**How To Use This Template**

This template contains two types of text: instruction/explanatory and example.

**Instruction/explanatory text** are indicated by *italics and highlighted*. This text provides information on the content that should be included. It also notes if a section should be left blank. For example, many headings include the­­­ instruction, “*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*”

**Example text** is included to further aid in protocol writing and should either be modified to suit the study intervention, design, and conduct of the planned clinical trial or deleted. Example text is indicated in [regular font]. Within example text, a need for insertion of specific information is notated by <angle brackets>.

Instruction/explanatory text and footnotes to instructional text should be deleted. Example text can be incorporated as written or tailored to a particular protocol. If it is not appropriate to the protocol, however, it too should be deleted. The section headers include formatting to generate a table of contents. Use the outlining tool bar at the top of the page if you need to add additional sections to the protocol to ensure the table of contents structure is maintained. Use the insert caption tool to insert tables and figure headings.

Version control is important to track protocol development, revisions, and amendments. It is also necessary to ensure that the correct version of a protocol is used by all staff conducting the study. With each revision, the version date on each page should be updated. When making changes to an approved and “final” protocol, the protocol amendment history should be maintained (see section 13.2).

Some sections in this template were taken from the NIH/FDA published template found here:

https://grants.nih.gov/policy/clinical-trials/protocol-template.htm

However, this template is not applicable for drug studies or device studies regulated by the FDA. Please contact the protocol development team if you have a drug and/or device study.

([RHITCREGULATORY@uvahealth.org](mailto:RHITCREGULATORY@uvahealth.org)).

**<Title>**

*The title should be easy to remember, recognizable by administrative support staff, and sufficiently different from other protocol titles to avoid confusion. Brevity with specificity and neutrality is the goal. If there is a “short title” (e.g., an abbreviation used to refer to the study title, include here and that can be used throughout this document in place of the full title).*

**Protocol Number: < Number>**

**National Clinical Trial (NCT) Identified Number: <Number, if available>**

**Principal Investigator:** **< Principal investigator>**

**Funded by: <Funding Source>**

**Version Date: <Day Month Year>**

*All versions should have a version date. Use the international date format (day month year) and write out the month (e.g., 23 June 2015).*

**Confidentiality Statement**

The information contained in this document is the property of the <*insert as applicable -for cancer trials with OCR/HITC:* University of Virginia Cancer Center Office of Clinical Research and the Human Immune Therapy Center>. Distributing, copying, or disclosing information contained in this document requires prior authorization from the < *insert as applicable*, *for cancer trials:* University of Virginia Comprehensive Cancer Center>, except that this document may be disclosed to the appropriate institutional review boards.

**Key Roles and Study Governance**

|  |  |  |
| --- | --- | --- |
| **Principal Investigator** | **<Name, address, and contact information>** | |
| **Sub-Investigators at the University of Virginia** *Optional to include – if there are many co-I’s or they are likely to change, don’t include* | **< Name, address, and contact information>**  Note: If there are multiple co-investigators, you may not want to list them all here, but do make sure they are listed with the IRB. Include name and contact information. |  |
| **Biostatisticians:** | **< Name, address, and contact information>** |  |
| **Authors:** | **<Optional to list authors>** | |
| **Data Coordinating Center:** | **<Name, address, contact information>**  **<University of Virginia School of Medicine Multi-site Clinical Research Office (UVA SOM MCRO)>**  ***Note: If this not a multi-center study, remove this line*** | |

# STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with applicable United States (US) Code of Federal Regulations (CFR) and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award (*include NIH if applicable*). International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines will be incorporated consistent with institutional practice. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Principal Investigator and documented approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection <and GCP Training> *(if applicable)*.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

*For single site UVA investigator-initiated trials. (delete for multi-site trials)*

**Principal Investigator**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_**

**Name (print) Signature Date**

*For all multi-site trials (delete for single site trials)*

**Lead Principal Investigator**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_**

**Name (print) Signature Date**

**Investigator**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_**

**Name (print) Signature Date**

# TABLE OF CONTENTS

[STATEMENT OF COMPLIANCE 3](#_Toc152927522)

[TABLE OF CONTENTS 4](#_Toc152927523)

[ABBREVIATIONS 6](#_Toc152927524)

[1 PROTOCOL SUMMARY 8](#_Toc152927525)

[1.1 Synopsis 8](#_Toc152927526)

[1.2 Schema 9](#_Toc152927527)

[2 INTRODUCTION 10](#_Toc152927528)

[2.1 Study Rationale 10](#_Toc152927529)

[2.2 Background 10](#_Toc152927530)

[2.3 Risk/Benefit Assessment 10](#_Toc152927531)

[3 OBJECTIVES AND ENDPOINTS 11](#_Toc152927532)

[4 STUDY DESIGN 11](#_Toc152927533)

[4.1 Overall Design 11](#_Toc152927534)

[4.2 End of Study Definition 12](#_Toc152927535)

[5 STUDY POPULATION 12](#_Toc152927536)

[5.1 Inclusion Criteria 12](#_Toc152927537)

[5.2 Exclusion Criteria 13](#_Toc152927538)

[5.3 Justification for Study Population 14](#_Toc152927539)

[5.4 Lifestyle Considerations 14](#_Toc152927540)

[5.5 Screen Failures 15](#_Toc152927541)

[5.6 Strategies for Recruitment and Retention 16](#_Toc152927542)

[6 STUDY INTERVENTION 16](#_Toc152927543)

[6.1 Description of Study Intervention(s) 16](#_Toc152927544)

[6.2 Registration, Randomization and Blinding 17](#_Toc152927545)

[6.3 Concomitant Therapy 19](#_Toc152927546)

[7 STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION or WITHDRAWAL 19](#_Toc152927547)

[7.1 Study Discontinuation and Closure 19](#_Toc152927548)

[7.2 Participant Discontinuation/Withdrawal 20](#_Toc152927549)

[7.3 Dose-Limiting Toxicity 21](#_Toc152927550)

[7.4 Procedures for Discontinuation of Study Intervention 21](#_Toc152927551)

[7.5 Lost to Follow-Up 21](#_Toc152927552)

[8 STUDY ASSESSMENTS AND PROCEDURES 22](#_Toc152927553)

[8.1 Clinical Assessments 22](#_Toc152927554)

[8.2 Research Specimen Collection 24](#_Toc152927555)

[8.3 Correlative Studies 24](#_Toc152927556)

[8.4 Participant Reported Outcomes 24](#_Toc152927557)

[9 DATA AND SAFETY MONITORING PLAN 24](#_Toc152927558)

[9.1 Adverse Events and Serious Adverse Events 25](#_Toc152927559)

[9.2 Reporting Events to Participants 32](#_Toc152927560)

[9.3 Events of Special Interest 32](#_Toc152927561)

[9.4 Reporting of Pregnancy 33](#_Toc152927564)

[9.5 Unanticipated Problems 33](#_Toc152927565)

[9.6 Data Breach 35](#_Toc152927566)

[9.7 Protocol Deviation 35](#_Toc152927567)

[9.8 Participant Withdrawals/Dropouts Prior to Study Completion 37](#_Toc152927568)

[10 STATISTICAL CONSIDERATIONS 37](#_Toc152927569)

[10.1 Sample Size Determination 37](#_Toc152927570)

[10.2 Populations for Analyses 37](#_Toc152927571)

[10.3 Statistical Analyses 38](#_Toc152927572)

[11 REGULATORY AND OPERATIONAL CONSIDERATIONS 41](#_Toc152927573)

[11.1 Regulatory and Ethical Considerations 41](#_Toc152927574)

[11.2 Data Handling and Record Keeping 49](#_Toc152927575)

[11.3 Publication and Data Sharing Policy 50](#_Toc152927576)

[11.4 Conflict of Interest Policy 51](#_Toc152927577)

[11.5 Additional Considerations 51](#_Toc152927578)

[12 REFERENCES 51](#_Toc152927579)

[13 APPENDICES 52](#_Toc152927580)

[13.1 Schedule of Activities (SoA) 52](#_Toc152927581)

[13.2 Reporting Table 53](#_Toc152927582)

[13.3 Protocol Amendment History 55](#_Toc152927583)

# ABBREVIATIONS

*(Modify table as needed – add study-specific abbreviations and delete abbreviations that are not used)*

|  |  |
| --- | --- |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| DRE | Disease-Related Event |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GWAS | Genome-Wide Association Studies |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator’s Brochure |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| ISO | International Organization for Standardization |
| ITT | Intention-To-Treat |
| LSMEANS | Least-squares Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMC | Safety Monitoring Committee |
| SOA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| US | United States |
| UVA | University of Virginia |
| UVA CC DSMC | University of Virginia Cancer Center Data Safety Monitoring Committee |
| UVA SOM MCRO | University of Virginia School of Medicine Multi-site Clinical Research Office |

