PREFACE
Remove this **Preface** before finalizing and distributing the clinical trial protocol.

This Clinical Trial Protocol Template is a suggested format for Phase 2 or 3 clinical trials supported by the National Institutes of Health (NIH) that are being conducted under a Food and Drug Administration (FDA) Investigational New Drug Application (IND) or Investigational Device Exemption (IDE). Investigators for such trials are strongly encouraged to use this template when developing protocols for NIH supported clinical trial(s). However, others may also find this template beneficial for other clinical trials not named here.

This template is provided to aid the investigator in writing a comprehensive clinical trial protocol that meets the standard outlined in the *International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (ICH-E6)*. In order to facilitate review by NIH and FDA, investigators should retain the sections in the order provided.

How To Use This Template
Throughout this template, the user will find three different types of text: instruction, explanatory and example.

Instruction and explanatory text are indicated by *italics* and should either be replaced in your protocol with appropriate, trial specific text or deleted. Footnotes to instructional text should also be deleted.

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

If this document is used to develop your clinical trial protocol, as noted above, instruction and explanatory text must be deleted and example text must be removed or revised to suit your study. Alternatively, an accompanying blank protocol template shell is provided and may be used. The blank protocol template shell does not contain instruction, explanatory and example text. It only includes the headers below which the writer can add protocol text for the specific study. The headers include styles to generate a table of contents.

Version control is important to track protocol development, revisions and amendments, and to ensure that the correct version of a protocol is used by all staff conducting the study. With each revision, update the version number and date located on the bottom of each page. When making changes to an approved and "final" protocol, it is recommended to maintain a summary of the changes.

References
Relevant references that may be useful when drafting a clinical trial protocol include:

- *Citing Medicine, 2nd edition: The NLM Style Guide for Authors, Editors, and Publishers*
- CMS: Clinical Laboratory Improvement Amendments
- *CONSORT statement*
- FDA: Compliance Actions and Activities
- *FDA: Federal Food, Drug, and Cosmetic Act (FD&C Act*)

- *FDA: Food and Drug Administration Amendments Act (FDAAA) of 2007*
- FDA Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring
- FDA Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs – Improving Human Subject Protection
- FDA: Regulations Relating to Good Clinical Practice and Clinical Trials
- *HHS: The HIPAA Privacy Rule*
- ICH Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance
- ICH Guidance for Industry, M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- ICH Guideline for Industry, E3 Structure and Content of Clinical Reports
- *ICH Guidance for Industry, E9 Statistical Principles for Clinical Trials*
- *ICMJE: Recommendations*
- ISO Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice (ISO 14155:2011)
- *NIH Guide Notice: Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)*
- NIH Guide Notice: Required Education in the Protection of Human Research Participants
- NIH: Award Management
- NIH: Certificates of Confidentiality (CoC) Kiosk
- NIH: Detailed Application Instructions for Certificate of Confidentiality: Extramural Research Projects
- NIH: Financial Conflict of Interest
- *NIH: NIH Grants Policy Statement, Section 8.2 Availability of Research Results: Publications, Intellectual Property Rights, and Sharing Research Resources*
- NIH: Inclusion Of Women And Minorities As Participants In Research Involving Human Subjects-Policy Implementation Page
- *NIH: NIH Public Access Policy Details*
- OHRP: Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
- OHRP: Human Subject Regulations Decision Charts
- OHRP: Informed Consent Checklist
- OHRP: IRBs and Assurances
- OHRP: Policy & Guidance Index
- OHRP: Vulnerable Populations
- OHRP: Tips on Informed Consent
- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 56: Investigational Review Boards
- 21 CFR Part 312: Investigational New Drug Application
- 21 CFR Part 812: Investigational Device Exemptions
- 45 CFR Part 46; Protection of Human Subjects Research

<Title>

The title should be easy to remember, recognizable by administrative support staff, and sufficiently different from other protocol titles to avoid confusion. Brevity with specificity is the goal.

Protocol Identifying Number: < Number>

Principal Investigator: < Principal investigator>

IND/IDE Sponsor: <Sponsor name, if applicable>

Do not include IND/IDE number

Sponsor means an individual or pharmaceutical or medical device company, governmental agency, academic institution, private organization, or other organization who takes responsibility for and initiates a clinical investigation.

Funded by: < NIH Institute & Center (IC)>

Draft or Version Number: v.<x.x>

<Day Month Year>

All versions should have a version number (v.0.x (for draft) or v.x.0 (for final); i.e., v0.1 for the first draft and v.1.0 for the first final version) and a submission date. Use the international date format (day month year) and write out the month (e.g., 23 June 2015).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, ICH E6 and the applicable regulatory requirements.

Example text provided as a guide, customize as needed:

(1) [The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following *(use applicable regulations depending on study location and sponsor requirements; examples follow):*

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.]

OR

(2) [The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the <NIH IC> Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.]

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

Principal Investigator: _____
Print/Type Name

Signed: _____ Date: _____
Signature

PROTOCOL SUMMARY

Title:	<Full title>
Précis:	*Provide a brief overview of the study design, including sample size, study groups, schedule of interventions, schedule for specimen or data collection, and analyses to be performed*. *The précis should be only a few sentences in length. A detailed schematic describing all visits and assessments (schedule of events) should be included in the* ***Schematic of Study Design****.*
Objectives:	*Insert objectives that are the same as the objectives contained in the body of the protocol. Include the primary objective and important secondary objectives.* <Primary Objective: Important Secondary Objectives: >
Endpoint	*Insert endpoints that are the same as the endpoints contained in the body of the protocol. Include the primary endpoint and important secondary endpoints.* <Primary Endpoint: Important Secondary Endpoints: >
Population:	*Specify sample size, gender, age, demographic group, general health status, geographic location.*
Phase:	<2 or 3>
Number of Sites enrolling participants:	*Insert a list of participating sites. If greater than 3 sites, indicate number (quantity) of sites only and refer to* ***Section 1, Key Roles*** *for a complete list of participating sites.*
Description of Study Agent :	*Describe the agent/intervention. If agent/intervention is a drug or biologic, include dose and route of administration. For other agents (e.g., device), provide brief description.*
Study Duration:	*Estimated time (in months) from when the study opens to enrollment until completion of data analyses.*
Participant Duration:	*Time (in months) it will take for each individual participant to complete all participant visits*

SCHEMATIC OF STUDY DESIGN

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 study design. Depending on the nature of your study, one example may be more appropriate than another. Regardless, 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. If you utilize Example 1, complete the tables with study-specific information and adapt the table(s) to illustrate your study design. If you utilize Example 2, 3, or 4, 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 ***Section 7.3, Study Schedule****, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.*

Example #1 provided as a guide, customize as needed: Table format *(e.g., dose escalation)*

