< INSERT PROTOCOL TITLE >

Protocol Number: < INSERT PROTOCOL NUMBER >

Version Date: < INSERT VERSION DATE >

Version Number: < INSERT VERSION NUMBER >

IDE Sponsor: <INSERT IDE SPONSOR >

Principal Investigator: < INSERT PRINCIPAL INVESTIGATOR >

IDE Number: <INSERT IDE 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 |
| ICH | International Conference on Harmonisation |
| IDE | Investigational Device Exemption |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| PI | Principal Investigator |

# 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.
* 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., superiority to placebo, effect of an intervention on 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

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

## 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:*

* Type of trial (Feasibility versus Pivotal).
* A description of the type/design of trial to be conducted (e.g., randomized, sham-procedure, etc.)
* 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 Device

*Describe, in detail, the study device that will be evaluated in each cohort or arm of the proposed clinical evaluation; to include, for each device component, its proprietary and generic name, FDA-approval status, functionality (e.g., worn on body, surgically implanted in body, emits external radiation, etc.), and duration of intervention.*

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

## Device Selection

*Summarize the following, if applicable:*

* Reason(s) why it is felt that the investigational device will be safe and effective for the clinical intended use 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 device in humans.
* Results of any prior clinical research studies of the investigational device that are relevant to the proposed clinical evaluation of the investigational device. For example:
* Existing information to the human safety profile
* Existing information related to the effectiveness of the investigational device(s) for the intended use for which it is being evaluated.

## Study Device Storage and Accountability

*Describe the procedures for ensuring proper accountability of the study device and that the device will be used only on participants and be used only by authorized investigators; to include the procedures for disposition of the study device upon completion or termination of the clinical research study.*

*(This information should be copied and pasted into PittPRO Device 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.)*

# 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 Device Intervention

Example Text:

Refer to section 6 of the protocol for information on use of the study device.

## Safety and Efficacy Assessments/Procedures During Intervention

## 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 Device

*List the known adverse effects related to the study device. A review of the published literature, and package label (if a marketed device) 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 device related adverse effects

*Describe any interventions that may be used in the event of device related adverse effect.*

*(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 Device Effects

Example text:

The proposed clinical trial will use the following definitions:

*Adverse effect.* Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

*Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s)*. There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

*Disability*. A substantial disruption of a person’s ability to conduct normal life functions.

*Life-threatening adverse effect*. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

*Serious adverse effect*. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

*Note: Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

*Unexpected adverse effect.* Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s).

*Unanticipated adverse device effect.* Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse effects will be assessed on each participant at regular intervals throughout participation. When an adverse effect 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 state.

## Assessment of Severity

Example text:

For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

Abnormal test findings: An abnormal test finding will be classified as an adverse effect if one or more of the following criteria are met:

* The test finding is accompanied by clinical symptoms.
* The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy. (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
* The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study.
* The test finding is considered an adverse effect by the investigator-sponsor.

Causality and severity assessment: The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the investigator-sponsor’s final determination of causality is “unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)”, the adverse effect will be classified as associated with the use of the investigational device or study treatment or diagnostic drug product(s) for reporting purposes. If the investigator-sponsor’s final determination of causality is “unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)”, this determination and the rationale for the determination will be documented in the respective subject’s case history.

## Relatedness

Example Text:

* Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The adverse effect, 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.
* Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The adverse effect, including an abnormal laboratory test result, occurs within a reasonable time after the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
* Possibly Related – There is some evidence to suggest a causal relationship (e.g., the adverse effect occurred within a reasonable time after the study intervention). However, other factors may have contributed to the adverse effect (e.g., the participant’s clinical condition, other concomitant events). Although an adverse effect 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 – An adverse effect, 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 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 adverse effect 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 device label or report of prior investigations section of the IDE application, 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 Unanticipated Adverse Device Effects

Example Text:

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

## FDA Reporting

The investigator-sponsor will submit a completed FDA Form 3500A to the FDA’s Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator’s follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) associated with the investigational device or, if applicable, other study treatment or diagnostic product(s); 2) a serious adverse effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor’s receipt of the respective information. Adverse effects which are 1) associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the investigator-sponsor’s receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator’s follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

## IRB Reporting

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) associated with the investigational device or, if applicable, other study treatment or diagnostic product(s); 2) a serious adverse effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor’s receipt of the respective information. Adverse effects which are 1) associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the investigator-sponsor’s receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator’s follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

# 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 the use of the device is stopped due to an unanticipated adverse device effect 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 subjects from study participation for reasons other than non-compliance or unanticipated adverse device effects. 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 unanticipated adverse device effects; 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 IDE 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 effect 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 effects, 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 812.46 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 on an 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 IDEicate 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)

Example Text:

All study staff will be responsible for ensuring knowledge of the study protocol and the

procedures outlined therein. Study staff will periodically audit study records to ensure compliance with the IRB-approved protocol. Additionally, the University of Pittsburgh Education and Compliance Support Office will periodically conduct clinical site monitoring to ensure compliance.

If events of non-compliance are detected, the following procedures will be followed:

* Events of non-compliance which present risk to human subjects or others, adversely affect the rights and welfare of human subjects, or significantly compromise the quality of research data will be reported to the University IRB.
* Events of non-compliance that do not meet the above criteria will be recorded in a protocol deviation log. The investigator and other study staff will regularly monitor this log.
* The PI will assess which events of non-compliance are reportable.

If a case arises in which the investigator feels a deviation will be necessary or allowable (given

there is no evidence of increased risk to subjects or compromised quality of the research data),

prospective approval will be obtained from the University IRB prior to such a deviation.

# 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 IDEicated throughout study intervention. | | | | | | | | | | | | | | | |