# PROTOCOL SUMMARY

*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*

## Synopsis

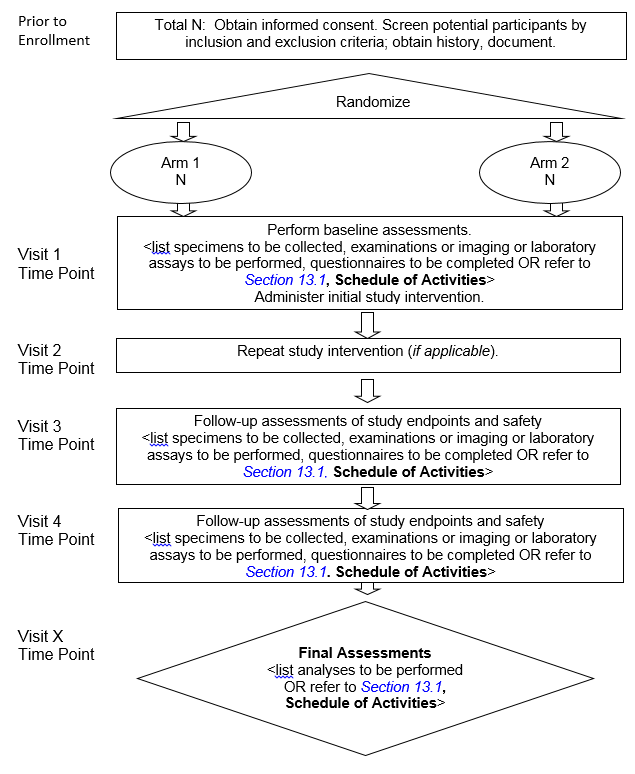
|  |  |
| --- | --- |
| **Title:** | <Full title> |
| **Study Description:**  **Objectives & Endpoints:** | *Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length.*   |  |  | | --- | --- | | **Objectives** | **Endpoints** | | **Primary** |  | | <Primary Objective> | <Primary Endpoint> | | **Secondary** |  | | <Secondary Objective> | <Secondary Endpoint> | | **Exploratory** |  | | <Exploratory Objective> | <Exploratory Endpoint> | |
|  | *Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol.* |
|  | *Include the primary endpoint and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol.*  *Refer to* section 3 *for instructions on objectives and endpoints.* |
| **Study Population** | *Specify the sample size, gender, age, demographic group, general health status, and geographic location.* |
| **Description of Sites/Facilities Enrolling Participants:** | *Provide a brief description of planned facilities/participating sites enrolling participants.* |
| **Description of Study Intervention:** | *Describe the study intervention.* |
| **Study Duration:** | *Estimated time (in months) from when the study opens to enrollment until completion of accrual and data analyses.* |
| **Participant Duration:** | *Time (e.g., in months) it will take for each individual participant to complete all participant visits.* |

## Schema

*This section should include a diagram that provides a quick “snapshot” of the study and ideally be limited to 1 page. An example is provided below.*

<Insert text>

***Example -Flow diagram*** *(e.g., randomized controlled trial)*



# INTRODUCTION

No text is to be entered in this section; rather, it should be included under the relevant subheadings below.

## Study Rationale

State the problem or question and the reason for conducting the clinical trial/hypothesis.

<Insert text>

## Background

This section should include a summary of information that is relevant to the intervention and the study.

<Insert text>

### Pre-Clinical Experience

<Insert text>

### Relevant Clinical Experience

<Insert text>

## Risk/Benefit Assessment

*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*

### Known Potential Risks

Include a discussion of known potential risks (physical, psychological, social, legal, economic etc.) from either clinical or nonclinical studies. <Insert text>

### Known Potential Benefits

Include a discussion of known potential benefits (physical, psychological, social, legal, economic etc.) from either clinical or nonclinical studies.

Note that payment to participants, whether as an inducement to participate or as compensation for time and inconvenience, is not considered a “benefit.” Provision of incidental care is also not to be considered a benefit.

<Insert text>

### Assessment of Potential Risks and Benefits

Include an assessment of known potential risks and benefits. Justify why the risk to benefit ratio is acceptable.

<Insert text>

# OBJECTIVES AND ENDPOINTS

*For purposes of registration and reporting to ClinicalTrials.gov, the terms Objectives and Endpoints as used in this template align with the terms Primary Purpose and Outcome Measures in ClinicalTrials.gov, respectively.*

| OBJECTIVES | ENDPOINTS |
| --- | --- |
| Primary |  |
| The primary objective is the main question. This objective generally drives statistical planning for the trial | The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective (e.g., “the study wins”). |
| Secondary |  |
| The secondary objective(s) are goals that will provide further information on the use of the intervention. | Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention’s effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases. |
| Tertiary/Exploratory |  |
| Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. | Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses. |

# STUDY DESIGN

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

## Overall Design

* *Include a brief description of arms of study (if applicable) and study intervention description.*
* *A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design)*
* *A description of methods to be used to minimize bias*
* *The number of study groups/arms and study intervention duration*
* *Indicate if single site or multi-site*
* *Name of study intervention(s)*
* *Name of sub-studies or optional procedures, if any, included in this protocol. Examples may include optional blood collection or biopsies, optional specimen or imaging analysis.*

This is a <multi/single center/dose escalating/open-label/double blinded/randomized> study of <intervention>

If applicable: Describe the rationale for the type and selection of control group.

<Insert text>

## End of Study Definition

The following language was taken from clinicaltrials.gov. Please do not change.

[Primary completion date is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes defined as the final date for the collection of data for the primary endpoint.

Study completion date is the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant’s last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.]

Collection and analysis of exploratory data may extend beyond the study completion date. The study may remain open with the IRB during this time.

# STUDY POPULATION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment. The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion).

## Inclusion Criteria

Example text provided as a guide, customize as needed:

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

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged <specify range>
4. In good general health as evidenced by medical history or diagnosed with <specify condition/disease> or exhibiting <specify clinical signs or symptoms or physical/oral examination findings>
5. <Specify laboratory test> results between <specify range> or specify Adequate Organ Function per the following criteria:

<Example Table>

|  |  |
| --- | --- |
| **System** | **Laboratory Value** |
| **Hematological** |  |
| Absolute neutrophil count (ANC) | ≥1000/mm3 |
| Platelets | ≥ 100,000/mm3 |
| Hemoglobin | ≥ 9 g/dL |
| **Renal** |  |
| Serum Creatinine | ≤ 1.5 x ULN |
| Hepatic |  |
| Bilirubin | ≤ 1.5 x ULN (except in patients with Gilbert’s disease, where bilirubin to 4x ULN is allowed). |
| AST and ALT | ≤ 2.5 x ULN |
| Alkaline phosphatase | ≤ 2.5 x ULN |
| **Additional** |  |
| HGB-A1C | <7.5% |

*Note: in at least 2 protocols, the FDA has requested that we use creatinine clearance rather than serum creatinine:*

*Consider having the baseline renal function for eligibility be based on creatinine clearance calculated by Cockroft-Gault instead of serum creatinine.*

*If you still want to include serum creatinine rather than CrCl, consider justifying the reason for this choice.*

1. Willing to adhere to the <study intervention> regimen
2. Agreement to adhere to Lifestyle Considerations (see Section 5.4) throughout study duration]

<Insert text>

## Exclusion Criteria

Example text provided as a guide, customize as needed.

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

1. Current use of < specify disallowed concomitant medications*>*
2. Presence of <specific devices (e.g., cardiac pacemaker)>
3. Pregnancy or lactation
4. Known allergic reactions to components of the <study intervention>, <specify components/allergens>
5. Febrile illness within <specify time frame*>*
6. Treatment with another investigational drug or other intervention within *<*specify time frame*>*
7. Current smoker or tobacco use within *<*specify timeframe*>*
8. < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>]

<Insert text>

## Justification for Study Population

If specific populations are excluded (e.g., elderly or pediatric populations, women or minorities), provide a clear and compelling rationale and justification.

<Insert text>

## Lifestyle Considerations

Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet and considerations for household contacts.

Example text provided as a guide, customize as needed:

[During this study, participants are asked to:

* Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from [X days] before the start of <study intervention> until after the final dose.
* Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for [x hours] before the start of each dosing session until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
* Abstain from alcohol for 24 hours before the start of each dosing session until after collection of the final PK and/or pharmacodynamic sample.
* Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.
* Abstain from strenuous exercise for [x hours] before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
* Minimize interactions with household contacts who may be immunocompromised.]

<Insert text>

Example text for contraception, customize as needed:

[**Women of Childbearing Potential**

Women of childbearing potential who are enrolled onto the study must agree to use adequate contraception prior to study entry and for at least <insert time frame> following last dose of study drug.

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy

The following birth control methods are allowed during the study:

1. Barrier methods
   * + - 1. Intra-uterine device (IUD)
         2. Diaphragm with spermicide
         3. Cervical cap with spermicide
         4. Condom with spermicide
2. Hormonal method
3. Hormonal contraceptives (such as the birth control pill)
4. Abstinence (no heterosexual activity)

**Non-vasectomized Males**

Non-vasectomized males who are enrolled onto the study must agree to use adequate contraception for at least <insert time frame> after the last dose of study drug.

For males whose partner is of child bearing potential, the following birth control methods are allowed during the study:

1. Barrier methods
2. Intra-uterine device (IUD)
3. Diaphragm with spermicide
4. Cervical cap with spermicide
5. Condom with spermicide
6. Hormonal method
7. Hormonal contraceptives (such as the birth control pill)
8. Abstinence (no heterosexual activity)

Males must also abstain from sperm donations for at least <insert time frame> days after the last dose of study drug.]

## Screen Failures

Participants who are consented to participate in the clinical trial and who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures. Define Screen failure for your particular study. Indicate how screen failures will be handled in the trial, including conditions and criteria upon which re-screening is acceptable, when applicable.

Example text provided as a guide, customize as needed:

[Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (for NIH studies) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial because of a <specify modifiable factor> may be rescreened.]