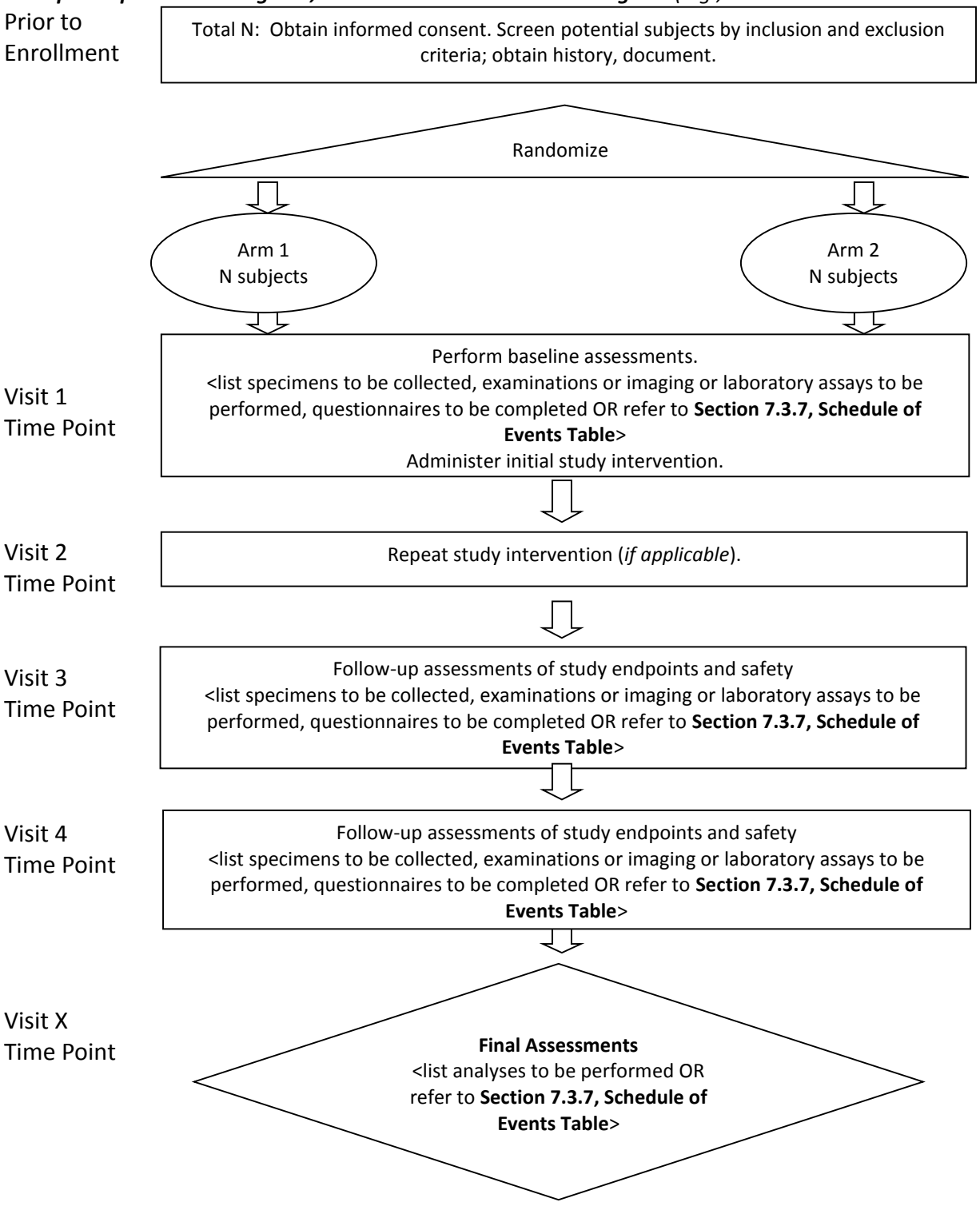
Cohort A	ARM 1	Sample Size	Intervention 1
Cohort A	ARM 2	Sample Size	Intervention 2

Include instructions for progressing to next phase (if applicable):

Interim Analysis

Cohort B	ARM 1	Sample Size	Intervention 1
Cohort B	ARM 2	Sample Size	Intervention 2

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



Example #3 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 subjects by inclusion and exclusion criteria
- Obtain history, document

Week/Day (Insert time) Randomization

- Treatment 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 **Section 7.3.7, Schedule of Events Table**>
- Administer initial study intervention

Week/Day (Insert time) 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 **Section 7.3.7, Schedule of Events Table**>

Week/Day (Insert time) 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 **Section 7.3.7, Schedule of Events Table**>

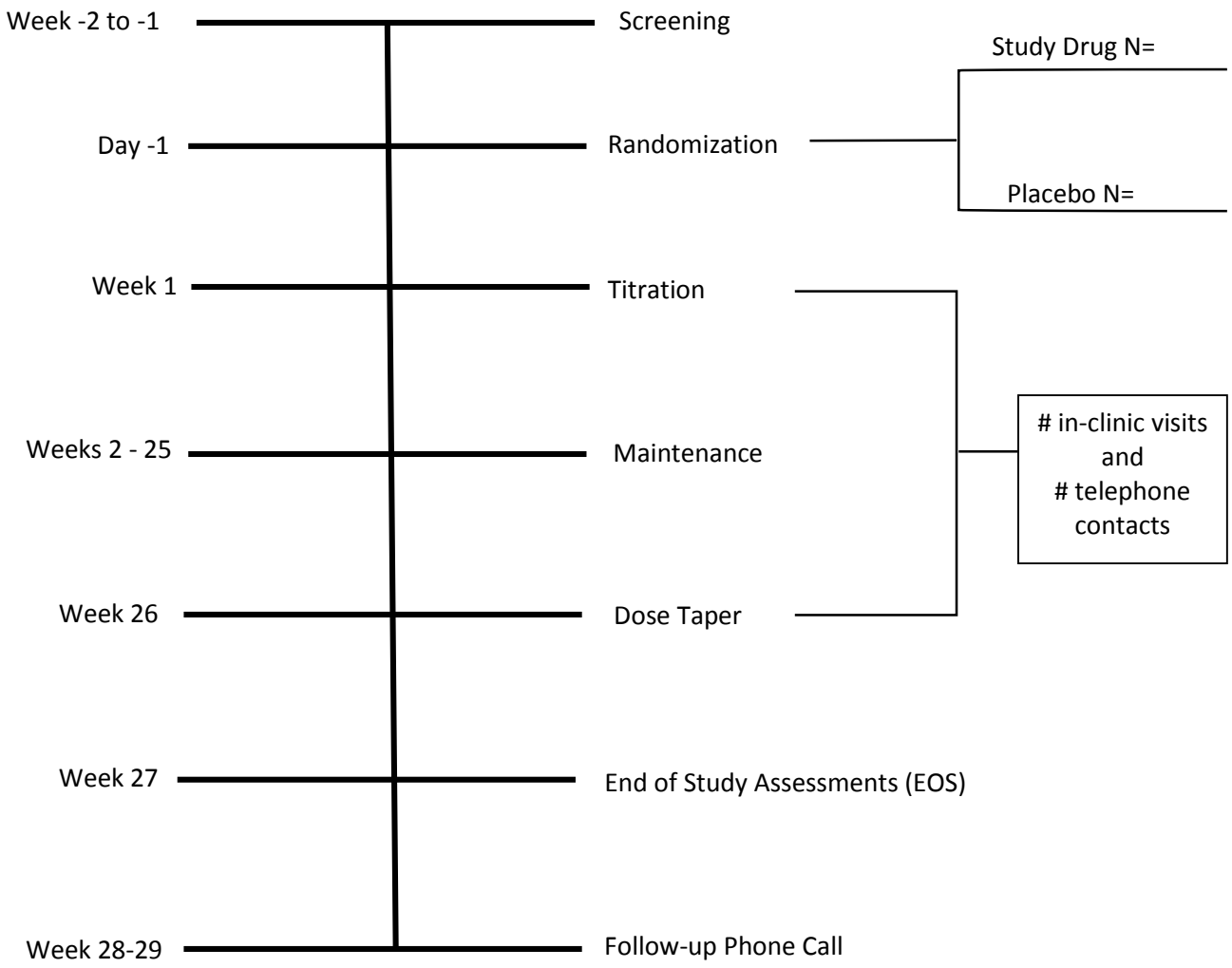
Week/Day (Insert time) End of Study Assessments

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 7.3.7, Schedule of Events Table**>

Week/Day (Insert time) Follow-up Telephone Call

- <List questionnaires to be completed OR refer to **Section 7.3.7, Schedule of Events Table**>

Example #4 provided as a guide, customize as needed: Timeline diagram *(e.g., randomized controlled trial)*



1 KEY ROLES

Provide a list of persons, companies, and/or groups serving in key roles in the conduct or oversight of the trial. This should include the sponsor's medical expert for the trial (medical monitor), investigator responsible for conducting the trial (principal investigator (PI)), qualified clinician responsible for the site's clinical decisions (site investigator), and any clinical laboratory(ies) or other institutions involved in the trial. Other key roles may include the NIH point of contact (program director or officer), regulatory specialist, biostatistician, data coordinating center (DCC), data management center, data manager, or industry partner.

