**CTMW Imaging-Based Therapy Protocol:**

**Guided Template for Radiology Trials**

Color-coded timetable of deadlines

**Orange Font: Draft due Sunday**

**Green Font: Draft due Tuesday**

**Blue Font: Draft due Wednesday**

**Purple Font: Final draft due Friday**

**Grey Font: Supplemental Material (Not due unless relevant)**

**How to use this template:**

1. The Table of Contents hyperlinks to the relevant section and is color-coded by due date. Click on the page number.
2. Each section contains *instructions* *in italic font* on the expected content. Sample text is also provided in non-italic font.
3. As each section is completed, change font color to black and remove the instructional and sample text material.
4. After entering content, update the Table of Contents using by selecting the function on the dropdown when you click on it

**Disclaimer:**

This template is a comprehensive compilation of all the issues that might need to be addressed in a clinical trial protocol, and models that recommended by the NIH (https://osp.od.nih.gov/clinical-research/clinical-trials/). But not all of the sections and attendant requirements apply to every protocol. The lectures in the CTMW course will begin to explain which issues are important for you to understand in this template, and the Protocol Development Group (PDG) discussions will help you decide which issues are specifically relevant to your protocol.

**<Title>**

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

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

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

*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.*

**Version Number: v.<x.x>**

**<Day Month Year>**

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

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# PROTOCOL SUMMARY

## Synopsis

|  |  |
| --- | --- |
| **Title:** | <Full title> |
| **Study Description:** | *Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length.* |
| **Objectives:** | *Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol. These align with Primary Purpose in clinicaltrials.gov[[1]](#footnote-2).* |
|  | <Primary Objective: |
|  | Secondary Objectives: > |
| **Endpoints:** | *Include the primary endpoint and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol. These align with Outcome Measures in clinicaltrials.gov.*  <Primary Endpoint:  Secondary Endpoints: > |
| **Study Population:** | *Specify the sample size, gender, age, demographic group, general health status, and geographic location.* |
| **Phase:** | <2 or 3 or N/A> |
| **Description of Sites/Facilities Enrolling Participants:** | *Provide a brief description of planned facilities/participating sites enrolling participants. Indicate general number (quantity) of sites only and if the study is intended to include sites outside of the United States.* |
| **Description of Study Intervention:** | *Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration. For devices or procedures, provide a description of each important component, ingredient, property and the principle of operation.* |
| **Study Duration:** | *Estimated time (in months) from when the study opens to enrollment until completion of data analyses.* |
| **Participant Duration:** | *Time (e.g., in months) it will take for each individual participant to complete all participant visits.* |

|  |  |
| --- | --- |
|  |  |

## Schema

*This section should include a diagram that provides a quick “snapshot” of the study and ideally be limited to 1 page. Below are examples of schematics that show the level of detail needed to convey an overview of the study design. Depending on the nature of your study, one example may be more appropriate than another.*

*Diagrams and algorithms can be created on any graphics software of your choice, including Powerpoint. yEd is a freely available graphics software that makes the process less cumbersome and is fairly intuitive to learn to use. yEd runs on all major platforms (Windows, Unix/Linux, and macOS) and can be downloaded* [here](https://www.yworks.com/products/yed)*.*

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

Prior to

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

Enrollment

Randomize

Perform baseline assessments.

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Administer initial study intervention.

Week/Day #

Repeat study intervention (*if applicable*).

Week/Day #

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 1.3, Schedule of Activities**>

Week/Day #

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 1.3, Schedule of Activities**>

Week/Day #

**Final Assessments**

<list analyses to be performed OR refer to **Section 1.3, Schedule of Activities**>

Week/Day #

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

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

Day -7 to Day -1

Screening &

Baseline imaging

Day 1

Randomization

Week 1

Intervention

Weeks 2 - 25

Maintenance therapy

Week 26

Followup

imaging

Week 27

End of Study Assessments (EOS)

Week 28-29

Follow-up Phone Call

Study Intervention N=

Control Group N=

# in-clinic visits and

# telephone contacts

## Schedule of Activities (SoA)

***The schedule below is provided as an example and should be modified as appropriate. It is available as a separate Excel file for students to edit and import.***

*The schedule of activities must capture the procedures that will be accomplished at each study visit, and all contact with study participants e.g., telephone contacts. This includes any tests that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility and study objectives and endpoints.*