## Strategies for Recruitment and Retention

Identify general strategies for participant recruitment and retention.

In addition, this section should include justification for inclusion of vulnerable participants and recruitment strategy. If participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation, describe amount, form and timing of such compensation in relation to study activities (include financial and non-financial incentives).

*Sample text (edit as needed):*

[Potential participants will be identified from UVA’s outpatient clinics, referral from outside physicians, and self-referral. Potential participants may be identified by a treating clinician, or a potential participant may reach out to the study team directly in response to an advertisement or posting (e.g. clinicaltrials.gov).

Planned recruitment strategies include posting the trial information to clinicaltrials.gov. Additionally, the study team may use announcements of the trial sent to referring physicians and patient advocacy groups, local flyers and social media.

The target accrual and the anticipated accrual rate are described in section 10.1.

Procedures to enhance participant retention during follow-up: Follow-up visits will be conducted during standard of care visits to prevent burdening patients with additional study visits. These visits may be supplemented by telemedicine visits as needed. ]

<Insert text>

# STUDY INTERVENTION

No text is to be entered in this section; rather it should be included under the relevant subheadings below. This section may not be relevant for all studies (e.g., blood draw and analysis studies.) For drugs or device studies, please reach out to the protocol development team for a more detailed template.

## Description of Study Intervention(s)

*Describe the study intervention(s) and control product.*

If 2 or more interventions occur on the same day, specify the ordering in which events should occur. Specify the minimum and maximum number of days in between interventions (if applicable).

You may need to include the timing of administration of the intervention and the duration (e.g., the length of time study participants will be administered the study intervention). Be sure to include observation times following treatment and instructions for measurements during observation. For behavioral interventions, provide information about the “dose”/”route”/”timing” of the intervention (e.g., for exercise, type of exercise, number of minutes/day/week, if location is specified, intensity and if they’ll be ramping up for intensity/frequency, or for diet studies, what foods they should/should not eat and how often)

Describe any medications that should be taken prior to the investigational intervention, including dose(s), timing, and route of administration. This may be separated into a different subsection (e.g. Pre-medications) in cancer trials as necessary. State the starting dose and schedule of the study intervention and control product, including the maximum and minimum duration for those participants who continue in the study.

## Registration, Randomization and Blinding

*Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included*

*Consult the biostatistician to verify specifics of your protocol and have the biostatistician review the language in this section:*

<Insert text>

*Example text on registration*

[All participants must sign the consent form prior to determination of eligibility for this study.

*For multi-site studies using the UVA SOM MCRO as the DCC:*

When a site is ready to enroll a patient, the following documentation must be scanned and emailed to the UVA School of Medicine Multi-site Clinical Research Office (UVA SOM MCRO). The UVA SOM MCRO serves as the data coordinating center for this study.

* Patient and staff signed signature page of the current informed consent form (ICF)
* Completed Inclusion/Exclusion checklist demonstrating subject eligibility
* Supporting documentation needed to confirm eligibility (lab results, scan results etc.)

Consult the Study Reference Manual for instructions on sending this information. The UVA SOM MCRO will consult with the Overall Study PI if questions arise in confirming eligibility. The UVA SOM MCRO will communicate the subject number and treatment dose assignment to the enrolling site.

Registration will occur following verification of eligibility by the treating physician.

[Single site studies]Participants to the study should be registered in OnCore in accordance with the Clinical Trial Management System Policy via the UVa OnCore Resources link in Oncore.

[Multi-site studies using the UVA SOM MCRO] Participants to the study will be registered in OnCore by the UVA SOM MCRO in accordance with the Clinical Trial Management System Policy via the UVa OnCore Resources link in Oncore

[All studies]

Participants should receive their first study intervention within <insert time frame here e.g. 2 weeks> of registration.]

*Example language for randomization. The following language is for a multi-site trial.*

[Treatment allocation will be discussed with participants during the process of informed consent, and informed consent must be documented prior to randomization. Randomization will occur after registration and no sooner than 5 days prior to the start of treatment. Randomization will be based on equal allocation among allowable arms unless a weighted allocation scheme is triggered. Randomization will not be stratified by institution. The randomization codes are generated by the study statisticians and stored in the <identify location>. The <study team> will communicate with the outside site to let them know which study arm a participant has been randomized to.]

*If the study is non-randomized and treatment arms are allocated, the following language may apply.*

[Treatment allocation will be discussed with participants during the process of informed consent and will occur after registration. Treatment allocation will be based upon the study design until a safety bound has been triggered or target accrual has been met. Arm allocation slots are generated by the study statisticians. Treatment allocation will occur after registration and within <insert time frame here e.g. 1 week> of the start of treatment.]

*Examples for blinding language provided below. Choose 1 or provide an alternative to describe details for your study.*

*If the study is an open-label trial and the investigator and participant will be able to identify which treatment is administered, you may use the language below:*

[This study does not involve any blinding or masking procedures. Subjects will be told which treatment they are receiving.]

*If the study is a double-blind study, you may use the language below:*

[This study will be conducted in a double-blind, placebo-controlled manner. Subjects will be randomized 1:1 to study intervention and placebo. All study team members and subjects will be blinded to study intervention assignment with the exception of the statisticians.

Unblinded arm assignment for a subject will be made available to the Principal Investigator if the DSMB recommends unblinding.]

### Emergency Unblinding Procedures

*(If applicable, consider the following sample text)*

[Randomization codes and corresponding treatment assignment will be made available to the Investigator and the <Medical Monitor, PI, DSMB or UVA DSMC> for emergency use when applicable. When possible, the <Medical Monitor, PI, DSMB or UVA DSMC> should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the <Medical Monitor, PI, DSMB or UVA DSMC> in advance of unblinding, the Investigator must promptly document in the subject’s source record and should subsequently contact the <Medical Monitor, PI, DSMB or UVA DSMC> to explain any premature unblinding of treatment assignment (such as accidental unblinding or unblinding due to a serious adverse event (SAE)). Procedures for unblinding a subject’s treatment will be provided separately to the Investigator. The <Medical Monitor, PI, DSMB or UVA DSMC> will document within study correspondence the rationale, circumstances, and the person or persons being informed about the unblinding.

## Concomitant Therapy

*If applicable, this section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed.*

*Example text provided as a guide, customize as needed:*

[For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. *Add time period (e.g. from 28 days prior to first study procedure through <x days> following last study treatment and also meds taken for any treatment related SAEs after this time period)* *as applicable. Add option to restrict other investigational drugs or investigational devices, as applicable*]

# STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION or WITHDRAWAL

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

## Study Discontinuation and Closure

List possible reasons for termination or temporary suspension of the study.

*Example text provided as a guide, customize as needed:*

[This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency >. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that would warrant termination or suspension include, but are not limited to

Include/Exclude as applicable to the study:

* [Determination of unexpected, significant, or unacceptable risk to participants

*If applicable, refer to statistical analysis section for rules regarding exceeding the DLT rules*

* Demonstration of efficacy that would warrant stopping
* Insufficient compliance to protocol requirements
* Data that are not sufficiently complete and/or evaluable
* Determination that the primary endpoint has been met
* Determination of futility
* Change in funding status

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Principal Investigator, IRB, Data and Safety Monitoring Committee (if applicable).

Participants receiving study treatment at the time of study discontinuation should complete procedures described in section 7.4.]

<Insert text>

## Participant Discontinuation/Withdrawal

Provide a list of reasons participation may be discontinued (e.g. halting rules).

This section should include a discussion of replacement of participants who withdraw or discontinue early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data. This should be captured in the *Section 10***, Statistical Analyses.**

Example text provided as a guide, customize as needed:

[Participants are free to withdraw from participation in the study at any time upon request.

A participant’s study treatment would be discontinued for the following reasons:

*Include/Exclude and add additional criteria as applicable to the study*:

* Pregnancy
* Significant study intervention non-compliance
* If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant (see section 7.3 for dose-limiting toxicities)
* Disease progression which requires discontinuation of the study intervention
* If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
* Participant unable to receive <study intervention> for,<x days/weeks>.
* Participant decision to withdraw from study treatment and/or the study
* Initiation of prohibited intervention or medication

The reason for participant discontinuation or withdrawal from study treatment will be recorded on the <specify, e.g. case report form>. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, <will> or <will not> be replaced. Participants that withdraw from the study (not only from study treatment, but all study follow-up) will not be contacted for any further study visits.]

## Dose-Limiting Toxicity

If applicable, include definition.

<Insert text>

## Procedures for Discontinuation of Study Intervention

Describe the data to be collected at the time of study intervention discontinuation. Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable).

Example text provided as a guide, customize as needed:

[Discontinuation from <study intervention> does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected and procedures to be completed at the time of study intervention discontinuation are included in the schedule of assessments in *section 13.1*.]

<Insert text>

## Lost to Follow-Up

The protocol should describe the nature and duration of study follow-up.

Example text provided as a guide, customize as needed:

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

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

* The site will attempt to contact the participant and reschedule the missed visit <specify time frame> and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
* Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant *Indicate what efforts will be made prior to determining a participant as lost to follow-up.*
* These contact attempts should be documented in the study file.
* Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

# STUDY ASSESSMENTS AND PROCEDURES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The specific timing of procedures/evaluations to be done at each study visit are captured in *Section 13.1***, Schedule of Activities (**SoA) and the time points of these procedures do not need to be included here. In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.

