***Protocol Template for Interventional Clinical Trial Protocol***

***Guidance for using this template:***

*This protocol template is designed to help research teams develop a clinical trial protocol that includes an investigational intervention. This template can be used by investigators across the University of Pennsylvania and is not restricted to the Perelman School of Medicine (PSOM). If your department currently uses an internal template, this template may be used to enhance that template.*

*The term “investigational” refers to the product’s use in a clinical trial and does not speak to its regulatory (FDA) approval status. The template may be used in the development of any Penn investigator initiated clinical trial involving any sort of investigational product (drug, device, food or cosmetic.). This may be used for a study in which an IND, IDE or a foreign clinical trial application is involved but its use is not limited to studies involving any of those (exempt studies).*

***Directions for Using this Template:***

* *Language in green italics should be used as a guide for development of your protocol.*
* *Language in green non-italics, within brackets can remain in the protocol as long as it makes sense within the context of your protocol.*
* *Please be sure to remove the sections with directions and any template language that is not being used prior to submitting for approval.*
* *Please be sure to edit the header and footer with the appropriate protocol details.*
* *This template document is associated with a* [*separate guidance document*](https://www.med.upenn.edu/ocrobjects/library/Protocol_Template_Standard_Language.docx) *that may be used by research teams where Penn will be the only site. For example, you may need to use radiology services from CACTIS, CAMRIS, RRSC for your protocol. This [guidance document](https://www.med.upenn.edu/ocrobjects/library/Protocol_Template_Standard_Language.docx) will help you with standard language for several of the ancillary review committees at Penn, and other Penn specific resources for Recruitment, Investigational Drug Services, etc.*

CLINICAL RESEARCH PROTOCOL

*It is important to incorporate all sections of the template into your protocol and to do so in the same order.*

|  |  |
| --- | --- |
| INVESTIGATIONAL PRODUCT(S):For Device include the planned useFor Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment |  |
| STUDY NUMBER(S): | IRB Number |  |
| Other Protocol Identifiers If applicable, i.e. UPCC, NCT, or other ID given by the Sponsor |  |
| PROTOCOL(S) TITLE: |  |
| [IND/IDE/CTA] NUMBER:Delete whichever is not applicable. |  |
| REGULATORY SPONSOR:Sponsor, as defined by GCP, name and address |  |
| FUNDING SPONSOR(S): |  |
| MEDICAL DIRECTORName of qualified physician who is responsible for all trial-site related medical decisions |  |
| ORIGINAL PROTOCOL DATE: |  |
| VERSION NUMBER: |  |
| VERSION DATE: |  |

Note: This protocol template has been written with guidance from NIH, FDA, and ICH and it is intended to support University of Pennsylvania research teams/ Sponsors when writing a clinical study protocol.

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|  |  |

|  |
| --- |
| PRINCIPAL INVESTIGATOR SIGNATURE |
| STUDY SPONSOR: |  |
| STUDY TITLE: |  |
| STUDY IDPROTOCOL VERSION | [Insert IRB #] |
| I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines. |
| Principal Investigator Name  |  |  | Signature |  |
| Affiliation: |  |  | Date |  |
|  |  |  |  |  |

Abbreviations

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

|  |  |
| --- | --- |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| MP | 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 Harmonization  |
| 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 |
| DSMC | Data Safety Monitoring Committee |
| SoA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UADE | Unanticipated Adverse Device Effect |
| UP | Unanticipated Problem |
| US | United States |

# Study Summary

## Synopsis

|  |  |
| --- | --- |
| Title:  |  |
| Short Title: |  |
| Study Description:  | Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length. A detailed schematic describing all visits and a schedule of assessments should be included in the Schema and Schedule of Activities, Sections 1.3 and Appendix section 12.1, respectively. |
| Objectives:  | Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol. These align with Primary Purpose in clinicaltrials.gov:[https://prsinfo.clinicaltrials.gov/definitions.htm](https://prsinfo.clinicaltrials.gov/definitions.html) |
| Primary Endpoint:  | Include the primary endpoint. These endpoints should be the same as the endpoints contained in the body of the protocol. These align with Outcome Measures in clinicaltrials.gov: [https://prsinfo.clinicaltrials.gov/definitions.htm](https://prsinfo.clinicaltrials.gov/definitions.html) |
| Secondary Endpoints: | Include the secondary endpoints. |
| Study Population: | Specify the sample size, gender, age, demographic group, general health status, and geographic location. |
| Phase: | For drugs & biologics: <I, II, III or N/A> For devices: <Exploratory or Feasibility, Pivotal, Postmarket> |
| Description of Sites/Facilities  |  |
| Enrolling Sites: | Provide a brief description of planned facilities/participating sites enrolling participants. Indicate general number (quantity) of sites only and if the study is intended to include sites outside of the United States. |
| Description of Study Intervention: | Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration. For devices, provide a description of each important component, ingredient, property and the principle of operation of the device. |
| Study Duration: | Estimated time (in months) from when the study opens to enrollment until completion of data analyses. |
| Participant Duration: | Time (e.g., in months) it will take for each individual participant to complete all participant visits. |
|  |  |

## Key Roles and Study Governance

Provide the name and contact information of the Sponsor and the Medical (Director) Monitor.

|  |  |
| --- | --- |
| *Sponsor* | *Medical Director* |
| Name, degree, title | Name, degree, title |
| Institution Name  | Institution Name  |
| Address | Address |
| Phone Number | Phone Number |
| Email | Email |

In addition, you may briefly describe any study leadership committees (e.g.: Steering Committee, Executive Committee, Subcommittee) and their roles. Note that it is not necessary to list specific members. Also, describe country-specific administrative requirements or functions that materially affect the conduct of the study. The MOP should include a list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial.

## 1.3 Schema

This section should include a diagram that provides a quick “snapshot” of the study and ideally be limited to 1 page. Below are examples of schematics that show the level of detail needed to convey an overview of the study design. Depending on the nature of your study, one example may be more appropriate than another. The examples included here are intended to guide the development of a schematic that is appropriate to the planned study design and will need to be customized for the protocol. Revise with study-specific information and adapt the diagram to illustrate your study design (e.g., changing method of assignment to study group, adding study arms, visits, etc.). The time point(s) indicated in the schematic should correspond to the time point(s) in Appendix Section 12.1, Schedule of Activities, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.

***Schema Example #1 Flow diagram*** *(e.g., randomized controlled trial)*

Prior to

Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.

Enrollment

Randomize

Perform baseline assessments.

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Appendix Section 12.1, Schedule of Activities**>

Administer initial study intervention.

Visit 1
Time Point

Visit 2
Time Point

Follow-up assessments of study endpoints and safety

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Appendix Section 12.1, Schedule of Activities**>

Repeat study intervention (*if applicable*).