*Allowable windows should be stated for all visits.*

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

<Insert table>

# INTRODUCTION

## Study Rationale

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

<Insert text>

## Background

*This section should include:*

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

<Insert text>

## Risk/Benefit Assessment

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

* *Justification as to why the value of the information to be gained outweighs the risks of participation.*
* *Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design*

<Insert text>

# STUDY DESIGN

## Overall Design

*A single paragraph description of the trial design should be consistent with the* ***Protocol Synopsis (section 1.1) and Protocol Schema (section 1.2)*** *and include:*

* *Clinical trial is defined by the NIH as “A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.” A decision tree on whether your protocol would be considered a clinical trial is found* [here](https://grants.nih.gov/policy/clinical-trials/definition.htm)*.*
* *Phase of the trial - Phase I is safety and proof of concept (single center, <100 patients), Phase II is clinical utility (usually single center, usually 50-200 patients), Phase III is practice-changing validation of technology (multicenter, usually >300 patients)*
* *A description of the type/design of trial to be conducted (e.g., randomized, cohort, placebo-controlled, blinded/unblinded, open-label, superiority or non-inferiority design)*
* *The number of study groups/arms and study intervention duration*
* *Run-in phase if relevant*
* *Single site or multi-site*
* *Name of study intervention(s)*
* *Note if interim analysis or is planned*

# OBJECTIVES AND ENDPOINTS (OUTCOME MEAURES)

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

An objective is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., efficacy, effectiveness, safety) and/or specific purpose (e.g., superiority to control treatment, effect of an intervention on disease incidence, disease severity, or health behavior). All data points collected in the study should support an objective. Therefore, careful consideration should be given prospectively to the amount of data needed to support the study’s objectives.

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

## Primary Objective/Aim

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).

<Insert text>

### Primary Endpoint (Outcome Measure)

The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective (e.g., “the study wins”).

Some trials include two (but usually not more than two) primary objectives, and therefore a primary endpoint for each primary objective. For example, in many trials of medical devices there are primary endpoints for both safety and effectiveness. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold.

In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit.

<Insert text>

### Justification for the Primary Endpoint

*Briefly explain why the endpoint(s) was chosen.*

## Secondary Objective/Aim

The secondary objective(s) are goals that will provide further information on the use of the intervention.

Each secondary objective should be numbered, and corresponding endpoints and justifications should be numbered accordingly.

<Insert text>

### Secondary Endpoint(s)

Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention’s effect on the primary endpoint or demonstrate additional effects on the disease or condition. Each secondary endpoint should be numbered according to the secondary objective to which it corresponds.

<Insert text>

### Justification for Secondary Endpoint(s)

*Briefly explain why the endpoint(s) were chosen. Each justification should be numbered according to the secondary endpoint to which it corresponds.*

<Insert text>

## Tertiary/Exploratory Objective/Aim

Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. Each tertiary objective should be numbered, and corresponding endpoints and justifications should be numbered accordingly.

<Insert text>

### Tertiary/Exploratory Endpoint(s)

*Exploratory endpoints should be specified.* *Exploratory endpoints may include clinically important events that are expected to occur too infrequently or are included to explore new hypotheses.* *Each exploratory endpoint should be numbered according to the exploratory objective to which it corresponds.*

<Insert text>

### Justification for Tertiary Endpoint(s)

*Briefly explain why the endpoint(s) were chosen. Each justification should be numbered according to the exploratory endpoint to which it corresponds.*

<Insert text>

# STUDY POPULATION

* The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment.
* The risks of the study intervention should be considered in the development of the inclusion/exclusion criteria so that risks are minimized.
* The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤18 years old as an exclusion criterion).
* Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.

No text to be entered in this section

## Inclusion Criteria

Sample text provided as a guide, customize as needed.

NCI recommended text for some of the more commonly encountered inclusion/exclusion criteria, especially for cancer trials, can be downloaded [here](https://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Broadened_Eligibility_Criteria_Guidance.pdf).

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

1. Male or female, aged <specify range>
2. 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>
3. <Imaging exam> showing <imaging finding>
4. <Specify laboratory test> results between <specify range>
5. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration
6. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner
7. Provision of signed and dated informed consent form
8. Stated willingness to comply with all study procedures and availability for the duration of the study

<Insert text>

## Exclusion Criteria

Example text provided as a guide, customize as needed.