## Clinical Assessments

If an individual’s medical chart or results of diagnostic tests performed as part of an individual’s regular medical care are going to be used for screening or as a part of collection of trial data, Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements should be followed, as applicable. If this is the case, this section should note which information is to be obtained through review of existing data.

<Insert text>

### Physical Exam

*Example text, customize as needed:*

* **Physical examination** (e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). *If appropriate, discuss what constitutes a targeted physical examination.*
* **Vital signs** (e.g., temperature, pulse, respirations, blood pressure). *Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs.*

### Clinical Laboratory Assessments

* ***Biological specimen collection and laboratory evaluations****. Include specific test components and estimated volume and type of specimens needed for each test.*

Example text provided as a guide, customize as needed:

[The following laboratory values will be recorded in the eCRFs, graded using the CTCAE v5 (if a grading category exists), and reported as described in Sections 9.1.6 and 9.1.7]:

Include table of lab procedures (see example below) for studies with multiple lab assessments. Only include lab values that the investigator wants included in the eCRFs (e.g. for analysis).

| Table X: Clinical Labs | | | |
| --- | --- | --- | --- |
| **Hematology** | **Chemistry** | **Urinalysis** | **Other** |
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin (β-hCG)1 |
| Hemoglobin | Alkaline phosphatase | Glucose | ANA |
| Platelet count | Alanine aminotransferase (ALT) | Protein | Rf |
| WBC (total and differential)3 | Aspartate aminotransferase (AST) | Specific gravity | Blood for correlative studies: Section XX.XX |
| Red Blood Cell Count | Carbon Dioxide*(CO2 or bicarbonate)* | Microscopic exam *(If abnormal)* | HIV2 |
| Absolute Neutrophil Count3 | Calcium | Urine pregnancy test1 | HCV2 |
| Absolute Lymphocyte Count3 | Chloride |  | HGB-A1C |
| Absolute Eosinophil Count3 | Creatinine |  |  |
|  | Glucose |  |  |
|  | Potassium |  |  |
|  | Sodium |  |  |
|  | Total Bilirubin |  |  |
|  | Direct Bilirubin *(If total bilirubin is elevated above the ULN)* |  |  |
|  | Total protein |  |  |
|  | Blood Urea Nitrogen |  |  |
| 1 Perform on women of childbearing potential only. Either a urine pregnancy test or serum pregnancy test may be performed; however, if a urine pregnancy result cannot be confirmed as negative, a serum pregnancy test will be required.  2 Antibody screen; reflexive testing to determine whether active disease is present.  3 If WBC count falls below the institutional threshold for reporting of differential, differential values are not required (as they are not available) | | | |

### Imaging

* ***Radiographic or other imaging assessments****. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging.*
* *Include in this section a discussion of the results of any study specific procedures that will be provided to participant (e.g., radiographic or other imaging or laboratory evaluations).*

<Insert text>

### Assessment of Adverse Events

Example text provided below.

Note: For cancer clinical trials, please reference the CTCAE for the characterization and grading of adverse events. (<https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm>)

When grading a toxicity, if you are unable to find an adverse event term to match your adverse event, select the system organ class and “other” and add a description of the toxicity with the appropriate grade as described in the CTCAE.

[Each participant will be evaluated by a licensed clinician at each study visit. The [NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 (*if applicable*) <or other assessment mechanism> will be used for the characterization and grading of adverse events.

Toxicity diaries will be distributed to participants and reviewed by study personnel.]

### Other Clinical Assessments

If desired, you may add subsections with the assessment title for easier navigation

## Research Specimen Collection

Please do not include information here but feel free to add additional subsections using the outlining toolbar for other specimen types.

### Tissue

If tissue will be collected via biopsy, include information on how much tissue is required, instructions for collection, and what initial processing is necessary

### Research Blood

If research blood will be collected, include information on how much blood will be drawn, what tubes should be used, and what initial processing is necessary.

### Stool

## Correlative Studies

Specify any special assays or proceduresthat arerequired

## Participant Reported Outcomes

Include information on all questionnaires and/or diaries including time necessary for completion, whether they have been validated, and type of information they collect.

# DATA AND SAFETY MONITORING PLAN

*In the following section, there are references to “days”, “calendar days” and “working days”. References to “days” should be interpreted as calendar days. Working days include Monday through Friday with the exception of Federal holidays.*

## Adverse Events and Serious Adverse Events

Consider the risks of the study intervention. Review and reference the applicable sources of information. If your study is a minimal risk study (e.g., minimal risk behavioral intervention, blood draw and analysis study, etc.), you may consider stating the following:

[There are not expected to be frequent reportable adverse events; however, any adverse events that arise and that meet the definition for adverse event reporting will be reported as described].

### Definition of Adverse Events (AE)

Provide the definition of an AE being used for the clinical trial.

Example text:

[Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.]

### Definition of Serious Adverse Events (SAE)

Provide the definition of an SAE being used for the clinical trial.

Example text provided as a guide, customize as needed.

[An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, 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 participant 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.]

*You may also consider adding the following clarification:*

[A planned medical or surgical procedure is not, in itself, an SAE]

### Classification of an Adverse Event

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

#### Severity of Event

AEs will be assessed by the study clinician using a protocol defined grading system. Describe the method of grading an AE for severity.

#### Relationship to Study Intervention

AEs will have their relationship to study intervention or study participation assessed with a level of specificity appropriate to the study design.

If the table in the reporting section does not require reporting of grade 1 and or 2 events, then consider adding “reportable” in the first sentence before “adverse events”.

Example text provided as a guide, customize as needed:

[Adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

* **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 study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. [*Add “If applicable”, to the beginning of the next sentence for example, if there is one intervention/treatment]* The response to withdrawal of the study intervention (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 study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and [*add “if applicable” in cases where this may not apply]*, 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 study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) 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 intervention 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.]

#### Expectedness

Expected adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Identify the source of the reference safety information used to determine the expectedness of the AE. Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.

Example text provided as a guide, customize as needed:

[The <insert role> will be responsible for determining whether an adverse event (AE) is expected or unexpected by assessing all AEs against cumulative study drug experience. Expectedness for adverse events and expectedness for the purposes of expedited reporting will be determined based on review of the following reference documents that describe the nature, severity, and frequency of the events. ]

OR

[<Insert role> will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE 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 intervention.]

<Insert text>

Or

[Adverse events that are considered expected for the purposes of expedited reporting may be found in section [insert IB section number] of the investigator’s brochure.]

Or

[Table 1 includes adverse drug reactions for <insert drug name> that are considered expected for the purposes of expedited reporting.]

Include all expected adverse events in the table below. If you are aware of the maximum grade you’d expect for the event, indicate the maximum grade. If you are not aware of the maximum grade, then just list the event types.

Table 1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Adverse event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

### Abnormal Laboratory Values

Example text provided for three different options. Choose one, if applicable

1. *All abnormal lab results are also reported as AEs:*

[Abnormal lab results, regardless of clinical significance, will also be reported as AEs as described in section 9.1.6.]

1. *Abnormal lab results for items listed in* section *8.1.2*  *will also be reported as AEs, but other abnormal lab results will only be reported as AEs if they are considered clinically significant. If only select lab values in the table in section 8.1.2 should be reported, regardless of clinical significance, then these select labs should be marked (e.g. with bold formatting, an asterisk, or otherwise) and the language below should be altered as indicated (from “listed” to “bolded”, “starred”, etc.)*

[All abnormal results from lab values listed in *section 8.1.2* should be reported as AEs, regardless of clinical significance. Abnormal lab test values for labs that are not [listed/bolded, or starred (*depending on whether all labs listed in the table are excluded, or only those marked)*] in the table in *section 8.1.2* will not be reported as AEs unless they are considered clinically significant, meaning one or more of the following are true: there is an associated clinical condition for which the patient is being monitored or given treatment, the event indicates further testing to assess for a related clinical condition, concomitant treatment is altered, or the event is considered a serious adverse event. Abnormal lab values that are reported as AEs should be reported as described in section 9.1.6.]

1. *Abnormal lab results that are not considered clinically significant will not be reported as AEs. {Note that this would mean that abnormalities not considered clinically significant will not be on any weekly/monthly safety reports provided by Biostats, if this is usually available in your population}*

[Abnormal lab test values will not be reported as AEs unless they are considered clinically significant, meaning one or more of the following are true: there is an associated clinical condition for which the patient is being monitored or given treatment, the event indicates further testing to assess for a related clinical condition, concomitant treatment is altered, or the event is considered a serious adverse event. Abnormal lab values that are reported as AEs should be reported as described in section 9.1.6.]

### Time Period and Frequency for Event Assessment and Follow-Up

Describe how AEs and SAEs will be identified and followed until resolved or considered stable.

*Example text provided as a guide, customize as needed:*

[The occurrence of an adverse event (AE) or serious adverse event (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.

[AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (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. AEs occurring while on study must be documented appropriately regardless of relationship. AEs will be followed to adequate resolution.

Any medical condition (including a laboratory abnormality) that is present at the time that the participant is screened will be considered as baseline and not recorded as an AE. However, if the study participant’s baseline medical condition worsens at any time during the study, it will be recorded as an AE.

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.

