< INSERT PROTOCOL TITLE >

Protocol Number: < INSERT PROTOCOL NUMBER >

Version Date: < INSERT VERSION DATE >

Version Number: < INSERT VERSION NUMBER >

IND Sponsor: <INSERT IND SPONSOR >

Principal Investigator: < INSERT PRINCIPAL INVESTIGATOR >

IND Number: <INSERT IND NUMBER >

NCT Number: < INSERT NCT NUMBER, IF APPLICABLE >

Source of Funding: < INSERT SOURCE OF FUNDING >

DELETE INSTRUCTION BELOW BEFORE FINALIZING

Instructions for use of this Template:

The goal of this template is to assist investigators with writing a comprehensive clinical trial protocol. Instruction/explanatory text are indicated by *italics* and must be deleted.

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].

History of Protocol Versions:

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Sections Changed | Rationale for the Change |
| 1.0 | XXXX XX, 202X | N/A | N/A |
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ABBREIVATIONS AND ACRONYMS

*Include additional terms as needed*

|  |  |
| --- | --- |
| AE | Adverse Event |
| ADL | Activities of Daily Living |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator’s Brochure |
| ICH | International Conference on Harmonisation |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| PI | Principal Investigator |
| SAE | Serious Adverse Event |

# Protocol Overview

|  |  |
| --- | --- |
| Study Description | *Provide a short description of the protocol, including a brief statement of the primary objective. This should be only a few sentences in length.*  *(This information should be copied and pasted into PittPRO Basic Study Information page, #3.)* |
| Study Population: | *Specify the age, demographic group, required diagnosis, and general health status.* |
| Planned Sample Size: | Should be consistent with Section 12.2 Sample Size Determination. |
| Participating Institutions (if a multi-center clinical trial) |  |

## Study Schema

*This section should include a diagram that provides a quick “snapshot” of the study.*

# ****Background and Rationale****

## Background

*This section should include:*

* A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance
* A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies
* Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations should be listed in References)
* Applicable clinical, epidemiological, or public health background or context of the clinical trial
* Importance of the clinical trial and any relevant treatment issues or controversies

*(This information should be copied and pasted into PittPRO Study Aims page, #2.)*

## Rationale

*State the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy) and the reason for conducting the clinical trial.*

*(This information should be copied and pasted into PittPRO Study Aims page, #2.)*

# ****Hypotheses, Objectives and Endpoints****

## **Hypotheses**

### Primary Hypothesis

*(This information should be copied and pasted into PittPRO Study Aims page, #1.)*

### Secondary Hypothesis

*(This information should be copied and pasted into PittPRO Study Aims page, #1.)*

## ****Objectives****

*An objective is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., efficacy, effectiveness, safety) and/or specific purpose (e.g., dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behavior).*

### **Primary Objective:**

*(This information should be copied and pasted into PittPRO Study Aims page, #1.)*

### **Secondary Objective**

*(This information should be copied and pasted into PittPRO Study Aims page, #1.)*

### Exploratory Objectives

## Endpoints

*A study endpoint is a specific measurement or observation to assess the effect of the study variable (study intervention). Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. Give succinct, but precise definitions of the study endpoints used to address the study’s primary objective and secondary objectives (e.g., specific laboratory tests that define safety or efficacy, clinical assessments of disease status, assessments of psychological characteristics, patient reported outcomes, behaviors or health outcomes).*

*For an interventional study, an outcome measure is a measurement used to determine the effect of an experimental variable.*

* Primary: Outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation.
* Secondary: Outcome measure that is of lesser importance than a primary outcome measure but is part of a pre-specified analysis plan for evaluating the effects of the intervention or interventions under investigation in a clinical study and is not specified as an exploratory or other measure.
* Other pre-specified: Any other measurements, excluding post-hoc measures, that will be used to evaluate the intervention(s).

*All outcome measure components must be specific and precise, allowing someone not familiar with the study to understand the information:*

* Title: what will be measured.
* Description: how the outcome will be measured (i.e., metric used to characterize the outcome) and how data will be summarized for reporting. Include detailed information on any criteria, calculations or scales.
* Time Frame: when the outcome will be measured (i.e., timepoints or time span).