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

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

<Insert text>

## Strategies for Recruitment

Identify general strategies for participant recruitment and retention.

* Anticipated accrual rate and duration
* 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

<Insert text>

# STUDY INTERVENTION

## Study Intervention(s)

*Describe the study intervention(s) and, if relevant, the control group*

*In addition:*

* *Indicate if the study intervention is commercially available and is being used in accordance with standard of care (procedure) or approved labeling (drug). Note any modifications that have been performed for the study.*
* *Describe efforts toward minimizing variability among procedures and operators*
* *Describe what features or data from the intervention will be collected*
* *Refer to a separate procedure or imaging manual for technical details (e.g. devices, scanners, imaging protocols)*

<Insert text>

## Measures to Minimize Bias: Randomization and Blinding

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

*Include a statement regarding when unblinding may occur and who may unblind. Describe efforts to ensure that the study intervention and control group are as indistinguishable as possible. Include a description of your plans to manage and report inadvertent unblinding.*

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

<Insert text>

## Concomitant Therapy

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

*Describe the data that will be recorded related to permitted concomitant medications, treatments, and/or procedures. Include details about what the information regarding this will be collected and when (e.g., screening, all study visits).*

*.*

<Insert text>

# STUDY EFFICACY AND SAFETY ASSESSMENTS

## Efficacy (survival, quality of life, etc.) Assessments

*List and describe all study procedures and evaluations to be done as part of the study to support the determination of efficacy, as per the primary and secondary objectives outlined in this protocol.*

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

*Include any definitions used to characterize outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between transient ischemic attack and stroke), should be explained fully. For participants that may discontinue or withdraw early, it is important to capture the rationale during the final visit. See Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for details.*

*Note that the protocol should provide a high-level discussion of all procedures and detailed information can be further provided in a MOP (method of procedure) or SOP (standard operating procedure). Provide justification for any sensitive procedures (e.g., provocative testing, deception). In addition, note where approaches to decrease variability, such as centralized laboratory assessments, are being employed.*

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

* ***Physical examination*** *(e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities).*
* ***Radiographic or other imaging assessments****. State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standardized fashion and equipment specifications may be described in the study’s MOP or a separate SOP.*
* ***Biological specimen collection and laboratory evaluations****. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP.*
* ***Special assays or procedures required*** *(e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP.*
* ***Administration of questionnaires or other instruments*** *for patient-reported outcomes, such as a daily diary.*
* ***Procedures that will be completed during the study as part of regular standard of clinical care****.*

***Include in this section a discussion of the results of any study specific procedures that will be provided to participant (e.g., radiographic or other imaging or laboratory evaluations).***

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

<Insert text>

## Safety and Other Assessments

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

<Insert text>

# STUDY INTERVENTION NOT OR INCOMPLETELY PERFORMED AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. This section should state which adverse events would result in discontinuation of study intervention or participant discontinuation/withdrawal.

Participant withdrawal from study procedures raises questions on whether their data will be included in the final analysis. How data collected on discontinued participants will be handled for analysis should be stated here.

[Data collected from participants who discontinue or withdraw will be included in the final analysis.]

Estimate proportion of unanalyzable accruals.

<Insert text>

## Study Intervention Not or Incompletely Performed

Describe the criteria for discontinuing or not completing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Once enrolled, patient is considered still in the study if the intervention is not successfully completed.

Example text provided as a guide, customize as needed:

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

<Insert text>

## Participant Discontinuation/Withdrawal from the Study

Provide a list of reasons participation may be discontinued.

Example text provided as a guide, customize as needed:

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

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

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

The reason for participant discontinuation or withdrawal from the study will be recorded on the <specify> Case Report Form (CRF). ]

<Insert text>

## Lost to Follow-Up

The protocol should describe the nature and duration of study follow-up. Describe the plans to minimize loss to follow-up and missing data.