<Insert role or name> will record all reportable events with start dates occurring any time after the initiation of the intervention until [e.g. 30 days (for non-serious AEs) or until a participant begins a new anticancer therapy (if applicable), whichever occurs first, or anytime after the last day of study treatment for SAEs , if the investigator feels an SAE is reasonably related to study participation.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.] *Note: If desired (may be preferable if there will be an extended period from consent to first study intervention), revise to exclude events that occur between consent and start of study intervention unless at least possibly related to study-specific assessment).*

*Consider adding the following if applicable to your study/population: [*If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.]

### Adverse Event Reporting

This section addresses responsibilities of investigators for reporting of AEs.

<Insert text>

AEs must be recorded into the [enter location, e.g., UVA OnCore or Advarra database, RedCap, paper case report forms] per the following guidelines (Table 2).

*If applicable:* In the event of a DLT, site staff must report the occurrence within [time period, e.g. 24 hours] from the time the study team received knowledge of the event. A DLT must be reported by <method, e.g. email or phone> to <all required recipients, e.g. study PI (or designee), UVA School of Medicine Multi-site Clinical Research Office (UVA SOM MCRO)>, and the <form name, e.g. DLT CRF> must be completed. DLT’s that are deemed serious will be submitted according to the reporting guidelines in section 9.1.7.

*For Cancer Center Studies, SELECT A TABLE BASED ON RISK LEVEL. In some cases, changes may be made to the table based on the type of study. For example, if the low risk study is a likely safe behavioral intervention in a population that will likely have significant adverse events from other causes (disease, treatment), it may make sense to avoid reporting unrelated/unlikely related high grade events as listed in the table. Alternatively, the study may want to have low level events that are considered related to the intervention be listed so that they can present all risks in analysis/publication. If changes are made, these should be listed/described above the table and, in some cases, discussed with the DSMC prior to submission*

Table 2

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table A: High Risk Studies**  Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment | | | | | | | | |
|  | Grade 1 | Grade 2 | | Grade 3 | | | | Grade  4 & 5 |
| Expected  and  unexpected | Expected | Unexpected | Expected | | Unexpected | | Expected  and  Unexpected |
| Without  hospitalization | With  hospitalization | Without  hospitalization | With  hospitalization |
| Unrelated  Unlikely | 30 days | 30 days | 30 days | 30 days | 15 days | 30 days | 15 days | 7 days |
| Possible  Probable  Definite | 30 days | 30 days | 15 days | 30 days | 15 days | 7 days | 7 days | (24-hrs)\*  7 days |
| \*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment  Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table B: Medium Risk Studies**  Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment | | | | | | | | | |
|  | Grade 1 | Grade 2 | | Grade 3 | | | | Grade 4 & 5 | |
| Expected  and  unexpected | Expected | Unexpected | Expected | | Unexpected | | Expected | Unexpected |
| Without  hospitalization | With  hospitalization | Without  hospitalization | With  hospitalization |
| Unrelated  Unlikely | Not required | Not required | Not required | 30 days | 15 days | 30 days | 15 days | 15 days | 15 days |
| Possible  Probable  Definite | 30 days | 30 days | 15 days | 30 days | 15 days | 15 days | 15 days | 15 days | (24-hrs)\*  7 days |
| \*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment  Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours | | | | | | | | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table C: Low Risk Studies**  Reporting requirements for AEs that that occur within 30 days of the last protocol specified treatment/intervention | | | | | |
|  | Grade 1-2 | Grade 1-2 | | Grade 3 | Grade 4-5 |
| Expected | Unexpected | | Expected or  Unexpected | Expected or  Unexpected |
|  | Without  hospitalization | With  hospitalization |
| Unrelated  Unlikely | Not required | Not required | Not required | Not required | 15 days |
| Possible  Probable  Definite | Not required | Not required | 30 days | 15 days | (24-hrs)\*  15 days |
| \*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment  Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours | | | | | |

### 

### Serious Adverse Event Reporting

This section addresses responsibilities of investigators for reporting of SAEs. Describe the SAE reporting procedures, including timeframes.

*Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included* ***in* Section 9.1.2**, ***Definition of Serious Adverse Events*** *must be submitted on an SAE form to the Data Coordinating Center (DCC) if one exists for the study. Studies overseen by a DSMB or other independent oversight body (e.g., safety monitoring committee, independent safety monitor), may be required to submit expedited notification of all SAEs or only SAEs thought to be related to study intervention.*

*Example text provided as a guide, customize as needed:*

[The study clinician will report any serious adverse event, whether or not considered study intervention related, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. [Applicable for multi-site studies: Other supporting documentation of the event may be requested by the UVA School of Medicine Multi-site Clinical Research Office (<*select appropriate choice-UVA SOM MCRO/Principal Investigator*>) and should be provided as soon as possible].

**Single Site Studies *(Where UVA-IRB-HSR is the IRB of record)***

* Internal Event Resulting in death that is deemed DEFINITELY related to (caused by) study participation
* Report to the UVA IRB-HSR within 24 hours. Report within 24 hours using IRB Online and a phone call.
* Report to < funding source > within <specify timeframe, e.g. 24 hours> of awareness of the event. *If applicable.* *Check contract for details*
* Internal, Serious, Unexpected, Related [*If “Related” is included here, be sure that the IRB application matches]*
  + Report to the UVA IRB-HSR within 7 days from the time the study team receives knowledge of the event. Timeline includes submission of signed hardcopy of AE form. Report using IRB Online.
* Internal, Serious
  + Report to < funding source > within <specify timeframe, e.g. 24 hours> of awareness of the event. *Check contract for details.*

**Multi-site Studies**

**Site Reporting Requirements**

**Any event deemed serious**

* Report to the [*select <UVA SOM-MCRO for multi-site non-FDA regulated studies coordinated by the SOM-MCRO, or Principal Investigator for other multi-site, non-FDA regulated studies*> within 24 hours from the time the study team received knowledge of the event.
* Report to your IRB in accordance with your IRB guidelines.

(For sites that use the UVA IRB-HSR as the IRB of record, the UVA SOM MCRO or the Principal Investigator will report to the UVA IRB-HSR)

<*select UVA SOM-MCRO for multi-site non-FDA regulated studies coordinated by the SOM-MCRO, or Principal Investigator for other multi-site, non-FDA regulated studies*>**Reporting Requirements**

* Report to < manufacturer/funding source> within <specify timeframe, e.g. 24 hours> of awareness of the event. *If applicable, check contract for details*
* Notify the UVA IRB-HSR of any event resulting in death that is deemed DEFINITELY related to (caused by) study within 24 hours from the time the study team received knowledge of the event. Report using IRB Online and by telephone.
* Notify the UVA IRB-HSR of any serious, unexpected, related adverse event within 7 calendar days from the time the study team receives knowledge of the event. Timeline includes submission of signed hardcopy of AE form. Report using IRB online.

## Reporting Events to Participants

Include content in this section if applicable, otherwise note as not-applicable.

Describe how participants will be informed about AEs and SAEs, and study-related results on an individual or aggregate level. In addition, describe plans for detecting and managing incidental findings associated with study procedures.

*Example text*:

[If there is any new information relevant to the participant’s willingness to continue to participate in the study, such as if there are new risks of the study treatment identified that were not included on the consent form that the participant signed, the study team will contact the participant to discuss this information. If the participant is still receiving study treatment, the study team will present the participant with an updated consent and confirm that he or she wants to continue receiving study treatment. The Principal Investigator will determine whether new risks are applicable to participants who are in follow-up, whether participants need to be notified, and whether re-consenting is required.]

## Events of Special Interest

Include content in this section if applicable, otherwise note as not-applicable.

Describe any other events that merit reporting to the Principal Investigator, study leadership, or IRB. For example, in oncology trials, secondary malignancies are often captured.

Include any other reportable events not already included in the previous sections, such as cardiovascular and death events, laboratory test abnormalities, and study intervention overdose.

<Insert text>

## Reporting of Pregnancy

Include content in this section if applicable, otherwise note as not-applicable. Pregnancy is not an adverse event, but some studies will require unique considerations if pregnancy was to occur during the study. Provide appropriate modifications to study procedures (e.g., discontinuation of study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).

<Insert text>

## Unanticipated Problems

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

### Definition of Unanticipated Problems (UP)

*The reporting of UPs applies to non-exempt human subjects research conducted or supported by HHS. Provide the definition of an UP being used for this clinical trial. An incident, experience, or outcome that meets the definition of an UP generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Other UPs may warrant corrective actions at a specific study site. Examples of corrective actions or changes that might need to be considered in response to an UP include:*

* *Modification of inclusion or exclusion criteria to mitigate the newly identified risks*
* *Implementation of additional safety monitoring procedures*
* *Suspension of enrollment of new participants or halting of study procedures for enrolled participants*
* *Modification of informed consent documents to include a description of newly recognized risks*
* *Provision of additional information about newly recognized risks to previously enrolled participants*.

*Example text provided as a guide; customize as needed:*

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs)(may include a data breach) 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 Institutional Review Board (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.

### Unanticipated Problem Reporting

*This section addresses responsibilities of investigators for reporting of UPs. Describe the UP reporting procedures, including timeframes.*

***Single Site Studies (UVA IRB-HSR is the IRB of Record)***

* Report UPs that are not adverse events, protocol deviations, or data breaches (see section 9.6 for reporting for data breaches) to the UVA IRB-HSR within 7 calendar days from the time the study team receives knowledge of the event. Report using the Unanticipated Problem Report form.
* Report UPs that are SAEs in accordance with the guidelines for SAE reporting.
* *For reporting to manufacturers of study interventions, refer to the contract for reporting requirements and include here (if applicable)*

**Multi-site Studies**

**Site Reporting Requirements**

* UPs that are SAEs will be reported in accordance with the guidelines for SAE reporting.
* UPs that are not adverse events, protocol deviations or data breaches (see section 9.6 for reporting for data breaches)
  + Report to the < Study Team/UVA SOM MCRO> within <include time frame, e.g. 2 calendar days> from the time the study team receives knowledge of the event.
  + Report to your IRB of record in accordance with your IRB guidelines.