Visit 3
Time Point

Follow-up assessments of study endpoints and safety

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Appendix Section 12.1, Schedule of Activities**>

Visit 4
Time Point

**Final Assessments**

<list analyses to be performed OR refer to **Appendix Section 12.1, Schedule of Activities**>

Visit X
Time Point

***Schema Example #2*** ***provided as a guide, customize as needed: Process diagram*** *(e.g., randomized controlled trial)*

|  |  |
| --- | --- |
| Week/Day (Insert time) | Screening |
| * Total n=x
 |
| * Obtain informed consent
 |
| * Screen potential participants by inclusion and exclusion criteria
 |
| * Obtain history, document
 |
| Week/Day (Insert time) | Randomization |
| * Intervention Group 1 (n=y)
 |
| * Placebo (n=z)
 |
| Week/Day (Insert time) | Baseline assessments/ Study Intervention |
| * <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to Appendix Section 12.1, Schedule of Activities>
 |
| * Administer initial dose of study intervention
 |
|  | Follow-up assessments of study endpoints and safety |
| * <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to Appendix Section 12.1, Schedule of Activities>
 |
|  | Follow-up assessments of study endpoints and safety |
| * <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to Appendix Section 12.1, Schedule of Activities>
 |
| Week/Day (Insert time) | End of Study Assessments |
| * <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to Appendix Section 12.1, Schedule of Activities>
 |
| Week/Day (Insert time) | Follow-up Telephone Call |  |
| * <List questionnaires to be completed OR refer to Appendix Section 12.1, Schedule of Activities>
 |

***Schema Example #3 provided as a guide, customize as needed: Timeline diagram*** *(e.g., randomized controlled trial)*

Day -7 to Day -1

Screening

Day 1

Randomization

Week 1

Titration

Weeks 2 - 25

Maintenance

Week 26

Dose Taper

Week 27

End of Study Assessments (EOS)

Week 28-29

Follow-up Phone Call

Study Intervention N=

Placebo N=

# in-clinic visits and

# telephone contacts

# Introduction and RationalE

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

The following subsections should include relevant background information and rationale for the clinical trial. This should be a brief overview (e.g., approximately 3-7 pages). Referring to the Investigator’s Brochure (IB) or Investigational Plan (for devices) for more detail is also appropriate.

The subsections should describe the information for the study intervention that is being tested in the clinical trial. The study intervention may be a drug (including a biological product), imaging intervention, or device subject to regulation under the Federal Food, Drug, and Cosmetic Act that is intended for administration to humans or use in humans, and that has been or has not yet been approved by the Food and Drug Administration (FDA). This also includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, when used for an unapproved indication or when used to gain further information about an approved use (including in combination with other products).

If multiple study interventions are to be evaluated in the trial, **Section 2.2 Background** and **Section 2.3 Risk/Benefit Assessment** and their accompanying subsections, should clearly differentiate between each product.

## Study 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

## Background

The robustness of this section will be based on phase of the trial, endpoints, target product profile (label), established safety data, and established efficacy information.

This section should include:

* A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance. For devices, include bench testing as part of the non-clinical studies, as applicable.
* 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 Section 11, References).
* Applicable clinical, epidemiological, or public health background or context of the clinical trial, including a description of the population being studied.
* Importance of the clinical trial and any relevant treatment issues or controversies.
* Description of and justification for the route of administration, dosage, dosage regiment, and treatment period(s).

For example, provide information about pharmacokinetics, preclinical pharmacology, potential for drug-drug or drug-device, or device-device interactions, clinical adverse event profile, elevations in liver function tests, potential risk of testicular injury, potential risk to fetal development, etc.

### Pharmacokinetics, Pharmacodynamics and Toxicology

### Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

Insert information about potential interaction among all study products (drug, device, food, cosmetic); i.e.: drug-drug, drug-device, device-device, etc.

### Clinical Adverse Event Profile

### Dosing Rationale

## Risk/Benefit Assessment

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

The following subsections should include a discussion of known risks and benefits, if any, to human participants for all investigational products and for their combination (if any).

### Known Potential Risks

Include a discussion of known potential risks from either clinical or nonclinical studies. If a package insert or device labeling from a licensed or approved product is available, it should be used as the primary source of risk information. If the product is investigational, the IB should be the primary source of the risk information. In addition, relevant published literature can also provide relevant risk information. If the risk profile cannot be described from the package insert, device labeling, or the IB, the risk information discussion will result from published literature and should be included and referenced appropriately in a manner easily presented to the user.

Describe any physical, psychological, social, legal, economic, or any other risks to participants by participating in the study that the GCP Sponsor foresees, addressing each of the following:

* Immediate risks
* Long-range risks
* If risk is related to proposed procedures included in the protocol, describe alternative procedures that have been considered and explain why alternative procedures are not included

### Known Potential Benefits

Include a discussion of known potential benefits from clinical and/or nonclinical studies. If a package insert or device labeling from a commercial product is available, it should be used as the primary source of potential benefit information. If the product is investigational, the IB should be the primary source of the potential benefit information. In addition, relevant published literature can also provide potentially relevant benefit information. If the potential benefit cannot be described from the package insert, device labeling, or the IB, the potential benefit information discussion will result from published literature and should be included and referenced appropriately.

Describe any physical, psychological, social, legal, or any other potential benefits to individual participants or society in general, as a result of participating in the study, addressing each of the following:

* Immediate potential benefits
* Long-range potential benefits

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. Additional information can be found in [*Standard Language & Guidance for Penn Sites Only*](https://www.med.upenn.edu/ocrobjects/library/Protocol_Template_Standard_Language.docx).

### Assessment of Potential Risks and Benefits

Include an assessment of known potential risks and benefits, addressing each of the following:

* Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design
* Justification as to why the risks of participation in the study do not outweigh the value of the information to be gained

# Study 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. Provide a description of the study objectives and endpoints, as well as a justification for selecting the particular endpoints, in the table format included below. This will provide clear articulation of how the selected primary and secondary endpoint(s) are linked to achieving the primary and secondary objectives and an explanation of why endpoint(s) were chosen. Data points collected in the study should support an objective or have a regulatory purpose. Therefore, careful consideration should be given prospectively to the amount of data needed to support the study’s 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).

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). Include the study visits or time points at which data will be recorded or samples will be obtained. Describe how endpoint(s) will be adjudicated, if applicable.

Primary and secondary endpoints should be adjusted for multiplicity. If a claim is sought for the secondary endpoints, the statistical plan for adjustment for multiplicity should be aligned with those objectives.

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
| --- | --- | --- |
| Primary |  |  |
| The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing). | 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”). Often Phase 2 and 3 trials include primary objectives, and therefore primary endpoints, to demonstrate effectiveness. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold. However, this is not always the case. For example, in many trials of medical devices there are primary endpoints for both safety and effectiveness.In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit. | Briefly explain why the endpoint(s) were chosen. |
| 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. | Briefly explain why the endpoint(s) were chosen. |
| Tertiary |  |  |
| Tertiary objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. | Tertiary or subsequent endpoints should be specified 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.Endpoints that are not listed in an alpha conserving plan will be considered exploratory. | Briefly explain why the endpoint(s) were chosen. |

# Study Plan

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

## Study Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should be consistent with the Protocol Synopsis (Section 1.1) and Protocol Schema (Section 1.3) and include:

* A statement of the hypothesis
* 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)
* A description of methods to be used to minimize bias, including randomization and blinding
* Dose escalation or dose-ranging details should be contained in Section 6.1.2, Dosing and Administration
* The number of study groups/arms and study intervention duration
* Indicate if single site or multi-site
* Name of study intervention(s)
* Note if interim analysis is planned and refer to details in Section 9.4.6, Planned Interim Analysis
* 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 Section 9.4.7, Sub-Group Analyses
* Name of sub-studies, if any, included in this protocol

## Scientific Rationale for Study Design

Describe the rationale for the type and selection of control (e.g. placebo, sham device, active drug, dose-response, historical) and study design (e.g., non-inferiority as opposed to superiority). Discuss known or potential problems associated with the control group chosen in light of the specific disease and intervention(s) being studied.