Include the following information for each individual:

Name, degree, title
Institution Name
Address
Phone Number
Email

<Insert text>

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC 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 scientific rationale for the clinical trial.

2.1 BACKGROUND INFORMATION

Include:

- *The name and description of the study agent (i.e., intervention/investigational products(s))*
- *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance*
- *A summary of relevant clinical research*
- *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 17, Literature References**)*
- *Applicable clinical, epidemiological, or public health background or context of the study*
- *Importance of the study and any relevant treatment issues or controversies*

<Insert text>

2.2 RATIONALE

State the problem or question under study (e.g., describe the disease and current limitations of knowledge or therapy). Include a statement of the hypothesis. Include a justification for the route of administration, dosage, dosing regimen of the study agent, intervention periods, and selection of study population. Describe the rationale for the type and selection of control (e.g. placebo, no treatment, active drug, dose-response, historical). Discuss known or potential problems associated with the control group chosen in light of the specific disease and therapies being studied.

<Insert text>

2.3 POTENTIAL RISKS AND BENEFITS

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.

2.3.1 KNOWN POTENTIAL RISKS

Include a discussion of known potential risks from either clinical or nonclinical studies. If a package insert 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 Investigator's Brochure (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 or the IB, the risk information discussion will result from published literature and should be included and referenced appropriately.

Describe in detail any physical, psychological, social, legal, economic, or any other risks to participants by virtue of participation in the study that the PI foresees, addressing each of the following:

- *Immediate risks*
- *Long-range risks*
- *Rationale for the necessity of exposing human participants to such risks*
- *Why the value of the information to be gained outweighs the risks involved*
- *If risk is related to proposed procedures included in protocol, any alternative procedures that have been considered and explanation on why alternative procedures not included*

<Insert text>

2.3.2 KNOWN POTENTIAL BENEFITS

Include a discussion of known potential benefits from either clinical or nonclinical studies. If a package insert from a licensed or approved 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 potential relevant benefit information. If the potential benefit cannot be described from the package insert or the IB, the potential benefit information discussion will result from published literature and should be included and referenced appropriately.

Describe in detail any physical, psychological, social, legal, economic, or any other potential benefits to participants by virtue of participation in the study that the PI foresees, addressing each of the following:

- *Immediate potential benefits*
- *Long-range potential benefits*

Note: Payment to participants, whether as an inducement to participate or as compensation for pain and inconvenience, is not considered a "benefit." Provision of incidental care is also not to be considered a benefit.

<Insert text>

3 OBJECTIVES AND PURPOSE

Provide a detailed description of the primary objective and any secondary objectives of the study. An objective is the reason for performing the study in terms of the scientific question to be answered. 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). Secondary objectives are goals that will provide further information on the use of the intervention.

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., feasibility, acceptability, 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).

<Insert text>

4 STUDY DESIGN AND ENDPOINTS

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 design and endpoints.

4.1 DESCRIPTION OF THE 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 Summary*** *and include:*

- *A description of the type/design of trial to be conducted (e.g., placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging)*
- *Phase of the trial*
- *The number of study groups/arms*
- *Single or multi-center*
- *Name of study agent/intervention(s)*
- *Changes in scheduling, such as dose escalations*
- *Any stratifications.*

<Insert text>

4.2 STUDY ENDPOINTS

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

The following subsections should include the methods for assessing how the study objectives are met. A study endpoint utilizes a specific measurement or observation to assess the effect of the study variable (study agent). 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, behaviors or

health outcomes). Include the study visits or time points at which data will be recorded or samples will be obtained.

4.2.1 PRIMARY ENDPOINT

The primary endpoint used to determine primary efficacy should be clearly specified. Although the critical efficacy measurements may seem obvious, the protocol should clearly articulate how the selected primary endpoint(s) is linked to achieving the primary objective. This section should include an explanation of why primary endpoint(s) was chosen and its importance and role in the analysis and interpretation of study results. 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.

<Insert text>

4.2.2 SECONDARY ENDPOINTS

Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. The protocol should clearly articulate how the selected secondary endpoints are linked to either adding more information about the primary objective or addressing secondary objectives. This section should include an explanation of why secondary endpoints were chosen and their importance and role in the analysis and interpretation of study results.

<Insert text>

4.2.3 EXPLORATORY ENDPOINTS

Exploratory endpoints should be specified.

<Insert text>

5 STUDY ENROLLMENT AND WITHDRAWAL

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, participant recruitment, and issues related to participant withdrawal. The study population should be appropriate for the stage of the study and the development stage of the study agent.

Use the following guidelines when developing participant eligibility criteria to be listed in ***Sections 5.1 Participant Inclusion Criteria and 5.2 Participant 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 participants. Determine if screening procedures will be performed under a separate screening consent form.*
- *The risks of the intervention should be considered in the development of the inclusion/exclusion criteria so that risk is 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).*
- *Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.*

- *If reproductive status (i.e., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g., licensed hormonal or barrier methods).*

5.1 PARTICIPANT INCLUSION CRITERIA

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. Women and members of minority groups and their subpopulations 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, 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:

- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female, aged <specify range>
- 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>
- <Specify laboratory test> results between <specify range>
- Ability to take oral medication and be willing to adhere to the medication regimen
- For females of reproductive potential: use of highly effective contraception
- For males of reproductive potential: use of condoms]

<Insert text>

5.2 PARTICIPANT EXCLUSION CRITERIA

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 women and minorities are excluded, provide a clear and compelling rationale and justification to establish to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects 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.

Example text provided as a guide, customize as needed:

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

- < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>
- < Specify use of disallowed concomitant medications>
- Presence of <specific devices (e.g., cardiac pacemaker)>
- Febrile illness within <specify time frame>
- Pregnancy or lactation
- Known allergic reactions to components of the study agent
- Treatment with another investigational drug or other intervention *within* <specify time frame>
- Current tobacco or tobacco use within <specify timeframe>
- Household contacts who are immunocompromised]

<Insert text>

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Identify strategies for participant recruitment and retention. *Specify approach(es) for conforming with NIH Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects. Include numbers of women and minorities expected to be recruited, or provide justification if women and/or minorities will not be recruited.*

If appropriate, include justification for inclusion of vulnerable participants and recruitment strategy. Vulnerable participants include those who lack consent capacity, including the mentally ill, prisoners, cognitively impaired participants, pregnant women, children, and employee volunteers. Include safeguards for protecting vulnerable populations. Please refer to the Office for Human Research Protections (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 (for example, if a participant becomes a prisoner during the study).
If participants will be compensated or provided any incentives (e.g. vouchers, iPads) for study participation, describe amount, form and timing of any 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 adult, state if payment will be provided to the participant or to a guardian.

If the study requires long-term participant participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).

In addition, consider inclusion of the following information:

- *Target sample size; identify anticipated number to be screened in order to reach the target enrollment (should be consistent with information contained in **Section 10.5, Sample Size**)*
- *Anticipated accrual rate*
- *Number of sites and participants to be enrolled from U.S. and outside U.S.*
- *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 advertisements planned (e.g. national newspaper, local flyers; specific names are not needed)*

<Insert text>

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

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 terminate a participant from the study.

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Provide a list of reasons participation may be terminated. 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 at any time.

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 terminate participation in the study 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
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.]