(For sites that use the UVA IRB-HSR as the IRB of record, the UVA SOM MCRO or the Principal Investigator will report to the UVA IRB-HSR)

<*select UVA SOM-MCRO for multi-site non-FDA regulated studies coordinated by the SOM-MCRO, or Principal Investigator for other multi-site, non-FDA regulated studies*>**Reporting Requirements**

* Report UPs that are not adverse events or protocol deviations to the UVA IRB-HSR within 7 calendar days from the time the study team receives knowledge of the event. Report using the Unanticipated Problem Report form.
* *For reporting to manufacturer/funding source, refer to the contract for reporting requirements and include here*.
* All UPs will be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with institutional policies.

### Reporting Unanticipated Problems to Participants

*Include content in this section if applicable, otherwise note as not-applicable.*

*Describe how participants will be informed about UPs on an individual or aggregate level.*

*Example text provided below.*

[If during the course of the study there is an unanticipated problem that affects current or past participants, affected participants will be contacted if needed.]

## Data Breach

*No text entered in this section.*

### Definition of Data Breach

An unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

### Reporting a Data Breach

**Single Site Studies**

* Report to the UVA Corporate Compliance and Privacy Office as soon as possible and no later than 24 hours from the time the incident is identified. Report by telephone.
* Report to InfoSec if the breach involves electronic data. Report as soon as possible and no later than 24 hours from the time the incident is identified. Refer to the following for details: <http://security.virginia.edu/report-information-security-incident>.
* Report to UVA police if the breach includes such things as stolen computers. Report by telephone.

**Multi-site Studies**

**Site Reporting Requirements**

* Report to the <*select Principal Investigator or UVA SOM MCRO*> within 24 hours from the time the study team receives knowledge of the event.
* Report to your IRB of record in accordance with your IRB guidelines.

(For sites that use the UVA IRB-HSR as the IRB of record, the UVA SOM MCRO or the Principal Investigator will report to the UVA IRB-HSR)

<*select UVA SOM-MCRO for multi-site non-FDA regulated studies coordinated by the SOM-MCRO, or Principal Investigator for other multi-site, non-FDA regulated studies***>Reporting Requirements**

* Report to the UVA Corporate Compliance and Privacy Office as soon as possible and no later than 24 hours from the time the incident is identified. Report by telephone.
* Report to ITC if the breach involves electronic data. Report as soon as possible and no later than 24 hours from the time the incident is identified. Refer to the following for details: <http://security.virginia.edu/report-information-security-incident>.
* Report to UVA police if the breach includes such things as stolen computers. Report by telephone.

## Protocol Deviation

No text entered in this section.

### Definition of Protocol Deviation

Plans for detecting, reviewing, and reporting deviations from the protocol should be described. A statement should be included to indicate that deviations are not allowed, unless a statement is included in the investigator agreement. Provisions for approval of deviations can be described.

Example text provided as a guide, customize as needed:

[A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

* 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.

Or

**[A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution’s IRB prior to its initiation or implementation, OR deviation from** standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. **Protocol violations may or may not be under the control of the study team or UVa staff.** These protocol violations may be major or minor violations.]

### Reporting of a Protocol Deviation

[It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to <if applicable, specify NIH Institute or Center (IC)> Program Official and <specify Data Coordinating Center >. *Include NIH center, DCC and Principal Investigator as applicable.*

**Single Site Studies**

* Report to the UVA IRB-HSR major deviations within 7 calendar days from the time the study team received knowledge of the event. Report using the Protocol Deviation and Protocol Exception Reporting Form.
* Report major deviations on the eCRF within 7 calendar days from the time the study team received knowledge of the event.
* For minor deviations, please reference the IRB-HSR for tips for recording minor deviations. These deviations should be recorded in a log.

**Multi-Site Studies**

**Site Reporting Requirements**

* Report major deviations to the <*select UVA SOM MCRO or Principal Investigator*> within 4 calendar days from the time the study team receives knowledge of the event. Refer to the [Study Reference Manual] for instructions on recording minor deviations.
* Report to your IRB of record in accordance with your IRB guidelines.

(For sites that use the UVA IRB-HSR as the IRB of record, the UVA SOM MCRO will report to the UVA IRB-HSR as required)

[select “UVA SOM-MCRO” for multi-site non-FDA regulated studies coordinated by the SOM-MCRO, or “Principal Investigator” for other multi-site, non-FDA regulated studies **Reporting Requirements**

* Report to the UVA IRB-HSR major deviations within 7 calendar days from the time the study team received knowledge of the event. Report using the Protocol Deviation and Protocol Exception Reporting Form.
* Minor deviations do not need to be reported to the UVA IRB-HSR; however, they will be recorded in a log. ]

<Insert text>

## Participant Withdrawals/Dropouts Prior to Study Completion

Participants who withdraw consent and those dropping out of the study secondary to an AE will be reported to the IRB of record according to IRB guidelines.

# STATISTICAL CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

## Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

Discuss whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term, *section 10.3.9***, Exploratory Analyses**).

<Insert text>

### Randomization and Measures to Minimize Bias

This section should contain a description of randomization and blinding procedures (if applicable to the study design).

## Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each). As a guide, this may include, but is not limited to, any or all of the following:

* *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
* *Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one dose of study intervention and/or have some particular amount of follow-up outcome data)*
* *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)*
* *Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)*
* *Other Datasets that may be used for sensitivity analyses*

<Insert text>

## Statistical Analyses

*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*

### General Approach

*As a guide, the following should be addressed, as appropriate:*

* *For descriptive statistics, describe how categorical and continuous data will be presented (e.g., percentages, means with standard deviations, median, range).*
* *For inferential tests, indicate the p-value and confidence intervals for statistical significance (Type I error) and whether one or two-tailed.*
* *Indicate whether covariates will be pre-specified in the sections below or later in a SAP.*
* *State whether checks of assumptions (e.g., normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests).*

<Insert text>

### Analysis of the Primary Efficacy Endpoint(s)

*For each primary endpoint:*

* *Define the measurement or observation and describe how it is calculated, if not readily apparent*
* *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure*
* *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here.*
* *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
* *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)*
* *Describe the Populations for which the analysis will be conducted, as discussed in* section 10.2***, Populations for Analyses***
* *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up*
* *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

### Analysis of the Secondary Endpoint(s)

*For each secondary endpoint:*

* *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint*
* *Define the measurement or observation and describe how it is calculated, if not readily apparent*
* *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure.*
* *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, ANCOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.*
* *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (LSMEANS) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, and number-needed-to-treat).*
* *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests).*
* *Describe the Populations for which the analysis will be conducted as discussed in* section 10.2***, Populations for Analyses.***
* *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up.*
* *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

*Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.*

<Insert text>

### Safety Analyses

Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in *section 10.3.2***, Analysis of the Primary Efficacy Endpoint(s)** should be included here. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing. The information included here should be consistent with the information contained within *section 8.1.4*.

<Insert text>

### Baseline Descriptive Statistics

Include content in this section if applicable, otherwise note as not-applicable.

Intervention groups should be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Discuss planned baseline descriptive statistics, indicate whether inferential statistics will be used.

<Insert text>

### Planned Interim Analyses

*Include content in this section if applicable, otherwise note as not-applicable.*

*This section should describe the types of statistical interim analyses and halting guidelines (if any) that are proposed, including their timing and who reviews the interim analyses. In addition, if the interim analyses could result in an adjusted sample size, discuss the statistical algorithm to be used when evaluating results. Pre-specify, to the extent possible, the criteria that would prompt an interim review of safety and efficacy data and trial futility. Describe who performs the statistical analysis and who reviews the analysis. In addition, discuss whether they are unblinded and how the blinding will be preserved.*

If statistical rules will be used to halt enrollment into all or a portion of the study (e.g., for safety or futility), describe the statistical techniques and their operating characteristics. If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

Describe safety findings that would prompt temporary suspension of enrollment and/or study intervention use until a safety review is convened (either routine or ad hoc). Provide details of the proposed rules for halting study enrollment or study intervention/administration of study product for safety, including whether they pertain to the entire study, specific study arms or participant subgroups, or other components of the study.

State how endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed halting guidelines. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

This section should be consistent with *section 7***, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal.**

<Insert text>

### Sub-Group Analyses

*Describe how the primary endpoint will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).*

*Describe how the secondary endpoint(s) will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).*

<Insert text>

### Tabulation of Individual Participant Data

*State whether individual participant data will be listed by measure and time point.*

<Insert text>

### Exploratory Analyses

*Exploratory analyses cannot be used as confirmatory proof for registration trials. All planned exploratory analyses should be specified in the protocol.*

<Insert text>

# REGULATORY AND OPERATIONAL CONSIDERATIONS

*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*

## Regulatory and Ethical Considerations

*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*

### Informed Consent Document

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB’s written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

Example text provided as a guide, customize as needed:

[Consent forms will be written in accord with federal regulations and will be reviewed and approved by the UVA IRB-HSR prior to use. Signed consent forms and other research records will be retained in a confidential manner.]