### Primary Endpoint

*(This information should be copied and pasted into PittPRO Study Design page, #3.)*

### Secondary Endpoint

*(This information should be copied and pasted into PittPRO Study Design page, #3.)*

# Research Design

*To include:*

* Phase of the trial
* 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)
* Name of study intervention(s)
* 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
* Note if interim analysis is planned and refer to details in appropriate statistical section, if applicable
* Note if the study includes any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose) and refer to details in appropriate statistical section, if applicable
* Name of sub-studies, if any, included in this protocol

*(This information should be copied and pasted into PittPRO Study Design page, #2.)*

# Human Subjects

## Subject Population

*General description including number of subjects in each group. Discuss the inclusion of any vulnerable populations such as: adults with impaired decision-making capacity, children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA),*

*Children who are Wards of the State, Neonates of uncertain viability, Non-viable neonates, Non-English speakers, etc.*

## Inclusion Criteria

*(This information should be copied and pasted into PittPRO Study Design page, #5.)*

## Exclusion Criteria

*(This information should be copied and pasted into PittPRO Study Design page, #6.)*

## Recruitment Methods

*Describe:*

* Who will be recruiting individuals for participation
* All methods to be used for recruitment (i.e., Directly approaching potential subjects in-person, Email/Listserv/Electronic Mailing List, Flyers/Posters or Brochures, Letters sent to potential participants, Newspaper/Magazine advertisements, etc.)
* Details on recruitment methods
* Any compensation offered to participants

*(This information should be copied and pasted into PittPRO Recruitment Methods page.)*

## Screen Failures

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

*(This information should be copied and pasted into PittPRO Recruitment Methods page.)*

# Study Drug

*Describe, in detail, the study drugs that will be administered to each cohort or arm of the proposed clinical evaluation of the investigational drug(s); to include, for each drug product, its proprietary and generic name, FDA-approval status, dose (including maximum dose), dosing schedule, route/mode of administration, duration of administration, and treatment period.*

*(This information should be used to complete the PittPRO Drugs page.)*

## Dose Selection

*Summarize the following, if applicable:*

* Reason(s) why it is felt that the investigational drug(s) will be safe and effective for the clinical indication for which it is being evaluated.
* Safety and efficacy findings from non-clinical (i.e., animal or in-vitro) studies that support the evaluation of the investigational drug(s) in humans.
* Results of any prior clinical research studies of the investigational drug(s) that are relevant to the proposed clinical evaluation of the investigational drug(s) under this IND application. For example:
* Existing information related to the human pharmacokinetics and any existing information related to the human safety profile
* Existing information related to the effectiveness of the investigational drug(s) for the clinical indication for which it is being evaluated under this IND application.

## Study Drug Preparation and Dispensing

*Describe the source and formulation of each of the study drugs (e.g., investigational drug, placebo, comparator drug[s]) and how they will be packaged and labeled for use in the clinical research study.*

*Describe the procedures for the on-site preparation, if applicable, and dispensing of the study drug(s).*

## Dose Delays and Modifications

*Describe the circumstances under which study drug would be held, delayed, or discontinued. Also, describe when modifications to the study drug dose would be initiated. Examples: Dose adjustments or delays due to adverse reactions, approved drug holidays, hospitalization, etc. Consider using a table format to describe dosing modifications for adverse events. If not dose adjustments are allowed, state this.*

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #2.)*

Example Text:

All subjects will be monitored for adverse events throughout participation in this trial. Adverse events requiring a dose delay or adjustment are described below.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Starting Dose** | **Dose Level -1** | **Dose Level -2** | **Dose Level -3** |
| **Drug X** | 40 mg/m2 | 30 mg/m2 | 20 mg/m2 | Discontinue |