<Insert text>

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Describe efforts that will be made to continue follow-up of withdrawn or terminated participants or participants who discontinue study agent but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Every effort must be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). In studies of implantable devices, a discussion should be included of any pertinent information that will be provided to withdrawn or terminated patients (e.g., how to replace batteries, how to obtain replacement parts, who to contact).

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

<Insert text>

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision or sponsor/funder decision). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform the IRB and sponsor and provide the reason(s) for the termination or temporary suspension. State what criteria or review will be done to determine if study can resume.

Example text provided as a guide, customize as needed:

[This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency, the IND/IDE sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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 of futility

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

<Insert text>

6 STUDY AGENT

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 agent that is being tested for safety and effectiveness in the clinical investigation, and any control product being used in the clinical investigation. The study agent may be a drug (including a biological product), imaging agent, or device subject to regulation under the Federal Food, Drug, and Cosmetic Act that is intended for administration to humans and that has been or has not yet been approved by the FDA. ***Note:*** *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.*

Note: *If multiple study agents are to be evaluated in the trial,* ***Section 6.1 Study Agent(s) and Control Description*** *should clearly differentiate between each product. Address placebo or control product within each part of* ***Section 6.1****. If the control product is handled differently than the study agent, be sure to state how they are each handled separately. If the control product is handled the same as the study agent, state as such.* ***In addition, all sections may not be relevant for the trial. If not relevant, note as not applicable in that section.***

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

No text is to be entered in this section; rather it should be included under the relevant subheadings below. However, if study is IND exempt or IDE is waived, provide justification here.

The following subsections should include a description of the study agent and control product. Product information can usually be obtained from:

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

6.1.1 ACQUISITION

Describe how the study agent and control product will be acquired and shipped to the investigator (e.g., a study agent may be supplied by the manufacturer or IND/IDE sponsor, an approved product may be acquired from the hospital pharmacy).

<Insert text>

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Describe the formulation, appearance, packaging, and labeling of the study agent and control product as supplied. Information in this section can usually be obtained from the IB or the package insert. The package insert may be attached as an appendix to the protocol. This section should include the name of the manufacturer of the study agent and control product. Also, discuss availability of product (e.g., investigational or commercially marketed) and if the product proposed is available for human use in the form, route, dose planned in this trial or if product must be formulated to meet the trial plan.

<Insert text>

6.1.3 PRODUCT STORAGE AND STABILITY

Describe study agent's and control product's storage needs. Include storage requirements and stability (e.g., temperature, humidity, security, and container). Provide additional information regarding stability and expiration time for studies in which multidose vials are utilized (i.e., the seal is broken).

<Insert text>

6.1.4 PREPARATION

Describe the preparation of study agent and control product, including what preparation is required by study staff and/or study participant. Include thawing, diluting, mixing, and reconstitution/preparation instructions, as appropriate. Detailed information may be provided in a separate document such as a Manual of Procedures (MOP) or standard operating procedure (SOP).

<Insert text>

6.1.5 DOSING AND ADMINISTRATION

Describe the procedures for selecting each subject's dose of study agent and control product. The timing of dosing (e.g., time of day, interval) and the relation of dosing to meals should be described. Any specific instructions to study participants about when or how to take the dose(s) should be described. Include any specific instructions or safety precautions for administration of the study agent. Discuss the maximum hold time once thawed/mixed, if appropriate, before administration.

<Insert text>

6.1.6 ROUTE OF ADMINISTRATION

Describe the planned route of administration (e.g., oral, nasal, intramuscular).

<Insert text>

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

State the starting level of the study agent and control product.

If applicable, describe the dose escalation scheme and treatment 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.

<Insert text>

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

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 AEs that are known to be associated with the planned study agent. 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 treatment, the protocol should specify whether treatment would progress to still higher doses. If appropriate, provide a dose de-escalation schema with treatment modifications. Do not restate reasons for withdrawal of participants. Cross-reference relevant sections, as appropriate.

<Insert text>

6.1.9 DURATION OF THERAPY

*Discuss the duration of therapy for each active phase and what duration is the minimum necessary for an "evaluable" participant (should be consistent with **Section 10, Statistical Considerations** and/or Statistical Analysis Plan (SAP)).*

<Insert text>

6.1.10 TRACKING OF DOSE

Discuss what procedures will be in place to monitor dosing and adherence for each participant.

<Insert text>

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

If conducting a study with a device, the following information should be included, otherwise note as not-applicable:

- *Device size(s)*
- *Device model(s)*
- *Device settings and programming (if applicable)*
- *Duration of implant or exposure (if applicable)*
- *Frequency of exposure (if applicable)*

<Insert text>

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Describe plans for how and by whom the study agent(s) will be distributed including participation of a drug repository or pharmacy, frequency of product distribution, amount of product shipped, documentation of adequate and safe handling, and plans for return of unused product.

<Insert text>

7 STUDY PROCEDURES AND SCHEDULE

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 study procedures and outline the schedule of visits and procedures to be performed at each visit.

Allowable windows should be stated for all visits. The schedule must include clinic visits and all contacts, e.g., telephone contacts. To determine the appropriate windows, consider feasibility and relevance of the time point 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). Further details should be provided in the MOP.

7.1 STUDY PROCEDURES/EVALUATIONS

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

In the following subsections, describe procedures for collection of all study data including clinical observations, laboratory results, biospecimens, images, questionnaire responses.

7.1.1 STUDY SPECIFIC PROCEDURES

All procedures listed here should be specific to the study and not part of standard clinical care.

List and describe all study procedures and evaluations to be done as part of the study. Possible content includes:

- *Medical history (describe what is included for history, e.g., time-frame considerations, whether history will be obtained by interview or from medical records)*
- *Medication history (e.g., describe if a complete medication history is needed, or if only medications currently taken should be included; prescription and over-the-counter medications). Assessment of eligibility should include a review of permitted and prohibited medications.*
- *Physical examination (list the vital signs [including height and weight] and organ systems to be assessed. Address details in the MOP.); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur.*
- *Radiographic or other imaging assessments. State the specific imaging required and, as appropriate, provide description of what is entailed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion may be described in a separate document such as a MOP or SOP.*
- *Biological specimen collection and laboratory evaluations. If biological specimen and laboratory procedures require further detail, they may be described in **Section 7.2 Laboratory Procedures/Evaluations** below, or in a separate document such as a MOP or SOP. At minimum, the biological specimens and purpose should be listed.*
- *A discussion of If the results of any study specific procedures (e.g., radiographic or other imaging or laboratory evaluations) will be provided to participant.*
- *Counseling procedures*
- *Assessment of study agent adherence*
- *Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary.*

<Insert text>

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Describe and summarize all procedures completed during the study as part of regular standard of clinical care.

<Insert text>

7.2 LABORATORY PROCEDURES/EVALUATIONS

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

*Include content in this section if it is not already included in **Section 7.1 Study Procedures/Evaluations**, otherwise note as not-applicable. This section header may be modified to describe other procedures/evaluations such as Imaging Procedures/Evaluations or Surgical Procedures.*

7.2.1 CLINICAL LABORATORY EVALUATIONS

List all laboratory evaluations to be done as part of the study (e.g., hematology, clinical chemistry, urinalysis, pregnancy testing). Differentiate screening laboratory test(s) from those taken after enrollment. 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.

Examples include:

- ***Hematology**: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Biochemistry**: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).*
- ***Urinalysis**: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.*
- ***Pregnancy test**, usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.*

<Insert text>

7.2.2 OTHER ASSAYS OR PROCEDURES

List special assays or procedures required to determine study eligibility or assess the effect of the intervention (e.g., immunology assays, pharmacokinetic studies, images, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. For procedures, provide special instructions or precautions or refer to the study's MOP. If more than one laboratory will be used, specify which assays will be done by each laboratory.