## Justification for Dose

Provide a justification for the route of administration, planned maximum dosage, and dosing regimen, including starting dose, of the study intervention(s) and control product(s).

## End of Study Definition

A clinical trial is considered completed (End of Study) when participants are no longer being examined or the last participant’s last study visit has occurred (including long follow up visits or contacts).

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1.

# Study Population

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

The following subsections should include a description of the study population and participant recruitment. The study population should be appropriate for clinical trial phase and the development stage of the study intervention. Given the continuing challenges in achieving clinically relevant demographic inclusion in clinical trials, it is important to focus on clinically relevant potential participants at the earliest stages of protocol development. Therefore, it is essential that the population’s characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the study intervention under evaluation (e.g., elderly and pediatric populations, women, and minorities).

Use the following guidelines when developing participant eligibility criteria to be listed in Sections 5.1 Inclusion Criteria and 5.2 Exclusion Criteria:

* The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment.
* If participants require screening, distinguish between screening participants vs enrolling (ICF has been signed) participants. Determine if screening procedures will be performed under a separate screening consent form.
* The risks of the study intervention should be considered in the development of the inclusion/exclusion criteria so that risks are minimized.
* 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). Note that for device trials, age <22 years is considered pediatric population.
* Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.
* If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g., licensed hormonal or barrier methods).
* If you have more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation.
* Consider whether an assay, lab developed test, or in vitro diagnostic will be used to determine eligibility, and whether the test/diagnostic is FDA approved or cleared and whether this test is used in usual care for the patient population. Risks of false positives and false negatives should be considered and discussed with participants.

## Inclusion Criteria

Inclusion criteria are characteristics that define the population under study, e.g., those criteria that every potential participant must satisfy, to qualify for study entry. Provide a statement that individuals must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion. If the study is NIH funded, women and members of minority groups must be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects.

Some criteria to consider for inclusion are: provision of appropriate consent and assent, willingness and ability to participate in study procedures, age range, health status, specific clinical diagnosis or symptoms, background medical treatment, laboratory ranges, and use of appropriate contraception. Additional criteria should be included as appropriate for the study design and risk.

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>
6. Ability to take oral medication and be willing to adhere to the <study intervention> regimen
7. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration
8. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner
9. Agreement to adhere to Lifestyle Considerations (see section 5.3) throughout study duration]

## Exclusion Criteria

Exclusion criteria are characteristics that make an individual ineligible for study participation. Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. If specific populations are excluded (e.g., elderly or pediatric populations, women or minorities), provide a clear and compelling rationale and justification, to establish that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Limited English proficiency cannot be an exclusion criterion.

Some criteria to consider for exclusion are: pre-existing conditions or concurrent diagnoses, concomitant use of other medication(s) or devices, known allergies, other factors that would cause harm or increased risk to the participant or close contacts, or preclude the participant’s full adherence with or completion of the study. Additional criteria should be included as appropriate for the study design and risk.

Include a statement regarding equitable selection or justification for excluding a specific population.

Example text provided as a guide, customize as needed (including adding a statement about equitable selection):

[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>]

## Lifestyle Considerations

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

Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, timing of meals relative to dosing, intake of caffeine, alcohol, or tobacco, or limits on activity), and considerations for household contacts. Describe what action will be taken if prohibited medications, treatments or procedures are indicated for care (e.g., early withdrawal).

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.]

## 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.

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 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 (screen failure) because of a <specify modifiable factor> may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.]

## Strategies for Recruitment and Retention

Identify general strategies for participant recruitment and retention. This section may refer to a separate detailed recruitment and retention plan in the manual of procedures (MOP) and site-specific plans could be included in a site-specific standard operating procedure (SOP). Consider inclusion of the information below either in this section or the MOP.

* Target study sample size by gender, race and ethnicity, and age; identify anticipated number to be screened including women and minorities in order to reach the target enrollment (should be consistent with information contained in Section 9.2, Sample Size Determination)
* Anticipated accrual rate
* Anticipated number of sites and participants to be enrolled per country in
* Source of participants (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public)
* Recruitment venues
* How potential participants will be identified and approached
* Types of recruitment strategies planned (e.g. patient advocacy groups, national newspaper, local flyers; social media, specific names of where advertisements may be planned are not needed)
* If the study requires long-term participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).
* As applicable, include specific strategies that will be used to recruit and retain historically under-represented populations in order to meet target sample size and conform with the NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects. Include the number of women and minorities expected to be recruited or provide justification on those rare occasions where women and/or minorities will not be recruited.

In addition, this section should address:

* If appropriate, include justification for inclusion of vulnerable participants and recruitment strategy. Vulnerable participants include, but are not limited to pregnant women, those who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, children, and employee volunteers. Include safeguards for protecting vulnerable populations. Please refer to OHRP guidelines when choosing the study population. Note that these regulations apply if any participants are members of the designated population, even if it is not the target population (e.g., if a participant becomes a prisoner during the study).
* 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). Describe who will receive incentives (if not the participant). For example, if minors, state whether the minor or the parent/guardian will receive the incentive. If incapacitated adults, state if payment will be provided to the participant or to a legally authorized representative or guardian.

# Study Intervention

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

The following subsections should describe the study intervention that is being tested for safety and effectiveness in the clinical trial, and any control product being used in the trial. The study intervention may be a drug (including a biological product), imaging intervention, device, biologic, vaccine, cosmetic, supplement, food etc. subject to regulation under the Federal Food, Drug, and Cosmetic Act that is intended for administration to humans or use in humans, and that has been or has not yet been approved by the Food and Drug Administration (FDA). This also includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, when used for an unapproved indication or when used to gain further information about an approved use.

If multiple study interventions are to be evaluated in the trial, Section 6.1 Study Intervention(s) Administration and Section 6.2 Preparation/Handling/Storage/Accountability and their accompanying subsections, should clearly differentiate between each product. Address placebo or control product within each part of Section 6.1 and Section 6.2. If the control product is handled differently than the study intervention, be sure to state how they are each handled, separately. If the control product is handled the same as the study intervention, state as such. In addition, all sections may not be relevant for the trial. If not relevant, note as not applicable in that section.

