UCCC/UCHealth will be entered into OnCore according to timetable for reporting specified in section 10.1.5.

The sponsor-investigator must notify FDA and all participating PIs in an IND safety report of potential serious risks as soon as possible, but in no case later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting. (21 CFR 312.32(c)(1))

The sponsor-investigator must notify FDA of any unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor-investigator's initial receipt of the information. (21 CFR 312.32(c)(2)).

All SAEs will be followed until satisfactory resolution or until the site PI deems the event to be chronic or the adherence to be stable. <<If applicable, include for multi-site studies>> Other supporting documentation of the event may be requested by the sponsor-investigator and should be provided as soon as possible.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form unless funding sponsor or drug manufacturer requires use of proprietary form. SAE form can be found at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit an SAE, email as follows within <<24 hours>> of becoming aware of the event:

To: <<INSERT PI and any other applicable emails>>

DSMC@cuanschutz.edu (EMAIL USED FOR EXTERNAL SITES ONLY)

<<INSERT Funding Sponsor Email (if applicable)>>

Subject: <<INSERT COMIRB #>> SAE Report Form

Attach: SAE form completed and signed by the Investigator

Follow-up of unresolved serious adverse events

Any SAEs that are unresolved at the time of the initial report submission should be followed up by the investigator for as long as medically indicated, and an updated SAE report submitted at the time new information regarding the event becomes available.

REQUIRED TEXT FOR STUDIES WHERE PI DOES NOT HOLD IND/IND EXEMPT/NON-FDA REGULATED:

The investigator must record all serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.5. Per institutional policy, all serious adverse events occurring at UCCC/UCHealth will be entered into OnCore according to timetable for reporting specified in section 10.1.5.

<< If applicable, INSERT – Text from funder/drug manufacturer re: reporting timelines>>

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the <<funder/drug manufacturer>> within 24 hours of site awareness.
- Other SAEs, regardless of relationship, will be submitted to the <<funder/drug manufacturer>> within <<24>> hours of site awareness.

To submit an SAE, email as follows within <<24 hours>> of becoming aware of the event:

To: <<INSERT PI and any other applicable emails>>

DSMC@cuanschutz.edu (EMAIL USED FOR EXTERNAL SITES ONLY)

<<INSERT Funding Sponsor Email (if applicable)>>

Subject: <<INSERT COMIRB #>> SAE Report Form

Attach: SAE form completed and signed by the Investigator

Follow-up of unresolved serious adverse events

Any SAEs that are unresolved at the time of the initial report submission should be followed up by the investigator for as long as medically indicated, and an updated SAE report submitted at the time new information regarding the event becomes available.

8.3.8 ADVERSE EVENT OF SPECIAL INTEREST REPORTING

All Adverse Events of Special Interest will be reported using the FDA 3500A Mandatory MedWatch report. Reporting form can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit an AESI or special situation, email as follows within 24 hours of becoming aware of the event.

To:	<<INSERT PI and any other applicable emails>> *DSMC@cuanschutz.edu* (EXTERNAL SITES ONLY) <<INSERT Funding Sponsor Email (if applicable)>>
Subject:	<<INSERT COMIRB #>> SAE Report Form
Attach:	MedWatch 3500A Form completed and signed by the Investigator

Per institutional policy, all adverse events of special interest occurring at UCCC/UCHealth will be reported to the DSMC according to timetable for reporting specified in section 10.1.5.

8.3.9 REPORTING OF PREGNANCY

<<INSERT acceptable methods of contraception for persons with reproductive potential and/or define reproductive status(es) i.e. post-menopausal>>.

REQUIRED TEXT

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Pregnancies and lactations will be reported on a MedWatch Form and submitted within 24 hours from first becoming aware. Please follow the instructions for Serious Adverse Event Reporting specified in section 8.3.6.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

REQUIRED TEXT FOR SINGLE-SITE STUDIES:

This study will use the COMIRB definition of UAP. An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

REQUIRED TEXT FOR MULTI-SITE STUDIES:

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

8.4.2 REPORTING OF UNANTICIPATED PROBLEMS

REQUIRED TEXT FOR SINGLE-SITE STUDIES:
This study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements (discussed below). AEs, noncompliance and protocol violations will be recorded and reported as required either promptly or at the time of the study's continuing review.

It is the responsibility of the PI to report incidents or events that meet the criteria for UAPs reporting to their IRB using the IRB's standard UAP form. The PI is also responsible for reporting the UAP to the UCCC DSMC.