<Insert text>

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Special instructions for the preparation, handling, and storage of specimens should be explained clearly in this section (or refer to the study's MOP), including specific time requirements for processing, required temperatures, aliquots of specimens, where they will be stored, and how they will be labeled.
<Insert text>

7.2.4 SPECIMEN SHIPMENT

State the frequency with which specimens are to be shipped and to what address. Include contact information for laboratory personnel. Include days and times shipments are allowed, and any labeling requirements for specimen shipping. Also, include any special instructions such as dry ice or wet ice or the completion of a specimen-tracking log (or refer to the study's MOP).
<Insert text>

7.3 STUDY SCHEDULE

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

This section should include a description of those procedures/evaluations planned throughout the study. Consideration should be given to the level of detail included in the protocol versus the MOP, noting that any changes to the protocol require a protocol amendment or will need to follow the plan outlined in ***Section 14.3, Protocol Deviations****.*

7.3.1 SCREENING

Include a description of only those procedures/evaluations necessary to assess whether a participant meets eligibility criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List 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.

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, written informed consent must be obtained prior to review of that information and in accordance with Health Insurance Portability and Accountability Act (HIPAA), as applicable.

The procedures/evaluations to be done may be listed individually in this section, or alternatively, refer to ***Section 7.3.7, Schedule of Events****.*

Example text provided as a guide, customize as needed:

[**Screening Visit (Day -X to -Y)** <include a window that is appropriate for the study>

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect blood/urine *for* <specify tests>.
- Schedule study visits for participants who are eligible and available for the duration of the study.

- Provide participants with <specify instructions needed to prepare for first study visit>.]

<Insert text>

7.3.2 ENROLLMENT/BASELINE

Include a description of those procedures/evaluations necessary to assess or confirm whether a participant still meets the eligibility criteria and may be enrolled and those procedures/evaluations that are required at baseline for later endpoint comparison after study intervention (e.g., baseline signs and symptoms prior to administration of study agent).

Discuss the sequence of events that should occur during enrollment and/or initial administration of study agent. List any special conditions that must be achieved at this visit (e.g., results of the pregnancy test must be negative and available prior to administration of study product). List the procedures for administering the study agent and follow-up procedures after administration (e.g., assessment of vital signs).

The evaluations to be done may be listed individually in this section or, alternatively, refer to ***Section 7.3.7, Schedule of Events****.*

Example text provided as a guide, customize as needed:

[**Enrollment/Baseline Visit (Visit 1, Day 0)**

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Obtain urine pregnancy test.
- Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
- Record vital signs, results of examinations, other assessments.
- Collect blood/urine for <specify baseline laboratory tests required for the study>.
- Administer the study treatment.
- <Specify procedures, instructions provided to participants, observations after the intervention>.]

<Insert text>

7.3.3 FOLLOW-UP

Include a discussion of procedures/evaluations required to assess or confirm study endpoints and study evaluations. Discuss the sequence of events that should occur during the visit, if applicable. Include, as applicable, counseling, medications, assessment of AEs, etc. Consider specifying an appropriate range of time, or visit window, when the visit should occur to allow feasible scheduling, safety and other data collection considerations.

If multiple follow-up visits are planned, repeat for each visit, providing a study-appropriate window for each visit.

The evaluations to be done may be listed individually in this section or, alternatively, refer to ***Section 7.3.7, Schedule of Events****.*

Example text provided as a guide, customize as needed:

[**Follow-up Visit (Visit 2, Day X+/- Y)** *include a window that is appropriate for the study*

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <specify examinations or other assessments, including the information to be recorded>.
- Collect blood/urine for <specify follow-up laboratory tests>.
- Administer the study agent *or* provide additional medication to the participant, in accordance with <specify procedures, instructions provided to participants>.
- Record participant's adherence to treatment program.

Follow-up Visit (Visit 3, Day X+/- Y) *include a window that is appropriate for the study*

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <specify examinations or other assessments, including the information to be recorded>.
- Administer the study agent *or* provide additional medication to the participant, in accordance with <specify procedures, instructions provided to participants>.
- Record participant's adherence to treatment program.]

<Insert text>

7.3.4 FINAL STUDY VISIT

Include a discussion of procedures/evaluations required to assess or confirm study endpoints and study evaluations. Define when the final study visit should occur. Describe provisions for follow-up of ongoing AEs/SAEs. Consider discussing if or when participants will be informed of study results. Consider specifying an appropriate range of time, or visit window, when the visit should occur to allow feasible scheduling, data collection and study completion considerations.

The evaluations to be done may be listed individually in this section or, alternatively, refer to ***Section 7.3.7, Schedule of Events****.*

Example text provided as a guide, customize as needed:

Final Study Visit (Visit X, Day X+/- Y) *include a window that is appropriate for the study*

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of <specify examinations or other assessments, including the information to be recorded>.
- Collect blood/urine for <specify final laboratory tests>.
- Record participant's adherence to treatment regimen.
- Provide <specify final instructions> to participant.]

<Insert text>

7.3.5 EARLY TERMINATION VISIT

Specify which of the procedures/evaluations required for the final study visit should be done at a termination visit if early termination occurs and if the participant is willing. Clearly differentiate between what procedures/evaluations are to be done in each of these circumstances.

<Insert text>

7.3.6 UNSCHEDULED VISIT

Specify how unscheduled visits(s) will be handled and documented.

<Insert text>

7.3.7 SCHEDULE OF EVENTS TABLE

This section should capture the procedures that will be accomplished at each study visit and correspond to the descriptions in the above sections.

Procedures	Screening	Enrollment/Baseline (Visit 1)	Follow-Up (Visit 2)	Follow-Up (Visit 3)	Follow-Up (Visit 4)	Follow-Up (Visit 5)	Follow-Up (Visit 6)	Follow-Up (Visit 7)	Follow-Up (Visit 8)	Follow-Up (Visit 9)	Follow-Up (Visit 10)	Follow-Up (Visit 11)	Follow-Up (Visit 12)	Final Study Visit (Visit 13)
Informed consent	X													
Demographics	X													
Medical history	X													
Randomization	X													
Administer Investigational Product		X			X			X			X			
Concurrent meds	X	X----------											X	
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts	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
Serum Pregnancy test [b]	X													
EKG (as indicated)	X													
Adverse event evaluation		X----------											X	X
Radiologic evaluation/Imaging	X				X				X					X
Other tests, as appropriate														

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).

<Insert table>

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Include content in this section if applicable, or if not already addressed elsewhere in this section, otherwise note as not-applicable.

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria. Describe the data that will be recorded related to permitted concomitant medications, 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 agents could be ascertained.

Example text provided as a guide, customize as needed:

[All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). 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 CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.]
<Insert text>

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Include content in this section if applicable, otherwise note as not-applicable.
Provide justification for any sensitive procedures (e.g., use of placebo, medication withdrawal, provocative testing, deception).
<Insert text>

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

If applicable, list all medications, treatments, and/or procedures for which there are precautions for concomitant use with the study agents. Include instructions for dose modification, if appropriate. Describe any drug and food interactions and toxicities for standard agents that are likely to be given in conjunction with this protocol.
<Insert text>

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Include content in this section if applicable, or if not already addressed elsewhere in this section, otherwise note as not-applicable.

List all medications, treatments, and/or procedures that are NOT permitted on study. Include drugs from the exclusion criteria if they are also prohibited while the participant is on study. 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:

[Treatment with <list specific drugs> will not be permitted unless discussed with and approved by the <study medical monitor/sponsor/investigator>.]
<Insert text>

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

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

List all medications, treatments, and/or procedures that will be provided as prophylaxis on study. For injectable medications, describe if topical numbing medications such as Emla cream may be used.
<Insert text>

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

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

List all medications, treatments, and/or procedures that may be provided on study for "rescue therapy."