<Insert text>

### Consent Procedures and Documentation

This section should describe the procedures for obtaining and documenting informed consent of study participants. Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of language other than English. Describe procedures for obtaining surrogate consent for those unable to consent on their own behalf. This section should be consistent with *section 5.6***, Strategies for Recruitment and Retention** when describing consent plans and special considerations for children or other vulnerable participants. Address re-consent processes for children who become adults or emancipated during a study.

Example text provided as a guide, customize as needed:

[Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. A member of the study team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant’s 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 should have the opportunity to discuss the study with their family or 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. Results from procedures completed prior to consent for standard of care purposes may be used for research purposes. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. 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.]

<Insert text>

### Confidentiality and Privacy

This section will describe protections for maintaining confidentiality of participant data, including, but not limited to forms, records and samples and participant privacy.

Include procedures for maintaining participant confidentiality, privacy protections, any special data security requirements, and record retention per the Principal Investigator’s requirements. Describe who would have access to records, including the investigator and other study staff, the clinical monitor, funding institutions, representatives of the NIH Institute or Center (IC), and representatives from the IRB

For some studies, a Certificate of Confidentiality (CoC) may be necessary. A CoC provides protection to researchers and research institutions from being forced to provide identifying information on study participants to any federal, state or local authority.

Example text provided as a guide, customization will be required to address all aspects that should be included in this section and to include/exclude multi-site and/or NIH language:

[Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. 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. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA. When possible, specimens will be coded with IDs (not MRN or name). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal I. *[Other written approvals may also be required. Please review contracts and local IRB regulations]*

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Principal Investigator, representatives of the Institutional Review Board (IRB), regulatory agencies 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 the reviewing IRB, Institutional policies, or Principal Investigator requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. *Include this sentence if it applies to your study:* 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 and by <specify name of Data Coordinating Center> research staff will be secured and password protected.

Certificate of Confidentiality *(if applicable)*

To further protect the privacy of study participants, a site may apply for a Certificate of Confidentiality. For NIH studies, this will automatically be issued by the National Institutes of Health (NIH) and an application is not necessary. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.]

<Insert text>

### Future Use of Stored Specimens and Data

If intended specimens or residual specimens are retained after the study is complete, include the provisions for consent and the options that are available for the participant to agree to the future use of his/her specimens, images, audio or video recordings. Specify the location(s), if other than the clinical site, where specimens or other data will be maintained, how long specimens or other data will be stored, if the site's IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens or data (e.g., specimens will be coded, bar-coded, de-identified, identifying information will be redacted from audio recording transcripts). Include a statement that genetic testing will or will not be performed.

See also *section 11.1.3*, Confidentiality and Privacy and *section 11.2*, Data Handling and Record Keeping, for further information on future use of study records.

Example text provided as a guide, customize as needed. Be sure that the following information is included: whether you plan to bank specimens and/or data, who is responsible for the specimens and/or data, and with what level of identifiers the specimens/data will be stored (deidentified, coded and linked, or fully identifiable):

[Data collected for this study will be analyzed and stored at the <specify name of Data Coordinating Center >. After the study is completed, the [de-identified/coded and linked], archived data will be transmitted to and stored at the <specify name of Data Repository>, for use by other researchers including those outside of the study. Permission to transmit data to the <specify name of Data Repository> will be included in the informed consent.

With the participant’s approval and as approved by local Institutional Review Boards (IRBs), [identified/de-identified/coded and linked] biological samples will be stored at the <specify name of Biosample Repository> with the same goal as the sharing of data with the <specify name of Data Repository>. These samples could be used to research the causes of <specify condition(s)>, its complications and other conditions for which individuals with < specify condition(s)> are at increased risk, and to improve treatment. *Remove if coded and linked:* [The <specify name of Repository> will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.]

During or after the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research.

When the study is completed, access to study data and/or samples will be provided through the <specify name of Repository>. At the end of the study, all study data/specimens will be [*indicate what will happen to the data/specimens at the end of the study - de-identified and archived, maintained by the PI, maintained by institutional policies].*]

<Insert text>

### Safety Oversight

Appropriate safety oversight should be used for each trial. This could include a Safety Monitoring Committee (SMC)[[1]](#footnote-2), Data Safety Monitoring Board (DSMB)[[2]](#footnote-3), Safety Assessment Committee[[3]](#footnote-4), and/or an Independent Safety Monitor (ISM)[[4]](#footnote-5). Independent oversight is an important component to ensure human subjects’ protection and data integrity and should be considered for each study. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety and data integrity in the study. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB.

Example text provided as a guide, customize as needed:

[Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including <list expertise>. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to <specify the Principal Investigator/National Institutes of Health staff/other>.]

*OR (For Cancer Center Studies-note, the DSMC does not provide oversight for studies that are non-interventional. The PI can provide oversight in these instances, for example.):*

[The University of Virginia Cancer Center Data and Safety Monitoring Committee (CC DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The UVA CC DSMC will review the following:

* All adverse events (*remove for “Low Risk” studies)*
* Audit results
* Application of study designed stopping/decision rules
* Whether the study accrual pattern warrants continuation/action
* Protocol violations

Monitoring by the DSMC begins at the time the first subject is enrolled to the study. Monitoring by the DSMC ends 30 days after the last active patient completes protocol treatment unless additional monitoring is deemed necessary by the Committee, PI, or IRB-HSR.

*For Cancer Studies at “Low Risk”*

[While Cancer Center Studies that are designated “Low Risk” are not regularly reviewed by the DSMC, they will receive post-approval monitoring audits and these will be reviewed by the DSMC chair.]

**PAM Review**

*All Studies*

Whenever a post-approval monitoring (PAM) review (described below ) is conducted, the results will be provided to the DSMC Chair for review.

*(Medium/High Risk studies):* The UVA CC DSMC will meet every month for aggregate review of data. Reports of the meetings are available to the PI for review. Issues deemed of immediate concern by the DSMC are brought to the attention of the Principal Investigator (and if appropriate to the PRC and IRB) and a formal response from the Principal Investigator is requested. Per the UVA Cancer Center NIH approved institutional plan, this study will be audited (post-approval monitoring) approximately every [6 months for high risk studies and 12 months for medium risk studies]. The audit may include direct access to source data/documents. For high-risk studies, if findings are satisfactory after two reviews, protocols will be audited once a year. Any time findings are unsatisfactory, auditing will return to the original schedule.

*Low risk studies:* Per the UVA Cancer Center NIH approved institutional plan, this study will be audited (post-approval monitoring) approximately once a year. Audits will be dependent upon active enrollment. The audit may include direct access to source data/documents.

*For ALL Studies:*

Any study under the purview of the University of Virginia HSR-IRB is subject to review of UVA documents. Studies are chosen for post-approval monitoring (PAM) either a) at random or b) requested by a study team member or any member of the IRB-HSR and the DSMC.

The purpose of Post-approval Monitoring audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled. A study will be triggered for an audit once 3 patients have been registered in OnCore. Post-approval monitoring is done by staff within the office of the Vice President for Research (VPR) in accordance with their Standard Operating Procedures. The conduct of an on-site review may include but is not limited to:

* requests for progress reports from investigators,
* examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
* contacts with research subjects, or
* observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:
* Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
* IRB is made aware of a complaint or concern with regard to the informed consent process; or
* IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

The DSMC biostatisticians will be responsible for randomly selecting the cases for audit. Audits will include review of all patient consent forms, as well as 10% or a minimum of 3 or a maximum of 10 complete records. The audit will also verify the accuracy of the study data and assure the timely and complete reporting of safety data. Compliance with the protocol, Good Clinical Practices (GCP) guidelines, and IRB-HSR policy will be assessed in the audit.

Written reports of the audit will be reviewed by the PAM Working Group, the PAM IRB-HSR Advisory Committee and the DSMC. Through this process, these committees will provide for quality assurance activities for cancer-related studies.]

<Insert text>

### Site Monitoring

This section should give a general description of how monitoring of the conduct and progress of the clinical investigation will be conducted (i.e., who will conduct the monitoring, the type, frequency, and extent of monitoring, who will be provided reports of monitoring, if independent audits of the monitoring will be conducted). This section may refer to a separate detailed clinical monitoring plan.

Sample Text, Modify in accordance with your monitoring practices

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial 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 International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

* <Insert detailed description of who will conduct the monitoring, the type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables)), and the distribution of monitoring reports>
* Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites.]

OR for multi-site studies using the UVA SOM-MCRO as the DCC use the following:

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial 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 International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

* The UVA SOM MCRO implement ongoing monitoring activities for this study to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion.
* Monitoring may be conducted either remotely or on-site.  For remote visits, each institution will be required to provide redacted source documents for review or appropriate access to the EMR. The UVA CC will provide the Participating Institution with a follow-up letter following completion of the monitoring  visit which should be maintained in the site regulatory files.  The schedule for monitoring may be adjusted according to subject accrual and data quality.  The Investigator will be notified in advance of each visit.

•        Independent audits may be conducted by each institution according to institutional guidelines. Results of these audits may be requested by the UVA SOM MCRO.]