Example text provided as a guide, customize as needed:

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

<Insert text>

# STATISTICAL CONSIDERATIONS

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

## Executive Summary

*In one paragraph, summarize the broad details of the protocol, such as study design (e.g., randomized or not, superiority trial, equivalence or non-inferiority trial, dose finding trial, blinded or not), target population, planned intervention, follow-up time, scientific objectives, and challenges.*

## Statistical Hypotheses

*State the endpoints, objectives, and associated statistical hypotheses that characterize the formal scientific hypotheses. Do this separately for the primary and secondary objectives. The endpoints are the observed outcomes (e.g., survival time, treatment failure, weight loss, toxicity). The objectives are a statement about the aggregation of the endpoints, and how that aggregation may change across treatment groups (e.g., to estimate the change in median survival between treatment groups). The statistical null and alternative hypotheses are quantitative translations of the objectives; they lay out the potential results for the trials as a whole (e.g., Null hypothesis: There will be no change in median survival between the groups; and Alternative hypothesis: The median survival in the treatment group will be 1 month longer).*

*If there will be a comparison between two or more groups, write the objectives as statements about estimating differences or changes between groups. The statistical hypotheses should be concordant with those used for sample size projections and specify the time period for which each endpoint will be analyzed.*

* Primary Efficacy Endpoint(s):

<Insert text or list>

* Primary Efficacy Objective(s):

<Insert aim (one sentence)> <State statistical hypothesis (one-two sentences)>

* Secondary Endpoint(s):

<Insert text or list>

* Secondary Objectives(s):

<Insert aim (one sentence)> < State statistical hypothesis (one-two sentences)>

## Sample Size Projections

*State the planned number of participants to recruit, screen, and enroll and justify this number by showing it yields the desired statistical precision or power for the stated objectives above. Must at least address the primary efficacy aim(s). Provide all information needed to validate your projection and judge the feasibility of enrolling and following the necessary number of participants. Note that this section depends on the planned statistical analyses, which is described in section 9.5 below. Thus, section 9.5 should be completed before this one.*

*In particular, specify all of the following:*

* *Endpoint used for calculations (almost always the primary endpoint)*
* *Statistical null and alternative hypotheses*
* *Justification of why the desired effect size is considered clinically meaningful*
* *Type of sample size projection (e.g., power or precision)*
* *For power, state the statistical test, the test statistic, the Type I Error rate (alpha), and the Power level (e.g., 80% power) at the desired alternative. Present a power curve whenever possible.*
* *For precision, state the estimator, its variance, the coverage probability of the confidence intervals, and the target length of the interval. Repeat this computation under the null and alternative hypotheses of interest, and present a precision curve (length versus hypothesis) whenever possible*
* *Be sure to state the assumptions clearly for each study arm, reference software used to perform computations (if any).*
* *Justification for assumptions based historical data (with references)*
* *Anticipated impact of dropout rates, withdrawal, cross-over to other study arms, missing data, etc. on study power (see also* ***9.4.2 Analysis of the Primary Efficacy Endpoint(s) and 9.4.3 Analysis of the Secondary Endpoint(s)****)*
* *Method for adjusting calculations for planned interim analyses, if any (****Section 9.4.6, Planned Interim Analyses****).*

*Be sure to present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.*

*Discuss or compute whether the sample size provides ‘sufficient’ power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term,* ***Section 9.4.9, Exploratory Analyses****).*

<Insert text>

## Populations for Analyses

*Clearly identify and describe any relevant analysis sets (e.g., sets of participants to be analyzed as a group). As a guide, this may include, but is not limited to, any or all of the following:*

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

<Insert text>

## Statistical Analyses

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

### General Approach

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

* *For descriptive statistics, describe how categorical and continuous data will be presented (e.g., percentages, means with standard deviations, median, range).*
* *For inferential statistics, indicate the significance value to be used for p-values and confidence intervals and whether they will be one or two-tailed. Also indicate if alternative methods for measuring statistical evidence will be used (e.g. Likelihood or Bayesian approach) and provide a description.*
* *Indicate whether covariates for regression models will be pre-specified or which variable selection procedure will be described. Describe how standard errors will be adjusted for the variable selection procedure and note where this is described (in the protocol or the statistical analysis plan).*
* *State whether checks of statistical assumptions will be performed and what corrective procedures will be applied, if any.*

<Insert text>

### Analysis of the Primary Endpoint(s)

*For each primary endpoint:*

* *Define the outcome 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., linear regression, generalized linear model, longitudinal model or mixed effects model). Describe the covariates and features in the model. Provide a rationale for covariate specification and covariate selection. 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, risk ratios, odds ratios, prevalence rates, number-needed-to-treat). All estimates should be accompanied with an uncertainly interval (e.g., confidence interval, support interval, credible interval).*
* *Describe details to check key assumptions (e.g., proportional hazards, missing data assumptions)*
* *Detail which analysis sets (e.g. ITT or as-Treated, as discussed in* ***Section 9.3, Populations for Analyses****) will be used for with which models.*
* *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up*
* *If there is more than one primary endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