*This section should be consistent with the medications restrictions in **Section 5.1, Participant Inclusion Criteria** and **Section 5.2, Participant Exclusion Criteria**.*
<Insert text>

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

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

Describe obligations to continue beneficial interventions after participants are no longer enrolled in the study.
<Insert text>

8 ASSESSMENT OF SAFETY

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

The subsections below are intended to highlight the specific assessments related to safety and the aspects of the study which are intended to ensure the safety of trial participants. Consider developing this section in consultation with the study Medical Monitor. Consider the risks of the study agent 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 treatment with placebo to population with 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 the sections below, consider the risks of the study agent. Review and reference the IB, package insert, literature and other sources that describe the study agent. Consider and describe how participant's risk will be minimized in the sections below.

8.1 SPECIFICATION OF SAFETY PARAMETERS

*Reference safety parameters that are study endpoints (**Section 4.2, Study Endpoints**). Include other parameters if not primary/secondary endpoints. Describe safety parameters that will be recorded in the safety reporting system. "Recording" refers to documenting data in the study database. Define what data will require reporting for protection of human subjects.*
<Insert text>

8.1.1 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 since this template is for phase 2 or 3 IND and IDE studies. For some studies, definitions from the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events; or ICH E6 definition may be more appropriate.

Example text provided as a guide, customize as needed:

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

8.1.2 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 since this template is for phase 2 or 3 IND and IDE studies. Note: The example text provided is from the drug regulations (i.e., (21 CFR 312.32 (a)). There is no definition for SAE in the device regulations. Therefore, investigators should develop an appropriate definition for their study. This definition could include an unanticipated adverse device effect, but an SAE is broader than that definition. According to 21 CFR 812.3(s), an "unanticipated adverse device effect means 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 (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

Example text provided as a guide, customize as needed:

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

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Provide a definition of an UP. An incident, experience, or outcome that meets the definition of an UP generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Other UPs may warrant corrective actions at a specific study site. Examples of corrective actions or changes that might need to be considered in response to an UP include:

- *Modification of inclusion or exclusion criteria to mitigate the newly identified risks*
- *Implementation of additional safety monitoring procedures*

- *Suspension of enrollment of new participants or halting of study procedures for enrolled participants*
- *Modification of informed consent documents to include a description of newly recognized risks*
- *Provision of additional information about newly recognized risks to previously enrolled participants*.

Example text provided as a guide, customize as needed:

[OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

This study will use the OHRP definition of UP.]

Additional example text, applicable for device protocol:
[This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]
<Insert text>

8.2 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.

8.2.1 SEVERITY OF EVENT

All AEs will be assessed by the 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 Medical Monitor.

Example text provided as a guide, customize as needed:

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

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

<Insert text>

8.2.2 RELATIONSHIP TO STUDY AGENT

All AEs will have their relationship to study agent or study participation assessed with a level of specificity appropriate to the study design. Describe the method of determining the relationship of an AE to a study agent. 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 agent must always be suspect.

Example text provided as a guide, customize as needed:

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

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

OR

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

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent

disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

<Insert text>

8.2.3 EXPECTEDNESS

Expected adverse reactions are AEs that are common and known to occur for the study agent being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Describe the method of determining the expectedness of an AE. Expectedness refers to the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study agent.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity 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 general investigational plan or elsewhere in the protocol, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Example text provided as a guide, customize as needed:

[<Insert name> will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.]

<Insert text>

8.3 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. Also describe how UPs will be recorded. Specify procedures for recording and follow-up of AEs, SAEs, and UPs that are consistent with the information contained within **Section 7, Study Procedures and Schedule**,*

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 occur 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 agent, etc." A solicited AE is one that is specifically solicited 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) and note how long SAEs are collected – usually collected through entire study.*

Example text provided as a guide, customize as needed:

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

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

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

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]
<Insert text>

8.4 REPORTING PROCEDURES

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

In the following subsections, describe the protocol-specific reporting procedures, including the individual responsible for each step (e.g., PI, DCC, Medical Monitor), which forms should be completed, timeframes for reporting, how reports will be distributed, and what follow-up is required.
Include specific details of reporting procedures for:

- *Deaths and life-threatening events*
- *Other SAEs*
- *Other AEs*
- *Other UPs*

The example text in the following sections may be customized by including IRB-specified reporting time frames or protocol-specific parameters (safety issues) that need to be reported in an expedited fashion, either to the IRB, sponsor, or other regulatory body.

8.4.1 ADVERSE EVENT REPORTING

Describe the AE reporting procedures, including timeframes. Include 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 AE reports. Describe who will receive notification of AEs.

<Insert text>

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Describe the SAE reporting procedures, including timeframes. Include 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. Describe 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 8.1.2, Definition of Serious Adverse Event*** *must be submitted on an SAE form to the DCC if one exists for the study. If a study is overseen by a Data and Safety Monitoring Board (DSMB), the DSMB may request to receive real-time notification of all SAEs or only SAEs thought to be related to study agent.*

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 8.1.2, Definition of Serious Adverse Event).** 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 complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See **Section 1, Key Roles** for contact information.
- Other SAEs regardless of relationship, will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.
The study sponsor will be responsible for notifying 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.]

OR

Example 2, 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 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 contact information is provided in **Section 1, Key Roles**. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs 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.]
<Insert text>

8.4.3 UNANTICIPATED PROBLEM REPORTING

Describe the UP reporting procedures, including timeframes. Include 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 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.

Example text provided as a guide, customize as needed:

[Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. 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 SAEs will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with 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 OHRP within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

Additional example text, applicable for device protocol:
[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 (21 CFR 812.150(a)(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 (21 CFR 812.150(b)(1)).
<Insert text>

8.4.4 EVENTS OF SPECIAL INTEREST

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

Describe any other events that merit reporting to the sponsor, study leadership, IRB, and regulatory agencies. For example, in oncology trials, secondary malignancies are often captured.
<Insert text>

8.4.5 REPORTING OF PREGNANCY

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

State the study's pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to the DCC or NIH, the IND or IDE sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of treatment while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).
<Insert text>

8.5 STUDY HALTING RULES

Describe safety findings that would prompt temporary suspension of enrollment and/or study agent until a safety review is convened (either routine or ad hoc). The objective of the safety review is to decide whether the study (or study agent for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group, a particular study site or for the entire study) is a potential outcome of a safety review.

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, DSMB, IRB, the sponsor(s), or the FDA or relevant local regulatory authorities may also result in suspension of further study agent administration at a site. The FDA and study sponsor(s) retain the authority to suspend additional enrollment and study agent for the entire study, as applicable.

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.

This section should be consistent with ***Section 5.5, Premature Termination or Suspension of Study*** *and* ***Section 10.4.7.1, Safety Review****.*

Example text provided as a guide, customize as needed:

[Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the DCC. The DCC will notify the study sponsor and investigators immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor/NIH. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.]
<Insert text>

8.6 SAFETY OVERSIGHT

Appropriate safety oversight should be considered for each trial. This could include a Safety Monitoring Committee (SMC)[1], DSMB[2], and/or a Medical Monitor[3]. Independent oversight is an important component to ensure human subjects' protection 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 in the study and the frequency of meetings. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB. The DSMB Charter should be provided with protocol to FDA and NIH for review.