| * All dose modifications for Drug X are based on dose level changes in the table above. * If event does not resolve back to ≤ Grade 1 within 1 week after modification, initiate instructions for the next occurrence. * Refer to section 9.1 for allowable supportive care medications. | | | |
| --- | --- | --- | --- |
| **Event / Grade** | **1st Occurrence** | **2nd Occurrence** | **3rd Occurrence** |
| **Hematology** | | | |
| **White blood cells** | | | |
| Grade 2  (list values for this grade) | Hold daily dose for 3 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level | Discontinue |
| Grade 3  (list values for this grade) | Hold daily dose for 7 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level & add supportive care med | Discontinue |
| Grade 4  (list values for this grade) | Hold daily dose for 7 days then ↓ two dose levels & add supportive care med | Discontinue | N/A |
| **Hemoglobin/hematocrit** | | | |
| Grade 2  (list values for this grade) | Hold daily dose for 3 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level | Discontinue |
| Grade 3  (list values for this grade) | Hold daily dose for 7 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level & add supportive care med | Discontinue |
| Grade 4  (list values for this grade) | Hold daily dose for 7 days then ↓ two dose levels & add supportive care med | Discontinue | N/A |
| **Platelets** | | | |
| Grade 2  (list values for this grade) | Hold daily dose for 3 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level | Discontinue |
| Grade 3  (list values for this grade) | Hold daily dose for 7 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level & add supportive care med | Discontinue |
| Grade 4  (list values for this grade) | Hold daily dose for 7 days then ↓ two dose levels & add supportive care med | Discontinue | N/A |
| **Liver function** | | | |
| **ALP, ALT, AST, or bilirubin** | | | |
| Grade 2  (list values for this grade) | Hold daily dose for 3 days then ↓ one dose level | Hold daily dose for 3 days then ↓ one dose level | Discontinue |
| Grade 3  (list values for this grade) | Hold daily dose for 7 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level or D/C | Discontinue |
| Grade 4  (list values for this grade) | Hold daily dose for 7 days then ↓ two dose levels | Discontinue | N/A |
| **Kidney function** | | | |
| **BUN (blood urea nitrogen) or Creatinine** | | | |
| Grade 2  (list values for this grade) | Hold daily dose for 3 days then ↓ one dose level | Hold daily dose for 3 days then ↓ one dose level | Discontinue |
| Grade 3  (list values for this grade) | Hold daily dose for 7 days then ↓ one dose level | Hold daily dose for 7 days then ↓ one dose level or D/C | Discontinue |
| Grade 4  (list values for this grade) | Hold daily dose for 7 days then ↓ two dose levels | Discontinue | N/A |
| **GI** | | | |
| **Diarrhea** | | | |
| Grade 2 | Maintain dose & add supportive care med | Hold daily dose for 3 days then ↓ one dose level & add supportive care med | Hold daily dose for 7 days then ↓ one dose level & add supportive care or D/C |
| Grade 3 | Hold daily dose for 7 days then ↓ one dose level & add supportive care med | Hold daily dose for 7 days then ↓ one dose level & add supportive care med or D/C | Discontinue |
| Grade 4 | Hold daily dose for 7 days then ↓ two dose levels & add supportive care med | Discontinue | N/A |
| **Vomiting** | | | |
| Grade 2 | Maintain dose & add supportive care med | Hold daily dose for 3 days then ↓ one dose level & add supportive care med | Hold daily dose for 7 days then ↓ two dose levels & add antiemetics or D/C |
| Grade 3 | Hold daily dose for 7 days then ↓ one dose level & add antiemetics med | Hold daily dose for 7 days then ↓ one dose level & add supportive care med or D/C | Discontinue |
| Grade 4 | Hold daily dose for 7 days then ↓ two dose levels & add supportive care med or D/C | Discontinue | N/A |
| **Other clinically significant AEs\*** | | | |
| Grade 2 | Maintain dose & add supportive care if available | Hold daily dose for 3 days then ↓ one dose level & supportive care if possible | Hold daily dose for 7 days then ↓ two dose levels & add supportive care if possible or D/C |
| Grade 3 | Hold daily dose for 3 days then ↓ one dose level & add supportive care if available | Hold daily dose for 7 days then ↓ one dose level & add supportive care if possible or D/C | Discontinue |
| Grade 4 | Hold daily dose for 7 days then ↓ two dose levels & add supportive care if available or D/C | Discontinue | N/A |
| \* Determination of "clinically significant" AEs is at the discretion of the investigator. | | | |

## Study Drug Compliance

*Describe the procedures that will be used to assess research subject compliance/adherence with the assigned study drug dosage regimen.*

*Specify the criteria and procedures for withdrawing research subjects from study participation due to non-compliance/adherence with the assigned study dosage regimen, the clinical research study procedures, or the instructions of the investigator or members of the investigator’s research staff.*

*Specify if subjects withdrawn from study participation due to noncompliance/adherence will be replaced and, if so, the corresponding procedures for their replacement.*

## Study Drug Storage and Accountability

*Describe the requirements (e.g., temperature, protection from light) for appropriate storage of each of the study drugs to ensure their stability throughout the assigned expiration period.*

*Describe the procedures for ensuring proper accountability of each of the study drugs and that administration of drugs so that they will be used only on subjects and be used only by authorized investigators; to include the procedures for destruction or other disposition of the study drugs upon completion or termination of the clinical research study.*