## Study Intervention(s) Administration

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

### Study Intervention Description

Describe the study intervention(s) and control product. Product information can usually be obtained from the:

* IB for an investigational drug or biologic
* Package insert for a licensed or approved drug or biologic or device labeling for a licensed device
* Proposed labeling, investigational plan, and/or material safety data sheet (MSDS) for an investigational device
* Final labeling for a marketed device

In addition:

* If a device study is being conducted under an IDE, and is determined to be non-significant risk, such that only abbreviated IDE requirements apply, provide justification here.
* Indicate if the study intervention is commercially available and is being used in accordance with approved labeling. For a device, note if any modifications have been performed for the study.
* If conducting a study with a device, the following information should be included:
	+ Device size(s)
	+ Device model(s)
	+ Description of each component
	+ Device settings and programming (if applicable)
	+ Duration of administration, implant or exposure (if applicable)
	+ Frequency of exposure (if applicable)
	+ If a device has not been approved or cleared for the indications the protocol is designed to investigate, then a summary/report of test validation studies should accompany this protocol

|  |  |  |  |
| --- | --- | --- | --- |
| Name of Device | Manufacturer | Marketing Status in the U.S. | FDA Device Classification (I, II, III) |
| Name | Manufacturer’s name | K##### |  |
| Name | Manufacturer’s name | P##### |  |

### Dosing and Administration

Describe the procedures for selecting each participant's dose of study intervention and control product. For drugs, that includes the timing of dosing (e.g., time of day, interval), the duration (e.g., the length of time study participants will be administered the study intervention), the planned route of administration (e.g., oral, nasal, intramuscular), and the relation of dosing to meals. For devices, this including timing of dosing, duration, and planned route of administration (e.g. part of the body, on the skin or pierces the skin, etc).

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. For example, in some oncology trials for participants with no available therapeutic alternatives, intervention continues even after disease progression. In this instance, consider alternative designs that enable participants to rollover to a continued treatment arm and include appropriate instructions to guide this implementation.

If applicable, describe the dose escalation scheme and dose regimen (using exact dose, rather than percentages). State any minimum period required before a participant’s dose might be raised to the next higher dose or dose range. If applicable, the protocol should state the conditions under which a dose change will be made, particularly in regard to failure to respond or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count in cancer chemotherapy). Address dose modifications for specific abnormal laboratory values of concern or other adverse events (AEs) that are known to be associated with the planned study intervention. The protocol must state explicitly the dose-limiting effects that are anticipated. Provide criteria that will be used to determine dose escalations. If a participant is responding positively to the intervention, the protocol should specify whether study intervention administration would progress to still higher doses. If appropriate, provide a dose de-escalation schema with intervention modifications. Do not restate reasons for withdrawal of participants. Cross-reference relevant sections, as appropriate.

Any specific instructions to study participants about when or how to prepare and take the dose(s) should be described, including how delayed or missed doses should be handled. Include any specific instructions or safety precautions for administration of the study intervention. Discuss the maximum hold time once thawed/mixed, if appropriate, before administration.

While much of the above section is specific to drugs, similar considerations apply to certain devices. For example, some devices have adjustable settings including those related to energy delivery to participants, not all devices are implanted, considerations would apply even to those devices that are administered. Other devices must be sized correctly for individual participants. Similar to the discussion above for dosage of drugs, such considerations should be described for devices, as applicable.

## Preparation/Handling/Storage/Accountability

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

### Acquisition and accountability

State how the study intervention and control product (both drugs and devices) will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product. Detailed information may be provided in a MOP or a separate SOP.

### Formulation, Appearance, Packaging, and Labeling

Describe all steps necessary to properly prepare the investigational product (and control product if applicable) for administration, including who will complete the preparation and where it will be prepared. Include information on reformulation, encapsulation, dissolution, size selection, configuration, etc. Include information on packaging (bottles, blister packs, single use device, multi-use package, etc. Information in this section can usually be obtained from the IB or the package insert, investigational plan, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

### Product Storage and Stability

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

### Preparation

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section, as appropriate, or within a MOP or SOP. For devices, include any relevant assembly or use instructions.

## Measures to Minimize Bias: Randomization and Blinding

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated). If adaptive randomization or other methods of covariate balancing/minimization are employed, include a cross link to the methods of analysis in Section 9, Statistical Considerations. In addition, details regarding the implementation of procedures to minimize bias should be included in this section. DO NOT include details that might compromise these strategies. Design techniques to avoid bias can be found in the ICH Guidance for Industry E9 Statistical Principles for Clinical Trials.

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. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

Sometimes blinding is attempted but is known to be imperfect because of obvious effects related to study intervention or control product in some participants (e.g., dry mouth, bradycardia, fever, injection site reactions, and changes in laboratory data). Such problems or potential problems should be identified and, if there are plans to assess the magnitude of the problem or manage it, these should be described (e.g., having endpoint measurements carried out by study staff shielded from information that might reveal study group assignment).

If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Describe efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible. Measures to prevent unblinding by laboratory measurements, if used, should be described.

Include a description of your plans to manage and report inadvertent unblinding. If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained (e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias). If blinding is considered desirable but not feasible, the reasons and implications should be discussed.

## Study Intervention Compliance

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries). Include a discussion of what documents are mandatory to complete (e.g., participant drug log) and what source documents/records will be used to calculate study intervention compliance.

## Concomitant Therapy

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

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe the data that will be recorded related to permitted concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures. Include details about when the information will be collected (e.g., screening, all study visits). Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints) and how the independent effects of concomitant and study interventions could be ascertained.

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.]

### Rescue Medicine

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

List all medications, treatments, and/or procedures that may be provided during the study for “rescue therapy” and relevant instructions about administration of rescue medications.

Example text provided as a guide, customize as needed:

[The study site <will/will not> supply <specify type> rescue medication that will be <provided by the sponsor/obtained locally>. The following rescue medications may be used <specify name(s)>.

Although the use of rescue medications is allowable <at any time during the study>, the use of rescue medications should be delayed, if possible, for at least <insert timeframe> following the administration of <study intervention>. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.]

# Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

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

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. This section should state which adverse events would result in discontinuation of study intervention or participant discontinuation/withdrawal. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Consider requiring separate documentation for study intervention discontinuation and participant discontinuation/withdrawal from the study. In addition, a dedicated Case Report Form (CRF) page should capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

## Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or rechallenging with study intervention.

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). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), unanticipated adverse device effects (UADEs), and unanticipated problems (UPs).

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 at the time of study intervention discontinuation will include the following:

* <Describe the procedures and data to be collected, as well as any follow-up evaluations>]

## Participant Discontinuation/Withdrawal from the Study

Provide a list of reasons participation may be discontinued. It may be appropriate to provide distinct discontinuation criteria for participants and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also, note that participants may withdraw voluntarily from the study or discontinue the study intervention at any time. But, investigators should seek to minimize participant discontinuation/withdrawal from study except for safety reasons.

In studies of implantable devices, a discussion should be included of any pertinent information that will be provided to withdrawn or discontinued participants (e.g., whether and how the device can be removed, how to replace batteries, how to obtain replacement parts, who to contact). In addition, it is important to capture the reason for withdrawal or discontinuation, as this may impact inclusion of participant data in the analysis of results (see Section 9, Statistical Analyses).

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 9, 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.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

* 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
* 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.]

The reason for participant discontinuation or withdrawal from the study will be recorded on the <specify> Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the <study intervention> may be replaced. Subjects 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.]

## Lost To Follow-Up

The protocol should describe the nature and duration of study follow-up. Validity of the study is a potential issue when participants are lost to follow-up, as information that is important to the endpoint evaluation is then lost. Participants are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures. Describe the plans to minimize loss to follow-up and missing data.