Example text provided as a guide, customize as needed:

[Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including <list expertise>. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to <specify the study sponsor/NIH staff/other>.]
<Insert text>

9 CLINICAL MONITORING

Site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Monitoring refers to the methods used by sponsors of investigational studies, or Contract Research Organizations (CROs) delegated site monitoring responsibilities, to oversee the conduct of, and reporting of data from, clinical investigations. Site monitoring includes ensuring appropriate clinical investigator supervision of study site staff and third party contractors. Monitoring activities include communication with the clinical investigator and study site staff; review

[1] An independent group of experts that advises the study investigators for Phase I and some Phase II trials. The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, test agent, and target population under study.
[2] An independent group of experts that advises the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. For example, a DSMB may be convened if a study meets one or more of the following criteria: will generate randomized, blinded data; is a multi-center protocol which presents more than minimal risk to participants; uses gene transfer or gene therapy methodology; or requires special scrutiny because of high public interest or public perception of risk.
[3] An independent medical expert that advises the study investigators and monitors participant safety. A study may choose to employ the services of, or may be appointed a Medical Monitor. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) be available to advise the investigators on trial-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor will remain blinded throughout the conduct of the clinical trial unless unblinding is warranted to optimize management of an adverse event or for other safety reasons.

of the study site's processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor.

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

A separate clinical monitoring plan (CMP) 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 CMP 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, electronic data capture, relative safety of the study agent, stage of the study, and quantity of data.

If a separate CMP is not used, include all the details noted above in this section of the protocol.

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

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

- Monitoring for this study will be performed by <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 CMP. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.]

OR

*Example text when a **separate CMP is <u>not</u> being used is provided as a guide, customize as needed**:*

[Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of

the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

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

<Insert text>

10 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.*
If a separate SAP will be developed, respective subsections below can be summarized. ***At a minimum, the following subsections should be included in the protocol:***

- ***10.2 Statistical Hypotheses,***
- ***10.3 Analysis Datasets,***
- ***10.4.1 General Approach,***
- ***10.4.2 Analysis of the Primary Efficacy Endpoint(s),***
- ***10.4.3 Analysis of the Secondary Endpoint(s),***
- ***10.4.4 Safety Analyses,***
- ***10.4.6 Baseline Descriptive Statistics,***
- ***10.4.7 Planned Interim Analyses (if applicable),***
- ***10.4.11 Exploratory Analyses, and***
- ***10.5 Determination of Sample Size.***

10.1 STATISTICAL AND ANALYTICAL PLANS

State whether there will be a formal 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).

<Insert text>

10.2 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):

<Insert text>

- Secondary Efficacy Endpoint(s):

<Insert text>

10.3 ANALYSIS DATASETS

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 investigational product 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 investigational product)*
- *Evaluable or 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 treatment according to the underlying scientific model (e.g., participants who took at least 80% of investigational product for 80% of the days within the maintenance period)*
- *Other Datasets*

<Insert text>

10.4 DESCRIPTION OF STATISTICAL METHODS

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.

10.4.1 GENERAL APPROACH

State the proposed formal design of the study (e.g., two-period crossover, two-by-three factorial parallel group, or case-control). If the design or interventions are complex, reference to ***Schematic of Study Design*** *may be appropriate. 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 for statistical significance (Type I error) and whether one or two-tailed.*
- *Indicate whether covariates will be pre-specified in the sections below or later in a SAP.*
- *State whether checks of assumptions (e.g.,normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests).*

<Insert text>

10.4.2 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 data (e.g., proportional hazards, transformations or nonparametric tests if non-normal)*
- *Describe the Analysis Set for which the analysis will be conducted, as discussed in **Section 10.3, Analysis Datasets***
- *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 loss to follow-up*

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

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary 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 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, number-needed-to-treat).*
- *Describe details to check assumptions required for certain types of data (e.g., proportional hazards, transformations or nonparametric tests if non-normal).*
- *Describe the Analysis Set for which the analysis will be conducted as discussed in **Section 10.3, Analysis Datasets.***
- *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 loss to follow-up.*

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

10.4.4 SAFETY ANALYSES

*Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in **Section 10.4.2, 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 agent 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, outcome, and duration). Also describe how AEs will be ascertained (e.g., adherence and/or PI reported). Adverse events leading to premature discontinuation from the study drug 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, Assessment of Safety****.*

<Insert text>

10.4.5 ADHERENCE AND RETENTION ANALYSES

Define how adherence to the protocol (e.g., medication consumption) will be assessed, calculated, and verified (if applicable, e.g., plasma assays). Similarly describe measures and calculations for assessing participation, study retention/loss to follow-up, and frequency of and reasons for discontinuation of the intervention.

<Insert text>

10.4.6 BASELINE DESCRIPTIVE STATISTICS

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

<Insert text>

10.4.7 PLANNED INTERIM ANALYSES

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

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

The following subsections should describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing. Within the two sections below, pre-specify, to the extent possible, the criteria that would prompt an interim review of safety and efficacy data, respectively. Describe who performs the statistical analysis and who reviews the analysis. In addition, discuss whether they are unmasked and how the blinding will be preserved.

10.4.7.1 SAFETY REVIEW

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. If statistical rules will be used to halt enrollment into all or a portion of the study, describe the statistical techniques and their operating characteristics, e.g., the probability of stopping under different safety event rates and the associated number of participants that would be enrolled.

State which safety endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

This section should be consistent with ***Section 5.5, Premature Termination or Suspension of Study*** *and* ***Section 8.5 Study Halting Rules****.*

<Insert text>

10.4.7.2 EFFICACY REVIEW

Provide the same information as in ***Section 10.4.7.1 Planned Interim Analyses****, but for efficacy endpoints. Also discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.*

If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.
<Insert text>

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Describe how the primary endpoint will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s).
Describe how the secondary endpoint(s) will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s).
<Insert text>

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Include content in this section if applicable, otherwise note as not applicable.
Generally, there should be just one primary endpoint that will provide a clinically relevant, valid and reliable measure of the primary objective. However, 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.
<Insert text>

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

State whether individual participant data will be listed by measure and time point.
<Insert text>

10.4.11 EXPLORATORY ANALYSES

Exploratory analyses serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. These analyses can't be used as confirmatory proof for registration trials. All planned exploratory analyses should be specified in the protocol.
<Insert text>

10.5 SAMPLE SIZE

Include number of participants to recruit, screen, and enroll to meet a goal of evaluable participants for the study. Provide all information needed to validate your calculations, and also to 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 alternate 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*
- *Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., also justified*
- *Approach to handling withdrawals and protocol violations, i.e., whether participants will be included in the "intent-to-treat" population*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Method for adjusting calculations for planned interim analyses, if any (**Section 10.4.7, Planned Interim Analyses**).*

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

*Consider discussing whether the sample size also provides sufficient power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term, **Section 10.4.11, Exploratory Analyses**).*
<Insert text>

10.6 MEASURES TO MINIMIZE BIAS

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 methods planned to minimize bias.

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

This section should contain a description of enrollment procedures and randomization (if applicable to the study design) and masking procedures. It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that masking or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not). It should also include a discussion of the impact of replacement of participants who discontinue early, if allowed, on the statistical analysis/power calculations.

Plans for the maintenance of trial randomization codes and appropriate masking 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 unmasking may occur and who may unmask.

Include a discussion of strategies to avoid bias, such as randomization and masking methods, or to decrease variability, such as centralized laboratory assessments. DO NOT include details that might compromise these strategies, such as the size of randomized blocks.

A description of the specific procedures to be used to carry out blinding should be provided (e.g., how bottles will be labeled, use of labels that reveal blind-breakage, sealed code list/envelopes, double dummy techniques).

Sometimes blinding is attempted but is known to be imperfect because of obvious drug effects in some participants (e.g., dry mouth, bradycardia, fever, injection site reactions, 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 people shielded from information that might reveal treatment 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. Measures taken to ensure that the study agent and placebo are indistinguishable and evidence that they are indistinguishable should be described. Measures to prevent unblinding by laboratory measurements, if used, should be described.

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.

<Insert text>

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Include content in this section if applicable, otherwise note as not-applicable.
Provide the criteria for determining the success of blinding.