*(This information should be copied and pasted into PittPRO Drug page, #4.)*

## Prohibited Medications

*Describe or list the medications that will not be permitted prior to (must match study inclusion/exclusion criteria) and/or during the subject’s participation in the clinical research study.*

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #2.)*

## Breaking the Blind

*Incorporate only if the proposed clinical study is blinded). Describe the procedures for breaking the blind should a given study participant suffer a serious adverse event wherein knowledge of the identity of the study drug received by the subject is necessary for effective emergency treatment of the event.*

## Rescue Medications

*Identify, if applicable, acceptable rescue medications that may be used by the subjects during their participation in the clinical study.*

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #2.)*

# Research Activities

*Provide a description of all activities that will be performed for the purpose of this clinical trial. Note that the protocol narrative should provide a high-level overview of all procedures. If the results of standard of care procedures are collected for research purposes, the procedures should be listed at the appropriate time points. It should be explained that results from the standard of care procedures will be collected from the medical record and that the procedures are not being performed for solely for research purposes.*

*Detailed information should be provided in a table outlining the schedule of activities. The table of research activities should be included as an appendix in the protocol and must be consistent with the narrative contained in this section. Ensure that any assessments/procedures required for eligibility are included in the screening procedures. The timing of study visits should incorporate flexibility [e.g., Visit 4 + 3 days] to account for potential scheduling problems as to minimize protocol deviations.*

## Screening Procedures

## Randomization/Study Entry Procedures

## Study Drug Administration

Example Text:

Refer to section 6 of the protocol for information on study drug administration. Also refer to section 6.3 for instruction on study drug dose delay and modification.

## Safety and Efficacy Assessments/Procedures During Treatment

## Safety and Efficacy Assessments/Procedures During Follow-up

## End of Study Safety and Efficacy Assessments/Procedures

## Early Discontinuation Safety Assessments

*(All information in section 7 and subsections should be copied and pasted into PittPRO Research Activities page, #1.)*

# Potential Risks and Benefits

## Reasonably Foreseeable Risks Related to Study Drug

*List the known toxicities related to study drug. A review of the Investigator’s Brochure, published literature, and package insert (if a marketed drug) must be performed in order to determine the reasonably foreseeable risks.*

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #1.)*

## Reasonably Foreseeable Risks Related to Research Interventions

*List the risks associated with research related activities. Risks related to standard of care clinical procedures should not be included in this section. Research related activities may include:*

* Venipuncture for research blood collection
* Non-standard of care radiologic imaging, MRIs, and PET scans
* Non-standard of care ECGs or other cardiac monitoring testing

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #1.)*

## Potential Benefits

*Describe the potential benefit that individual participants may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others.*

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #6.)*

# Protection Against Risks

## Management of drug related toxicity

*Describe any supportive care drugs that may be used in the event of drug related toxicity.*

Example text:

Refer to section 6.3 of the protocol for instructions on dose delays and modifications.

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #2.)*

## Management of research related risks

*Describe procedures to ensure:*

* Research procedures are performed by qualified and trained staff
* Confidentiality of paper-based and electronic data
* Minimization of additional research related risks

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #2.)*

Example Text:

All study team members will be properly trained on protocol requirements. Research procedures performed for study purposes will be performed by qualified individuals as evidenced by education, experience, and/or training. All members of the study team will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, coding CRFs and research specimens by study identification numbers rather than any personal identifying information to avoid revealing the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers.

# Adverse Events and Serious Adverse Events

*This section and subsections should be tailored for specific study characteristics, including but not limited to the following:*

* *The study requires use of a disease specific toxicity grading scale*
* *How long after discontinuation of study drug will SAEs be collected and reported (should be based on the pharmacokinetics of the investigational drug).*
* *The study is conducted at multiple sites and will require centralized safety oversight*

Example text:

The proposed clinical trial will use the FDA definition of an adverse event (AE). Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related.

The proposed clinical trial will use the FDA definition of SAE. A serious adverse event is any untoward clinical event that is thought by either the investigator or the sponsor to be unexpected and at least possibly related to the study and results in any of the following:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of an existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly or birth defect
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

Adverse events will be assessed on each participant at regular intervals throughout participation. When an adverse event is discovered, the event will be assessed for severity, relatedness and expectedness. All adverse events will be documented in the research records and followed until resolved or back to baseline grade.

## Severity

Example Text:

The severity of adverse changes in physical signs or symptoms will be classified as follows:

* Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.
* Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate ADL.
* Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care/ADL.
* Grade 4 (Life-threatening): consequences; urgent intervention indicated.
* Grade 5 (Death): event is a direct cause of death.