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 (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record or 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 Assessment and Procedures

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

## Efficacy Assessments

List and describe all study procedures and evaluations to be done as part of the study to support the determination of efficacy, as per the primary and secondary objectives outlined in this protocol. Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrollment within which screening procedures/ evaluations must be performed (e.g., within 28 days prior to enrollment). If a separate screening protocol is developed, describe how the screening protocol will be used to identify participants for this study. In addition, discuss any special conditions that must be achieved during the enrollment and/or initial administration of study intervention. Include the procedures for administering the study intervention and follow-up procedures after administration (e.g., assessment of vital signs), as well as any specifics about subsequent follow-up visits, and unscheduled visits. Also, note if a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments. Include any definitions used to characterize outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully.

For participants that may discontinue or withdraw early, it is important to capture the rationale during the final visit. See Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for details.

Note that the protocol should provide a substantial level of detail for all procedures, and operational details can be further provided in a MOP or SOP. For example: for radiology assessment provide details on which method will be used, which organ system will be assessed, whether sedation is needed etc. Operational level details on equipment specifications, software used can be in the MOP or SOP. Provide justification for any sensitive procedures (e.g., provocative testing, deception). In addition, note where approaches to decrease variability, such as centralized laboratory assessments, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in Appendix Section 12.1, 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.

This section may include a list and description of the following procedures/evaluations, as applicable. You may also consider re-structuring the layout of the assessments/ procedures based on study timepoints and cross- reference to the Schedule of Activities (SoA) table:

* 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.
* Radiographic or other imaging assessments. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study’s MOP or a separate SOP.
* Biological specimen collection and laboratory evaluations. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP.
* Special assays or procedures required (e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP.
* Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary.
* Procedures that will be completed during the study as part of regular standard of clinical care.

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). Address when endpoints will be assessed with respect to dosing of rescue medication, if applicable.

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.

## Safety and Other Assessments

List and describe all study procedures and evaluations to be done as part of the study to monitor safety and support the understanding of the study intervention’s safety or that are done for other purposes (e.g., screening, eligibility, enrollment).

Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrollment within which screening procedures/ evaluations must be performed (e.g., within 28 days prior to enrollment). If a separate screening protocol is developed, describe how the screening protocol will be used to identify participants for this study. In addition, discuss any special conditions that must be achieved during the enrollment and/or initial administration of study intervention.

Note that the protocol should provide a high-level discussion of all procedures and detailed information can be further provided in a MOP or SOP. In addition, note where approaches to decrease variability, such as centralized laboratory assessments, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in Section 1.3, 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.

This section may include a list and description of the following procedures/evaluations, as applicable:

* 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.
* Electrocardiograms (EKGs): specify if the EKG is for screening purposes only. Include any specific instructions for the collection and interpretation of the EKG (e.g., time points relative to dosing with study intervention or other evaluations). If EKGs will be analyzed at a central laboratory, instructions for the collection (e.g., equipment), transmission and archiving of the EKG data should be summarized in this protocol, and further outlined in the MOP. If the EKG will be read locally, indicate how these will be handled and in what format (e.g., digital or paper), as well as instructions with respect to local review.
* Radiographic or other imaging assessments. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study’s MOP or a separate SOP.
* Biological specimen collection and laboratory evaluations. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens may be briefly explained in this section; detailed discussion should be included in the study’s MOP.
* Special assays or procedures required (e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP.
* Counseling procedures, including any dietary or activity considerations that need to be adhered to during study participation.
* Assessment of study intervention adherence or see Study Intervention Compliance, Section 6.4.
* Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary.
* Assessment of adverse events. Describe provisions for follow-up of ongoing AEs/SAEs.

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).

As previously noted, 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.

## Adverse Events and Serious Adverse Events

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

The following subsections are intended to highlight the specific assessments related to safety and the aspects of the study which are proposed to ensure the safety of trial participants. This section should be developed in consultation with the study Medical Director. Consider the risks of the study intervention and other study procedures and the characteristics of the study population (e.g., vulnerable populations such as children). This section should be tailored for specific study characteristics, including but not limited to the following:

* The study involves an investigational new drug or investigational device
* The study involves washout from current medication regimen
* The study involves the use of placebo in a population with a diagnosed disease
* The study requires selection of an appropriate toxicity grading scale
* The study involves risks to individuals other than research participants (e.g., household or intimate contacts or communities, study clinicians, pharmacists or interventionists, etc.)
* Reporting of certain events (e.g., suspected child abuse or substance abuse) is mandatory because of the study population or study design characteristics
* The study is conducted at multiple sites, and will require centralized safety oversight

In developing this section, consider the risks of the study intervention. Review and reference the applicable sources of information, such as the IB, package insert, device labeling, literature and other sources that describe the study intervention.

### Definition of Adverse Events (AE)

Provide the definition of an AE being used for the clinical trial. The FDA definition of an AE is used in this template. For some studies, i.e. multicountry protocols, or funders’ requirements, definitions from the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events; or ICH GCP definition may be more appropriate. However, it is important to note that FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a) for studies performed under an IND, or 21CFR.812.(a1) [for investigators] & (b1) [for sponsors] for IDEs, regardless of the definition of AE used in the protocol. Check other Health Authorities reporting requirements as applicable.

Example text provided as a guide, customize as needed (based on FDA definition):

[An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.]

Assess whether additional language is needed in this section to clarify certain AEs, such as abnormal laboratory values. Sample language for abnormal laboratory values is included below but must be assessed to determine applicability to the protocol in question.

[Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any of the following conditions is met:

* The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
* The abnormality suggests a disease and/or organ toxicity.
* The abnormality is of a degree that requires active management.

Dose Limiting Toxicity

When a protocol includes Dose Limiting Toxicities (DLT), include description here.]

### Definition of Serious Adverse Events (SAE)

Provide the definition of an SAE being used for the clinical trial. The FDA definition of an SAE is used in this template. It is important to note that FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a) for studies performed under an IND, or 21CFR.812.(a1) [for investigators] & (b1) [for sponsors] for IDEs, regardless of the definition of SAE used in the protocol. Note that the example text provided is from the drug regulations (21 CFR 312.32 (a)). Check other Health Authorities reporting requirements as applicable.

Example text provided as a guide, customize as needed:

[Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

* fatal
* life-threatening
* requires or prolongs hospital stay
* results in persistent or significant disability or incapacity
* a congenital anomaly or birth defect
* an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
* required intervention to prevent permanent impairment or damage (for devices only)

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.]

### *Unanticipated Adverse Device Effect (UADE)*

When the protocol uses devices, including lab developed tests (LDTs) and in-vitro diagnostics (IVDs), include the below text for UADEs.

[Unanticipated Adverse Device Effect (UADE)

A UADE is 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 application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.]

### Classification of an Adverse Event

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

The following subsections will include a discussion of how AEs will be classified.

#### Severity of Event

All AEs will be assessed by the study clinician using a protocol defined grading system. Describe the method of grading an AE for severity. For example, many toxicity tables are available for use and are adaptable to various study designs. Selection of a toxicity table or severity scale should be made in consultation with the study Medical Director.

Example text provided as a guide, customize as needed:

[For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

* Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
* Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
* Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.]