<Insert text>

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

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 SAEs). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

<Insert text>

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH IC-sponsored or NIH IC -affiliated study, each site will permit authorized representatives of the NIH IC and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Describe in this section who will have access to records.

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 these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes 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 collected on CRFs and what data will be collected from other sources.

It is not acceptable for the CRF to be the only record of a patient's participation in the study. 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.

<Insert text>

12 QUALITY ASSURANCE AND QUALITY CONTROL

This section will indicate the plans for quality management, the system for assessing the quality of processes within a system. Quality management encompasses quality assurance (QA)[4] and quality control (QC)[5].

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

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

Regular monitoring and an independent audit, if conducted, must be performed according to ICH-GCP. See also ***Section 9, Clinical Monitoring****.*

Example text provided as a guide, customize as needed:

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

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

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

<Insert text>

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

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

---

[4] All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s) (ICH E6 1.46).

[5] The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 1.47).

The following subsections should include a description of the ethical considerations and context for the conduct of the trial.

Note: for NIH Intramural Research Program studies only: A statement referencing compliance with NIH Human Research Protections Program policies and procedures is adequate for ***Subsections 13.1 and 13.2****.*

13.1 ETHICAL STANDARD

Include in this section the guiding ethical principles being followed by the study.

Example text provided as a guide, customize as needed:

[The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.]

If the study is conducted at international sites, the statement could be as above and/or could reference compliance with the Declaration of Helsinki, Council for International Organizations of Medical Science (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the ***most*** *protection to human subjects.*

<Insert text>

13.2 INSTITUTIONAL REVIEW BOARD

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the US and in other countries, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate.

Example text provided as a guide, customize as needed:

[The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.]

<Insert text>

13.3 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.

Informed consent is required for all participants of an NIH-sponsored study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 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.

13.3.1 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 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 agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol <insert list>.]

<Insert text>

13.3.2 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. This section should be consistent with ***Section 5.3, Strategies for Recruitment and Retention*** *when describing consent plans and special considerations for children or other vulnerable participants.*

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. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by

emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.]

<Insert text>

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

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

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements. Describe who would have access to records, including the investigator and other study staff, the clinical monitor, funding institutions, IND sponsor, representatives of NIH IC, representatives from the IRB, 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 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.*
- *State 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).*

For some studies, it may be necessary to obtain a Certificate of Confidentiality. A Certificate of Confidentiality 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.

Example text provided as a guide, customize as needed:

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of 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 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 Coordinating Center>.

Certificate of Confidentiality (if applicable)

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the 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.

NIH Data Sharing Policy for Genome-Wide Association Studies (GWAS) (if applicable)

This study is a genome-wide association study and will comply with the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted GWAS, which calls for investigators funded by the NIH for GWAS to 1) share de-identified genetic (genotypic and phenotypic) data through a centralized NIH data repository; and 2) submit documentation that describes how the institutions have considered the interests of the research participants, such as privacy and confidentiality. Submission of data to the NIH GWAS repository will be consistent with the permissions and limitations delineated on the study consent signed by study participants.]

<Insert text>

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

This section should address each of the items listed below.

- *Intended use of stored samples, specimen or data.*
- *Storage: State whether samples or data will be retained, list type of samples and location of storage.*

- *Tracking: Describe method of tracking, such as the name of the software tracking program or other logging/tracking method*
    - *Disposition at the completion of the study: Describe the disposition of the specimens*
    - *Approach for responding to requests from participants for destruction of samples (if applicable)*

Example text provided as a guide, customize as needed:

- [Intended Use: Samples and data collected under this protocol may be used to study <specify condition>. No genetic testing will be performed.
- Storage: Access to stored samples will be limited using <specify approach>. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using <specify approach>.
    - Disposition at the completion of the study: All stored samples will be sent to a <specify repository>. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.]

<Insert text>

13.5 FUTURE USE OF STORED SPECIMENS

If residual specimens will be maintained 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 13.4, Participant and Data Confidentiality** and **Section 14.2, Study Records Retention**, 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 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>, under the supervision of <insert name>, 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 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 for research into 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 masking 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 with regard to biosample storage will not be possible after the study is completed.

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

<Insert text>

14 DATA HANDLING AND RECORD KEEPING

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 data handling and record keeping for the conduct of the trial.

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Provide details regarding the type(s) of data capture that will be used for the study. 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 should be provided in the MOP.

Briefly describe steps to be taken to ensure that the data collected are accurate, consistent, complete, and reliable and in accordance with ICH E6. The MOP or a separate data management plan will provide detailed descriptions of source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring.

Describe responsibilities for data handling and record keeping as they specifically relate to the IND/IDE sponsor (if applicable), the award site, clinical site(s), laboratory(ies), and DCC. Information should 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.

Indicate the roles of each party with regard to interpretation of data, plans for analysis, review of tables and listings, and plans for reporting.

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 PI. 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. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

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

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify DCC>. 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.

<Insert text>

14.2 STUDY RECORDS RETENTION

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

Indicate whether permission is required (and from whom) prior to destruction of records. If under an IND/IDE, records should not be destroyed without the IND/IDE sponsor's agreement. Pharmaceutical companies who supply unapproved products should be consulted.

Investigational product records may be addressed here if not addressed elsewhere in the protocol.

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 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 investigational product. 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.]

<Insert text>

14.3 PROTOCOL DEVIATIONS

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

Example text provided as a guide, customize as needed:

[A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

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

It is the responsibility of the site to use continuous vigilance to identify and report deviations within <specify number> working days of identification of the protocol deviation, or within <specify number> working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to <specify NIH IC> Program Official and <specify DCC>. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.]

<Insert text>

14.4 PUBLICATION AND DATA SHARING POLICY

The publication and authorship policies should be established and clearly outlined in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. Please refer to your specific contract grant and/or Clinical Trials Agreements. If details of the publication policy will be described in the study's MOP, refer to it here. The study must comply with the NIH Public Access Policy, the Food and Drug Administration Amendments Act of 2007 (FDAAA), and ClinicalTrials.gov. At the end of the study, the PI will make results of the research available to the research community and public at large. Refer to NIH Grants Policy Statement Section 8.2.

Example text provided as a guide, customize as needed:

[This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee

recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.]

<Insert text>

15 STUDY ADMINISTRATION

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 governance of the study and its committee structure. Alternately, this section may describe the role of the study team, its composition (e.g., those listed in ***Section 1, Key Roles****) and describe how study decisions and progress are communicated and reported. Some example text is provided below.*

15.1 STUDY LEADERSHIP

Include content in this section if applicable or rename for the appropriate study leadership body (e.g.: Steering Committee, Executive Committee, Subcommittee, Study Team), otherwise note as not-applicable. This section should reflect the entire scope of the study leadership.

Example text provided as a guide, customize as needed:

[The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman, the PI of the Coordinating Center, representatives of <sponsoring NIH IC>, the PI of the clinical sites, chairperson of the Study Coordinators subcommittee, and the PI of the Central Biochemistry Laboratory. The Steering Committee will meet in person at least annually.]

<Insert text>

16 CONFLICT OF INTEREST POLICY

This section should include a description of how the study will manage actual or perceived conflicts of interest. Refer to the Final Rule on Financial Conflict of Interest Regulations - Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding is Sought and Responsible Prospective Contractors.

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 trial. The study leadership in conjunction with the <specify NIH IC> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.]

<Insert text>

17 LITERATURE 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 ICMJE. Include citations to product information such as manufacturer's IB, package insert, and device product description.

Examples:

- ***Journal citation***
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
- ***Whole book citation***
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- ***Chapter in a book citation***
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
- ***Web Site citation***
  Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
- ***Electronic Mail citation***
  Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- ***References to package insert or investigational brochure or product description***
  Cite date accessed, version number, and source of product information.

APPENDIX

Version	Date	Significant Revisions