## Relatedness

Example Text:

* 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. 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 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

Example Text:

The Principal Investigator will be responsible for determining whether an 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. Note that the risks listed in Section 8.1 are considered expected and would not require reporting *unless* the frequency or severity is greater than expected. Events not listed in Section 8.1 but that are listed in the Investigator’s Brochure or FDA-approved package insert, should also be considered expected. In such cases, depending on the nature and severity of the event, an amendment may be necessary to add the risk to Section 8.1 and the consent form document.

## Reporting Serious Adverse Events

Example Text:

Any SAE, which is determined by the PI to be unexpected and at least possibly related to study intervention, will be reported to the sponsor and IRB as soon as possible. The sponsor is responsible for notifying the FDA within required timeframes. The IRB and FDA and will include all known details regarding the nature of the SAE. Outcomes of SAEs not previously reported will be reported to the sponsor, IRB and FDA via a follow-up report.

Life-threatening or fatal unexpected adverse events associated with the use of the study drug or procedures must be reported to the IRB within 24 hours of discovery of the incident with subsequent follow-up submission of a detailed written report.

The FDA will be notified of an adverse event that is fatal or life-threatening no later than 7 calendar days after receiving the respective human adverse event information, followed by the subsequent submission of a written IND Safety Report.

Serious and unexpected adverse events associated with the use of the study drug or procedures will be reported to the IRB with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB. A written IND Safety Report (i.e., Form FDA 3500A) will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the investigator-sponsor’s receipt of the respective adverse event information.

A summary of the SAEs that occurred during the previous year will be included in the FDA annual progress report as well as in the annual IRB continuing review.

## Events of Special Interest

*Include content in this section if applicable.*

*Describe any other events that merit reporting to the sponsor or study leadership regardless of severity or relatedness. An example of events of special interest would be the sponsor requiring reporting of all ≥ Grade 2 cardiac events because the investigational drug is known to be cardiotoxic. This section should capture the mechanism to document the events and how to report to the sponsor.*

# Withdrawal of Subjects and Stopping Rules

## Adverse Events Requiring Discontinuation

*Specify the criteria and procedures for withdrawing/discontinuing research subjects from study drug due to adverse events.*

* Specify if subjects discontinue study drug due to adverse events will be replaced and, if so, the corresponding procedures for their replacement.
* Address the nature and timing of any data that will continue to be collected from the discontinued subjects to ensure their safety.

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #8.)*

## Other Criteria Requiring Discontinuation

*Specify the criteria for and procedures for withdrawing research subjects from study participation for reasons other than non-compliance or adverse events. Specify if subjects withdrawn from the study participation due to these criteria will be replaced and, if so, the procedures for their replacement.*

*(This information should be copied and pasted into PittPRO Risks and Benefits page, #8.)*

## Clinical Trial Stopping Rules

List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision, sponsor/funder decision, regulatory or other oversight bodies; review of serious, unexpected, and related AEs; noncompliance; futility).

Example Text:

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: study participants, investigator, funding agency, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor 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 may warrant termination or suspension include, but are not limited to:

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

# Statistical Analysis

## General Approach

## Sample Size Determination

*(This information should be copied and pasted into PittPRO Study Design page, #8.)*

## Analysis of Primary Endpoint

## Analysis of Secondary Endpoint

## Planned Interim Analysis

## Exploratory Analysis

# Data and Safety Monitoring

*(The information in sections 13-13.5 should be copied and pasted into PittPRO Data Safety and Monitoring page, #1.)*

## Data Safety Monitoring Plan

Example Text:

Monitoring of subject safety and data quality will be the responsibility of all study personnel on the project, with primary responsibility and supervision by the Principal Investigator.

There will be an evaluation of the progress of the research study, including assessments of data quality, timelines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed. A summary report of data and safety monitoring meetings will be provided to the IRB at the time of the continuing review

## Parameters to be Monitored

Example Text:

The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

* An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.
* A review of collected data (including adverse events, unanticipated problems requiring reporting and those captured on the non-compliance log, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.
* An assessment of external factors or relevant information (e.g. pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.
* A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

## Frequency of Monitoring

Example Text:

The Investigator will review subject safety data as it is reported and documented. The Investigator, sub-investigators, and the research staff will meet on a monthly basis to review subject recruitment, data, source documentation and identification of adverse events, complaints and confidentiality of subjects.