#### Relationship to Study Intervention

All AEs will have their relationship to study intervention or study participation assessed with a level of specificity appropriate to the study design. The clinician’s assessment of an AE's relationship to study intervention (drug, biologic, device, food or cosmetic) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. Describe the method of determining the relationship of an AE to a study intervention. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. Some protocols may use a binary assessment (related/not related); others may have a scale of relatedness. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors. In a clinical trial, the study intervention must always be considered.

Example text provided as a guide, customize as needed:

[All 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 considered.

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

OR

* [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).
* Unrelated – 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 (e.g., IB, approved labeling). 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.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the protocol, IB, package insert, or device labeling or is not listed at the specificity, frequency or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol. For example, if the IB or package insert referred only to elevated hepatic enzymes or hepatitis, then, hepatic necrosis would be unexpected (by virtue of greater severity). Similarly, if the IB or package insert listed only cerebral vascular accidents, then cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity). "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the study intervention, but are not specifically mentioned as occurring with the particular study intervention under investigation.

List expected adverse events, including frequency and severity OR reference Investigator Brochure OR package insert OR another section of protocol, as relevant.

Example text provided as a guide, customize as needed:

[<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>.]

### 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. Specify procedures for recording and follow-up of AEs and SAEs that are consistent with the information contained within Section 8.2, Safety and Other Assessments including what assessment tools will be used to monitor AEs. Include duration of follow-up after appearance of events (e.g., 1 week, 2 months).

An unsolicited AE would be described by the subject without any prompting or in response to a general question such as “Have you noticed anything different since you started the study; began the study intervention, etc.” A solicited AE is one that is specifically asked about, such as “Have you noticed any dry mouth since you started the study medication?”

* Describe which AEs will be collected as solicited events. Plan the reporting and data collection system to avoid double capture (captured both as an unsolicited and a solicited AE).
* Describe how unsolicited events will be captured.
* Include time period of collection (e.g., Days 0 -28)

Ensure specific regulatory requirements are considered, i.e. long term follow up for studies involving gene therapy products, specific requirements for controlled substances, etc.

Example text provided as a guide, customize as needed:

CTCAE criteria are commonly used; however other description systems may be used. If another is chosen, modify the text in this section accordingly.

[Safety will be assessed by monitoring and recording potential adverse effects using the <enter *protocol defined grading system* being used> at each study visit. Participants will be monitored by medical histories, physical examinations, and <other studies>. If < protocol defined grading system > grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.]

### Adverse Event Reporting

This section addresses responsibilities of investigators for reporting of AEs. For Penn reporting requirements and timelines refer to [*Penn IRB definition of reportable events and reporting timelines*](https://irb.upenn.edu/reportable-event).

Describe the AE reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight (e.g., Data and Safety Monitoring Board (DSMB), safety monitoring committee, independent safety monitor) and regulatory groups, and what study staff are responsible for completing and signing off on the AE reports, and who will receive notification of AEs. According to 21 CFR 312.64(b), “…The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol”.

In addition, list any disease-related events (DREs) common in the study population (e.g., expected), which will not be reported per the standard process for reporting, as applicable. Describe how these events will be recorded and monitored.

Ensure specific regulatory requirements are addressed, i.e. long term follow up for gene therapy trials, specific requirements for controlled substances, etc.

Example text provided as a guide, customize as needed:

**Reporting Period**

Adverse events will be reported from the time of informed consent until study completion.

**Investigator Reporting: Notifying the Study Sponsor**

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the <insert role that will be receiving the notifications>.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

**Investigator Reporting: Local Reporting Requirements**

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

### Serious Adverse Event Reporting

This section addresses responsibilities of investigators for reporting of SAEs. For Penn reporting requirements and timelines refer to [*Penn IRB definition of reportable events and reporting timelines*](https://irb.upenn.edu/reportable-event).

Describe the SAE reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the SAE reports, and who will receive notification of SAEs.

Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in Section 8.3.2, 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 have a requirement to submit expedited notification of all SAEs or only SAEs thought to be related to study intervention.

According to 21 CFR 312.64(b), “An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor…”

According to 21 CFR 312.32(c)(1), “the sponsor must notify FDA and all participating investigators…in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.”

Furthermore, according to 21 CFR 312.32(c)(2), “the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.”

As noted previously, an unanticipated adverse device effect could be considered an SAE (Section 8.3.2, Definition of Serious Adverse Events). For IDE studies, according to 21 CFR 812.150(a)(1), “an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.” In addition, according to 21 CFR 812.150(b)(1), “A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.”

Example text provided as a guide, customize as needed:

Example 1, applicable for a drug or biologic protocol:

[The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered <study intervention> related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the <study intervention> caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the <study intervention> and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). 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. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The SAE reports to the Sponsor should be sent to : <insert role but not name>.

The study sponsor will be responsible for notifying the <enter Health Authority(ies), Food and Drug Administration (FDA), as applicable> of any unexpected fatal or life-threatening suspected adverse reaction per applicable regulations. In addition, the sponsor must notify <enter Health Authority(ies), FDA, as applicable> and all participating investigators of potential serious risks, from clinical trials or any other source, as per the applicable regulation.]

OR

Example 2, modify the previous one as applicable for device protocol:

[The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the <enter Health Authority(ies), Food and Drug Administration (FDA) as applicable> and to all reviewing IRBs and participating investigators per the applicable regulation.]

### 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.

### Events of Special Interest

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

Describe any other events that require reporting to the sponsor, study leadership, IRB, and regulatory agencies. 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, medical device incidents (including malfunctions), laboratory test abnormalities, and study intervention overdose.

### 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, or the participant may be asked to adhere *to contraceptive requirements (for men and women as applicable)*

State the study’s pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to the sponsor, study leadership, IRB, regulatory agencies, and the DCC or NIH, (as applicable). 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).

Example text provided as a guide, customize as needed:

[Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug or process may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject, and the fetus is exposed to study drug and/or process (maternally or paternally), the following procedures should be followed to ensure subject safety:

Include protocol specific language here, as appropriate. Sample language provided below.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.]

## 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 DHHS (Department of Human Health Services). 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 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 involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all 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 UPs. Describe the UP reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight (e.g., DSMB, safety monitoring committee, independent safety monitor) and regulatory groups, and what study staff are responsible for completing and signing off on the UP report forms.

Institutions engaged in human subjects research conducted or supported by Department of Health and Human Services (DHHS) must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)). Furthermore, for research covered by an assurance approved for federal wide use by OHRP, DHHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP. More guidance on how to identify Unanticipated Problems versus Adverse Events and how to report them are available in the [*Penn Manual.*](https://www.med.upenn.edu/pennmanual/secure/defining-and-identifying.html)

UP are generally non-medical events, as medical events would be captured under AEs

Example text provided as a guide, customize as needed:

[Unanticipated problems (UPs) such as:

* Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
* FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
* Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
* Breach of confidentiality
* Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
* Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the <Sponsor, reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI)>. The UP report will include the following information:

* Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
* A detailed description of the event, incident, experience, or outcome;
* An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
* A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

* UPs that are serious adverse events (SAEs) will be reported as any other SAE.
* Any other UP will be reported to the <Sponsor, IRB and to the DCC/study sponsor within <insert timeline in accordance with SOP and policy> of the investigator becoming aware of the problem.
* All UPs should 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) within <insert timeline in accordance with policy> of the IRB’s receipt of the report of the problem from the investigator.]