<Insert text>

### Quality Assurance and Quality Control

*This section will briefly describe the plans for quality management, the system for assessing the quality of processes within a system. Quality management encompasses quality assurance (QA)[[5]](#footnote-6) and quality control (QC)[[6]](#footnote-7).*

*Each site, both clinical and laboratory, should have SOPs for quality management that describe:*

* *How data and biological specimens (when applicable) will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.*
* *The documents to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.*
* *Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).*
* *Staff training methods and how such training will be tracked.*
* *If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.*

*Regular monitoring and an independent audit, if conducted, must be performed according to ICH GCP.*

*Example text provided as a guide, customize as needed:*

[Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion according to institutional policies.]

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 Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and 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 Principal Investigator, and inspection by local and regulatory authorities.]

<Insert text>

## Data Handling and Record Keeping

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

### Data Collection and Management Responsibilities

*Provide details regarding the type(s) of data capture that will be used for the study and any relevant data standards or common data elements that are being utilized as a part of the trial.*

Example text provided as a guide, customize as needed:

[Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator 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.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into [<specify name of data capture system>, a password-protected data capture system provided by the <specify Data Coordinating Center>] OR, if details are not clear for location [the study’s case report forms (e.g. Advarra, Oncore)]. Clinical data will be entered directly from the source documents.]

### Study Records Retention

Specify the length of time for the investigator to maintain all records pertaining to this study. The investigator should use the most conservative rule for document retention – i.e., retention should follow the rule that has the longest period. For NIH, grantees must retain records for a period of three years from the date of Federal Financial Report (FFR) submission. Check with the IRB website for guidance on record retention.

## Publication and Data Sharing Policy

*The publication and authorship policies should be described in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. Please refer to your specific contract, grant, and/or Clinical Trials Agreements. If details of the publication policy will be described in the study’s MOP, refer to it here. The study must comply with:*

* *The NIH Public Access Policy, the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, The Food and Drug Administration Amendments Act of 2007 (FDAAA), Clinical Trials Registration and Results Information Submission rule,*
* *The NIH Data Sharing Policy (if applicable),*
* *The NIH Genomic Data Sharing Policy, (if applicable), and*
* *The NIH Data Sharing Policy and Implementation Guidance,*
* *Contracts/Grants with drug/device manufacturers and/or others*
* *Any other relevant policies (e.g., NIH IC-specific data sharing or publication policy)*

*In addition, please review ICMJE guidelines related to publishing.*

*Example text* *provided as a guide, customize as needed:*

[This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public [*include if this is required for your study per clinicaltrials.gov or NIH]* has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

*Revise as applicable for non-NIH studies:* This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at [insert location, such as ClinicalTrials.gov], and results information from this trial will be submitted to [insert, such as ClinicalTrials.gov, or “in accordance with regulations/the contract, etc.]. In addition, every attempt will be made to publish results in peer-reviewed journals.

*NIH-funded studies involving genomic analysis:* In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.]

<Insert text>

## Conflict of Interest Policy

*This section should include a description of how the study will manage actual or perceived conflicts of interest.*

*Example text* *provided as a guide, customize as needed:*

[The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, 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. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the institution has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.]

<Insert text>

## Additional Considerations

*This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or IRB-related requirements.*

<Insert text>

# REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer’s IB, package insert, and device labeling.

# APPENDICES

## Schedule of Activities (SoA)

The schedule below is provided as an example and should be modified as appropriate.

The schedule of activities must capture the procedures that will be accomplished at each study visit, and all contact, with study participants e.g., telephone contacts. This includes any tests that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility and study objectives and endpoints. Other procedures should be done sparingly and with consideration, as they may add unnecessary complexity and detract from recruitment.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the visit time points to study endpoints (e.g., pharmacokinetic (PK) studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).

*Note – make sure that the “~30 day” post visit is consistent with the time period for assessment of AEs – be sure window only goes greater than the minimum time period (e.g. 30 days +4 days vs 30 days +/- 2 days)*

| **Procedures** | Screening  Day -7 to -1 | Enrollment/Baseline  Visit 1, Day 1 | Study Visit 2  Day 7 +/-1 day | Study Visit 3  Day 14 +/- 1 day | Study Visit 4  Day 21 +/-1 day | Study Visit 5  Day 28 +/-1 day | Study Visit 6  Day 35 +/-1 day | Study Visit 7  Day 42 +/-1 day | Study Visit 8  Day 49 +/-1 day | Study Visit 9  Day 56 +/-1 day | Study Visit 10  Day 63 +/-1 day | Study Visit 11  Day 70 +/- 1 day | Study Visit 12  Day 77 +/-1day | Final Study Visit 13 Day 84 +/-1 day |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Administer study intervention |  | X |  |  | X |  |  | X |  |  | X |  |  |  |
| Concomitant medication review | X | X---------------------------------------------------------------------------------------------X | | | | | | | | | | | |  |
| Physical exam | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Vital signs | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Performance status | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| serum chemistry a | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test b | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EKG (as indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event review and evaluation | X | X---------------------------------------------------------------------------------------------X | | | | | | | | | | | | X |
| Radiologic/Imaging assessment | X |  |  |  | X |  |  |  | X |  |  |  |  | X |
| Other assessments (e.g., immunology assays, pharmacokinetic) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.  b: Serum pregnancy test (women of childbearing potential). | | | | | | | | | | | | | | |

## Reporting Table

*Single site (UVA) or Multi-site with no sites relying on UVA-IRB HSR– do not include this section*

*Multi-site with at least 1 site relying on UVA IRB-HSR*

Principal Investigator/UVA SOM MCRO Reporting to UVA IRB-HSR: Applicable only for sites relying on the UVA IRB-HSR as their IRB of record

| **Type of Event** | **To whom will it be reported:** | **Time frame for reporting:** | **How reported?** |
| --- | --- | --- | --- |
| **Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation**  *An internal event is one that occurs in a subject enrolled in a UVa protocol* | IRB-HSR | Within 24 hours | IRB Online and phone call  [www.irb.virginia.edu/](http://www.irb.virginia.edu/) |
| **Internal, Serious, Unexpected adverse event**  ***(If only reporting related, include that here and make sure this section matches text.)*** | IRB-HSR | Within 7 calendar days from the time the study team received knowledge of the event.  *Timeline includes submission of signed hardcopy of AE form.* | IRB Online  [www.irb.virginia.edu/](http://www.irb.virginia.edu/) |
| **Unanticipated Problems** that are not adverse events or protocol deviations  This might include a Data Breach. | IRB-HSR | Within 7 calendar days from the time the study team received knowledge of the event. | Unanticipated Problem report form.  [Unanticipated Problem Report Form](http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Unanticipated_Problem_Report_Form.doc) |
| **Protocol Deviations/Noncompliance**  *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.* | IRB-HSR | Within 7 calendar days from the time the study team received knowledge of the event. | Protocol Deviation, Noncompliance and Protocol Exception Reporting Form  [Protocol Deviation Protocol Exception Reporting Form](http://www.virginia.edu/vpr/irb/HSR_docs/Forms/PROTOCOL_DEVIATION_PROTOCOL%20EXCEPTION_REPORTING_FORM.doc) |
| **Data Breach** | The UVa Corporate Compliance and Privacy Office  ITC: if breach involves electronic data  UVA Police if breach includes such things as stolen computers | As soon as possible and no later than 24 hours from the time the incident is identified.  As soon as possible and no later than 24 hours from the time the incident is identified.  IMMEDIATELY. | UVa Corporate Compliance and Privacy Office-Phone (434) 924-2938  ITC: [Information Security Incident Reporting procedure](https://policy.itc.virginia.edu/policy/policydisplay?id=IRM-012), <https://security.virginia.edu/report-information-security-incident>  UVA Police-Phone- (434) 924-7166 |

## Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Description of Change** | **Brief Rationale** |
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1. A Safety Monitoring Committee (SMC) is a small group of experts with at least two members who are independent of the protocol who review data from a particular study. Generally, independent investigators and biostatisticians should be included. The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, intervention, and target population under study. [↑](#footnote-ref-2)
2. A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises funding IC(s) and the study investigators. The members of the DSMB provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, intervention, or target population under study. [↑](#footnote-ref-3)
3. As noted on page 4 of the FDA Draft Guidance for Industry: Safety Assessment for IND Safety Reporting, “A group of individuals chosen by the sponsor to review safety information in a development program (i.e., across trials, INDs, and other sources) for IND safety reporting purposes...The safety assessment committee should oversee the evolving safety profile of the investigational drug by evaluating, at appropriate intervals, the cumulative serious adverse events from all of the trials in the development program, as well as other available important safety information (e.g., findings from epidemiological studies and from animal or in vitro testing) and performing unblended comparisons of event rates in investigational and control groups, as needed, so the sponsor may meet its obligations under § 312.32(b) and (c). The safety assessment committee’s primary role should be to review important safety information on a regular basis, with additional reviews as needed, and make a recommendation to the sponsor to help the sponsor determine whether an event or group of events meets the criteria for IND safety reporting. The safety assessment committee, possibly together with other parties (e.g., steering committees, data monitoring committees [DMCs]), can also participate in decisions about whether the conduct of the study should be revised (e.g., change ineligibility criteria, revision of informed consent). [↑](#footnote-ref-4)
4. An Independent Safety Monitor (ISM) is a physician, nurse, or other individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study. [↑](#footnote-ref-5)
5. All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with ICH GCP and the applicable regulatory requirement(s) (ICH E6 Section 1.46). [↑](#footnote-ref-6)
6. The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 Section 1.47). [↑](#footnote-ref-7)