REQUIRED TEXT FOR MULTI-SITE STUDIES:
Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report. It is the Site PI's responsibility to report UAPs to their IRB. Once a determination letter has been received by the Site PI, the site PI will immediately provide the letter and incident to the Lead PI for review. If the UAP was a result of a reportable SAE, then the Lead PI will report the UAP to the IRB and the UCCC DSMC within 5 business days of becoming aware of the UAP. If the UAP is not a result of a reportable SAE, then it shall be reported to the Lead PI's IRB with the continuing review.

The UAP report will include the following protocol-identifying information: protocol title and number, PI's name, and the IRB project number, in addition to:

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The following section must be reviewed by UCCC Biostatistics.

- Primary Efficacy Endpoint(s):
  <<INSERT - Text>>

- Secondary Efficacy Endpoint(s):
  <<INSERT - Text>>

- Justification for Endpoints:
  <<INSERT - Text>>

9.2 SAMPLE SIZE DETERMINATION

<<INSERT - Text>>

9.3 POPULATION FOR ANALYSES

<<INSERT - Text>>

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

<<INSERT - Text>>

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

<<INSERT - Text>>

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

<<INSERT - Text>>

9.4.4 SAFETY ANALYSES (REQUIRED FOR PHASE I STUDIES)

<<INSERT - Text>>

9.4.5 BASELINE DESCRIPTIVE STATISTICS

<<INSERT - Text>>

9.4.6 PLANNED INTERIM ANALYSES (REQUIRED FOR PHASE I STUDIES)

<<INSERT - Text>>

9.4.6.1 SUB-GROUP ANALYSES

<<INSERT - Text>>

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

<<INSERT - Text>>

9.4.8 EXPLORATORY ANALYSES

<<INSERT - Text>>

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

REQUIRED TEXT:

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

REQUIRED TEXT:

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speakingand non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.<If applicable>.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

<<INSERT - Text>>

10.1.3 CONFIDENTIALITY AND PRIVACY

REQUIRED TEXT:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor-investigator(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information

generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor-investigator, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at <INSERT LOCATION> t This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at <INSERT LOCATION>.

10.1.4 BANKING AND FUTURE USE OF STORED SPECIMENS AND/OR DATA

REQUIRED TEXT:

- **Intended Use:** Samples and data collected under this protocol may be used to study <<INSERT - specify condition>> in the future.
- **Storage:** Access to stored samples will be limited using <<INSERT - specify approach>>. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

REQUIRED TEXT *(if applicable)*:

The following information obtained from the subject's medical record may be recorded and may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if required
- Demographic data

These samples could be used for research into the causes of <<insert text>>its complications and other conditions for which individuals <<insert text>> are at increased risk, and to improve treatment. University of Colorado Pathology Shared Resource will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, and individual participant can choose to withdraw consent to have biological specimens stored for future research. If future use is denied or withdrawn by the participant, best efforts will be made to stop any additional studies and to destroy the specimens. However, withdrawal of consent with regard to bio- sample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Pathology Shared Resource.

Specimens will be stored indefinitely or until they are used up. However, once the study is completed, specimens must be transferred to a COMIRB approved tissue bank/data repository protocol designed specifically for secondary research.

10.1.5 SAFETY OVERSIGHT

REQUIRED TEXT:PLEASE INCLUDE APPLICABLE LANGUAGE AVAILABLE ON DSMC WEBSITE)

https://medschool.cuanschutz.edu/colorado-cancer-center/clinical-trials/dsmc

10.1.6 CLINICAL MONITORING

MONITORING IS REQUIRED FOR INVESTIGATIONAL DRUG IIT
EXAMPLE TEXT:

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by <ENTER MONITOR INFORMATION> in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP

describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

REQUIRED TEXT:
Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

****REQUIRED TEXT SINGLE SITE**

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI. Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

****REQUIRED TEXT MULTI SITE**

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI. Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

REQUIRED TEXT:

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. <DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.>

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <<INSERT - specify name of data capture system>>, OR a 21 CFR Part 11-compliant data capture system provided by the <<INSERT - specify name>> for high-risk studies with an Investigator held IND or IDE. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

REQUIRED TEXT:

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

REQUIRED TEXT:

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to <<INSERT – names of all entities to which reporting is required (i.e., DSMC, COMIRB, study agent manufacturer, etc.)>>. Protocol deviations must be sent to the local IRB per institutional guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

REQUIRED TEXT:

This study will ensure that the public has access to the published results of this research.

As required, either for publication (the ICMJE or other publication policy), or according to U.S. regulations (Section 801 of the Food and Drug Administration Amendments Act of 2007) this clinical trial will be registered in a public trials registry including ClinicalTrials.gov, which is sponsored by the National Library of Medicine, and the NCI CTRP Registry for cancer clinical trials.

10.1.11 CONFLICT OF INTEREST POLICY

REQUIRED TEXT:

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of

Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

11 REFERENCES

<<INSERT - text>>