### 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.

## Device Reporting

*When a protocol is conducted under an abbreviated (non-significant risk device) or a full (significant risk device) IDE, there are additional reporting requirements per* [*21 CFR 812.150*](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150)*. The following information must be reported to the IRB per IRB reporting timelines. Include this information in the protocol if you are working on a trial of a device.*

* *If investigator failed to obtain informed consent from a subject;*
* *Withdrawal of FDA approval (for a full IDE study);*
* *Any device recall, repair, or disposal;*
* *If there is reason to believe that the device determination has changed from non-significant risk to significant risk (i.e. the protocol may now require a full IDE).*

*This information must be relayed by the investigator to the sponsor. The sponsor is responsible for reporting the information to the IRB, although in most cases, this will likely go through the investigator. A sponsor-investigator is responsible both for IRB reporting and appropriate FDA reporting, as needed.*

Example

[Safety reporting for the device(s) will be according to 21 CFR 812.150.]

# Statistical Considerations

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

The following subsections should describe the statistical tests and analysis plans for the protocol. They should indicate how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH Guidance for Industry E9 Statistical Principles for Clinical Trials and the CONSORT statement which describes standards for improving the quality of reporting randomized controlled trials.

State whether there will be a formal Statistical Analysis Plan (SAP). A formal SAP should be completed prior to database lock and unblinding of the study data. The SAP generally includes additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies). If a separate SAP will be developed, subsections below can be summarized.

## Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

* Primary Efficacy Endpoint(s):
* Secondary Efficacy Endpoint(s):

## 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. In particular, specify all of the following:

* Outcome measure used for calculations (almost always the primary variable)
* Test statistic
* Null and alternative hypotheses
* Type I error rate (alpha)
* Power level (e.g., 80% power)
* Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible
* Statistical method used to calculate the sample size, with a reference for it and for any software utilized
* Anticipated impact of dropout rates, withdrawal, cross-over to other study arms, missing data, etc. on study power (see also 9.4.2 Analysis of the Primary Efficacy Endpoint(s) and 9.4.3 Analysis of the Secondary Endpoint(s))
* Method for adjusting calculations for planned interim analyses, if any (Section 9.4.6, Planned Interim Analyses)

Further, present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

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 9.4.9, Exploratory Analyses).

## 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

## Statistical Analyses

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

The following subsections should include a description of the planned statistical methods.

### 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).

### 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 9.3, 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.

### 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 9.3, 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.

### 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 9.4.2, Analysis of the Primary Efficacy Endpoint(s) should be included here. Describe how AEs will be coded (e.g., Medical Dictionary for Regulatory Activities (MedDRA)), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g., severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings) and what information will be reported about each AE (e.g., start date, stop date, severity, relationship, expectedness, outcome, and duration). 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 8.2, Safety and Other Assessments**.

### 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.

### 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 considered if this is a comparative effectiveness or pragmatic clinical trial with safety/efficacy endpoints.

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

### 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).

### Tabulation of Individual Participant Data

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

### Exploratory Analyses

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

# Supporting Documentation and Operational Considerations

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

## Regulatory, Ethical, and Study Oversight Considerations

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

The following subsections should include a description of the regulatory and ethical considerations, and context for the conduct of the trial. Of note, the guiding ethical principles being followed by this study are included in the Statement of Compliance at the beginning of this protocol. For NIH Intramural Research Program studies only: A statement referencing compliance with NIH Human Research Protections Program policies and procedures is adequate for Subsection 10.1.1, Informed Consent Process.

### Informed Consent Process

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

The following subsections should describe the procedures for obtaining and documenting informed consent of study participants. State if a separate screening consent will be used. If a separate screening consent will not be used, the study consent must be signed prior to conducting study screening procedures. If an assay, lab developed test, or in vitro diagnostic will be used to determine eligibility or even during the study, discuss whether the test/diagnostic is FDA approved or cleared and whether this test is used in usual care for the patient population. If the test used is not FDA approved or cleared, this should be noted in the consent form. Risks of false positives and false negatives should be included.

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. For alterations to the typical consent process, please refer to **guidance at this link.**

#### Consent/Assent and Other Informational Documents Provided To Participants

This section should demonstrate that the consent form contains all required regulatory elements. List all consent and/or assent documents and materials submitted with this protocol. Include consent and/or assent forms, printed or web-based materials, phone scripts and any other related material.

If needed, describe special documents or materials (e.g., Braille, another language, audio recording)

Example text provided as a guide, customize as needed:

[Consent forms describing in detail the <study intervention>, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering <study intervention>. The following consent materials are submitted with this protocol <insert list>.]

#### Consent Procedures and Documentation

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 from a legally authorized representative (LAR) for those unable to consent on their own behalf. This section should be consistent with Section 5.5, 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. The investigator 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. 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.]

### Study Discontinuation and Closure

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). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, the IRB, and sponsor and provide the reason(s) for the termination or temporary suspension.

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

Example text provided as a guide, customize as needed:

[This study may be temporarily suspended or prematurely terminated by the Sponsor or the PI at any site 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 Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (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 Food and Drug Administration (FDA).]

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects’ interests.

### 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 sponsor’s requirements. Describe (as applicable) who would have access to records, including the investigator and other study staff, the clinical monitor, funding institutions, IND/IDE sponsor, representatives from the IRB, regulatory agencies, representatives of the NIH Institute or Center (IC), and representatives of the pharmaceutical company supplying product to be tested. In addition, consider inclusion of the following information:

* Describe whether identifiers will be attached to data/samples, or whether data will be coded or unlinked.
* If unlinked or coded, and additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.
* If research data/samples will be coded, describe how access to the “key” for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.
* Include a discussion of the circumstances in which data or samples will be shared with other researchers.
* Include a discussion of plans to publish participant’s family pedigrees, with a description of measures to minimize the chance of identifying specific families.
* Describe any situations in which personally identifiable information will be released to third parties.
* Document who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access.
* Discuss any additional features to protect confidentiality (e.g., use of a certificate of confidentiality).
* Approaches to ensure privacy of study participants
* Note, where the study plans to enroll any participant residing in the European Union, additional regulatory requirements for data protection should be met. Contact the OCR for additional support.

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. Authorization comes from NIH through section 301 (d) of the Public Health Service Act (42 U.S.C. 241 (d)) which provides the Secretary of Health and Human Services the authority to protect the privacy of study participants. Refer to the NIH Certificate of Confidentiality Kiosk, for more details.

Example text provided as a guide, customization will be required to address all aspects that should be included in this section:

[Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, other authorized representatives of the sponsor, 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 sponsor 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>. 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. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

Certificate of Confidentiality (if applicable)

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). 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.]

### 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 10.1.3, Confidentiality and Privacy and Section 10.1.9, Data Handling and Record Keeping, for further information on future use of study records.

Example text provided as a guide, customize as needed:

[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, 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), de-identified 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. 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 the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent regarding biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the <specify name of Repository>.]