## Clinical Monitoring

*Incorporate if the study is being conducted by a sponsor-investigator.*

Example Text:

In accordance with 21 CFR 312.50 clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and that the conduct of the trial is in compliance with currently approved protocol/amendment(s).

## Data and Safety Monitoring Board

***It is up to the sponsor to determine if a DSMB is required.*** *The composition and frequency of monitoring should be included if applicable. As per the FDA guidance, DSMB’s are generally recommended for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. They are also generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, but not required or recommended for most clinical studies. DSMBs may not be needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes. DSMBs are required by some government agencies that sponsor clinical research (i.e., the NIH and VA) in certain trials and are required by the FDA (under 21 CFR 50.24(a)(7)(iv) and the University of Pittsburgh IRB for research studies in emergency settings in which the informed consent requirement is excepted. Guidance from the FDA can be found at* <https://www.fda.gov/media/75398/download>*.*

# Regulatory, Ethical, and Study Oversight

## IRB Approval

Example Text:

The Investigator will obtain, from the University of Pittsburgh IRB, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation. The Investigator should also notify the sponsor of this event.

The IRB will review and approve the Informed Consent Document for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or obtaining consent from any participants. Moreover, the study will be reviewed at a minimum of annual basis (or more frequently as deemed necessary) by the IRB committee. Each participant will sign the approved Informed Consent Form prior to participating in the study.

The University of Pittsburgh IRB operates in compliance with FDA regulations at [21 CFR Parts 50](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50&showFR=1) and [21 CFR 56](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=56&showFR=1), and in conformance with applicable ICH Guidelines on GCP.

## Informed Consent Procedures

*This section must include any waivers to informed consent for review of medical records or any exceptions for evaluation of an emergency procedure.*

*Describe the process you will employ to ensure that subjects are fully informed. This must include the following elements:*

* + - When will consent be obtained: indicate relationship to screening procedures, indicate how the research team will ensure the subjects have sufficient time to decide whether to participate
* Who will be involved in the consent process: NOTE for studies involving a drug, device or surgical procedure a listed physician investigator is required to obtain informed written consent unless an exception to this policy is approved by the University of Pittsburgh IRB
* Person who will provide consent: must address participants who are unable to consent for themselves
* Information communicated
* Any waiting period between informing the prospective participant and obtaining consent
* If subjects be informed about the outcome of the research

## Protocol Deviations

*Plans for detecting, reviewing, and reporting deviations from the protocol should be described. Reporting of deviations should include an appropriate corrective action plan. A statement should be included to indicate that deviations are not allowed. Provisions for obtaining IRB approval of planned deviations should be described.*

*It is strongly recommended that Chapter 17 of the University of Pittsburgh IRB Policies and Procedures be reviewed before finalizing this section.*

[*https://www.irb.pitt.edu/content/chapter-17-reportable-new-information*](https://www.irb.pitt.edu/content/chapter-17-reportable-new-information)

# References

# Appendix A – Schedule of Research Activities

Example Table:

| **Procedures** | | Screening  Day -7 to -1 | Enrollment/Baseline  Visit 1, Day 1 | Study Visit 2  Day 8 +/-3 days | Study Visit 3  Day 15 +/- 3 days | Study Visit 4  Day 22 +/-3 days | Study Visit 5  Day 29 +/-3 days | Study Visit 6  Day 36 +/-3 days | Study Visit 7  Day 43 +/-3 days | Study Visit 8  Day 50 +/-3 days | Study Visit 9  Day 57 +/-3 days | Study Visit 10  Day 64 +/-3 days | Study Visit 11  Day 71 +/- 3 days | End of Study Visit 12 Day 79 +/-3 days | Early Discontinuation Visit |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Informed consent | | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics and Medical History | | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Physical exam (including height and weight and vital signs) | | X | X |  |  | X |  |  | X |  |  | X |  | X | X |
| Performance status | | X | X |  | X |  | X |  | X |  | X |  | X | X | X |
| Concomitant medication review | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Registration/Randomization | |  | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Administer study intervention | |  | X |  |  | X |  |  | X |  |  | X |  |  |  |
| CBC w/ platelets and diff | | 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 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EKGc | | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event review  and evaluation |  | | X-----------------------------------------------------------------------------------------------------------------------------------------X | | | | | | | | | | | | |
| Radiologic/Imaging assessment | | X |  |  |  | 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 |
| 1. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium. 2. Serum pregnancy test (women of childbearing potential). 3. EKG at screening and as clinically indicated throughout study intervention. | | | | | | | | | | | | | | | |