### Safety Oversight

Appropriate safety oversight should be used for each trial. This could include a Data Safety Monitoring Committee (DSMC), Data Safety Monitoring Board (DSMB), Safety Assessment Committee, and/or an Independent Safety Monitor (ISM). 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 DSMC 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 DSMB 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 study sponsor>.]

### Clinical Monitoring

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 ICH GCP, and with applicable regulatory requirement(s).

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 monitoring plan.

A separate monitoring plan (MP) should describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. A MP ordinarily should focus on preventing or mitigating important and likely risks, identified by a risk assessment, to critical data and processes. The types (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)) of monitoring activities will depend on a range of factors, considered during the risk assessment, including the complexity of the study design, types of study endpoints, clinical complexity of the study population, geography, relative experience of the PI and of the sponsor with the PI, data capture, relative safety of the study intervention, stage of the study, and quantity of data.

If a separate MP is not used, include all the details noted above in this section of the protocol. Penn investigators may refer to the [*Sponsor Monitoring Plan Guide*](https://www.med.upenn.edu/ocr/secure/forms-tools-templates.html)**.**

Example text when a separate MP is being used is provided as a guide, customize as needed:

[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).

* Monitoring for this study will be performed by <insert text>.
* <Insert brief description of 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)>.
* <Insert text> will be provided copies of monitoring reports within <x> days of visit.
* Details of clinical site monitoring are documented in a Monitoring Plan (MP). The MP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
* Independent audits or compliance reviews may be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP.]

OR

Example text when a separate MP is not being used is provided as a guide, customize as needed:

[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 may be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites.]

### Quality Assurance and Quality Control

This section will briefly describe the plans for quality management for every study activity.

Principal Investigators must ensure they have adequate and qualified staff to conduct the study and must qualify all their vendors, including but not limited to laboratories, pharmacy, service providers, (i.e. radiology films, necropsy), etc. to ensure the vendors have the appropriate resources (i.e. qualified staff, finances, facilities, processes, quality assurance, etc.) and train them in the specifics of the protocol.

* How data and specimens (when applicable) will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.
* Describe 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.
* Document 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.

Example text provided as a guide, customize as needed:

[All monitoring and audits are to be performed according to ICH GCP E6(R2).

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site’s quality management.

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 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 sponsor, and inspection by local and regulatory authorities.]

### Data Handling and Record Keeping

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

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. Describe in this section who will have access to records.

The following subsections should include a description of the data handling and record keeping for the conduct of the trial.

#### 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. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs. Further details may be provided in the MOP or the data management plan, including detailed descriptions of source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of source data include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants’ memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be c ollected on CRFs and what data will be collected from other sources. Electronic source data are data initially recorded in electronic form.

It is not acceptable for the CRF to be the only record of a participant’s inclusion in the study. Study participation should be captured in a participant’s medical record. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

Describe responsibilities for data handling and record keeping as they specifically relate to the sponsor, the investigator(s) site(s), laboratory(ies), and DCC as applicable. Include the role in data collection, review of data, trial materials, and reports, as well as retention of source documents, files, and records. Describe coding dictionaries to be used and reconciliation processes (if applicable).

If data are to be generated in one location and transferred to another group, describe the responsibilities of each party.

Provide a list of planned data standards, formats, terminologies and their versions, used for the collection, tabulation, analysis of study data. If applicable, refer to the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format — Standardized Study Data, Study Data Technical Conformance Guide and FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

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 and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete).

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

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 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.]

If using the Penn CTMS, the following text may be included:

[[Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. This EDC (Velos version 9) supports programmable data entry validation rules and edit checks to identify data entry errors.]]

#### Study Records Retention

Specify the length of time for the investigator to maintain all records pertaining to this study. The sponsor should use and require the most conservative rule for document retention – i.e., retention should follow the rule that has the longest period.

Indicate whether permission is required (and from whom) prior to destruction of records.

Example text provided as a guide, customize as needed:

[Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the <study intervention>. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.]

### Protocol Deviations

During the course of a trial, the Principal Investigator (PI) or their study team may prospectively identify that specific elements of a protocol are unable to be met, or realize that protocol procedures/processes have not been followed. Penn specific guidance on protocol deviations and exceptions can be found in the [*Penn Manual*](https://www.med.upenn.edu/pennmanual/secure/protocol-deviations%2C-violations-and-exceptions.html).

The FDA defines protocol deviations as any change, divergence, or departure from the study design or procedures defined in the protocol.

It also defines important protocol deviations as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

Include 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:

[The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

* Who deviated from the protocol
* What was the deviation
* When did the deviation occur
* How did the deviation happen
* What is the impact of the deviation
* A root cause analysis of why the deviation occurred

If the assessment is determined to be of limited impact (minor deviation), the documentation for this assessment and the outcome should be reported to the Sponsor at the time of annual report. Reporting to the IRB should follow specific local requirements.

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

* having the potential to adversely affect subject safety; OR
* increases risks to participants; OR
* adversely affects the integrity of the data; OR
* violates the rights and welfare of participants, OR
* affects the subject’s willingness to participate in research.
* there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

These scenarios should be reported to the Sponsor within 10 business days of discovery. Reporting to IRB should follow local requirements.]

### Publication and Data Sharing Policy

The publication and authorship policies should be described in this section. Please refer to your specific contract, grant, and/or Clinical Trials Agreements. If details of the publication policy is described in a study MOP, refer to it here. Penn specific guidance around publications and template language based on funding, can be found in the *Penn Manual*.

All data sharing (outside your organization) requires a legal agreement. All protocols and data shared involving EU countries or EU citizens/residents require additional resources. Contact OCR for additional assistance.

Example text provided as a guide, customize as needed:

[This study will comply with the data sharing agreement.

The Sponsor must approve all sharing of information/data prior to its occurrence.]

### Conflict of Interest Policy

This section should include a description of how the study will manage actual or perceived conflicts of interest. Penn-specific guidance on existing policies, management and reporting, can be found in the [*Penn Manual*](https://www.med.upenn.edu/pennmanual/secure/conflict-of-interest.html)***.***

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.]

## 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/EC-related requirements.

## Protocol Amendment History

*Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by . A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.*

*Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. will submit protocol amendments to the appropriate regulatory authorities.*

*If in the judgment of, the sponsor, the IRB/IEC, and/or the investigator, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.*

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

| Version | Date | Description of Change  | Brief Rationale |
| --- | --- | --- | --- |
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# 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.

# **APPENDIX**

##  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).

| Procedures | ScreeningDay -7 to -1 | Enrollment/BaselineVisit 1, Day 1 | Study Visit 2 Day 7 +/-1 day | Study Visit 3Day 14 +/- 1 day | Study Visit 4Day 21 +/-1 day | Study Visit 5Day 28 +/-1 day | Study Visit 6Day 35 +/-1 day | Study Visit 7Day 42 +/-1 day | Study Visit 8Day 49 +/-1 day | Study Visit 9Day 56 +/-1 day | Study Visit 10Day 63 +/-1 day | Study Visit 11Day 70 +/- 1 day | Study Visit 12Day 77 +/-1day | Final Study Visit 13Day 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 (including height and weight) | 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 | 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 |
| Complete Case Report Forms (CRFs) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.Serum pregnancy test (women of childbearing potential). |

**END OF DOCUMENT**