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

<Insert text>

### Analysis of the Secondary Endpoint(s)

*For each secondary endpoint:*

* *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint*
* *Define the outcome and describe how it is calculated, if not readily apparent*
* *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure.*
* *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., linear regression, generalized linear model, longitudinal model or mixed effects model). Describe the covariates and features in the model. Provide a rationale for covariate specification and covariate selection. 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, risk ratios, odds ratios, prevalence rates, number-needed-to-treat). All estimates should be accompanied with an uncertainly interval (e.g., confidence interval, support interval, credible interval).*
* *Describe details to check key assumptions (e.g., proportional hazards, missing data assumptions)*
* *Detail which analysis sets (e.g. ITT or as-Treated, as discussed in* ***Section 9.3, Populations for Analyses****) will be used for with which models.*
* *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up.*
* *State the statistical adjustments used to control Type I error across secondary endpoints if deemed necessary. Give reasons why it was considered necessary or unnecessary.*

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

<Insert text>

### Safety Analyses

*Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in* ***Section 9.4.2, Analysis of the Primary Efficacy Endpoint(s)*** *should be included here. Describe how AEs will be coded (e.g., Medical Dictionary for Regulatory Activities (MedDRA)), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g., severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings) and what information will be reported about each AE (e.g., start date, stop date, severity, relationship, expectedness, outcome, and duration). Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing. The information included here should be consistent with the information contained within* ***Section 8.2, Safety and Other Assessments****.*

<Insert text>

### Baseline Descriptive Statistics

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

*Intervention groups are often compared on baseline characteristics to assess the degree to which randomization and sampling achieved scientific balance. State which demographics and laboratory measurements will be assess for balance using descriptive statistics. Discuss planned baseline descriptive statistics, and indicate which baseline variables will be included in statistical modeling. Provide justification for any baseline variables that will not be included in statistical models. Imbalance across study arms should be described by uncertainty intervals. No formal statistical tests should be conducted, because (1) these tests only examine univariate balance and ignore multi-dimensional imbalance, (2) statistical tests cannot provide support for the null hypothesis of balance, and (3) regression modeling that includes these baseline variables will correct for the osberved imbalances.*

<Insert text>

### Planned Interim Analyses

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

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

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

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

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

*Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I and II errors or the analogous probabilities of error in an alternative framework (e.g. Bayesian or Likelihood).*

*This section should be consistent with* ***Section 7, Study Intervention Not or Incompletely Performed and Participant Discontinuation/Withdrawal.***

<Insert text>

### Sub-Group Analyses

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

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

<Insert text>

### Tabulation of Individual participant Data

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

<Insert text>

### Exploratory Analyses

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

<Insert text>

# REFERENCES

*The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer’s IB, package insert, and device labeling.*

*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, device labeling or investigational brochure***

*Cite date accessed, version number, and source of product information.*

# APPENDIX I: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

## Regulatory, Ethical, and Study Oversight Considerations

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

### Informed Consent Process

*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.*

#### Consent/assent and Other Informational Documents Provided to participants

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

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

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

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

<Insert text>

#### Consent Procedures and Documentation

*Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of language other than English. Describe procedures for obtaining surrogate consent for those unable to consent on their own behalf. This section should be consistent with* ***Section 5.5, Strategies for Recruitment and Retention*** *when describing consent plans and special considerations for children or other vulnerable participants. Address re-consent processes for children who become adults or emancipated during a study.*

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

[Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant’s comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.]

<Insert text>

### Study Discontinuation and Closure

*List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision, sponsor/funder decision, regulatory or other oversight bodies; review of serious, unexpected, and related AEs; noncompliance; futility). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, the IRB, and sponsor and provide the reason(s) for the termination or temporary suspension.*

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

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

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

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

* Determination of unexpected, significant, or unacceptable risk to participants
* Demonstration of efficacy that would warrant stopping
* Insufficient compliance to protocol requirements
* Data that are not sufficiently complete and/or evaluable
* Determination that the primary endpoint has been met
* Determination of futility

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

<Insert text>

### Confidentiality and Privacy

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

*Include procedures for maintaining participant confidentiality, privacy protections, any special data security requirements, and record retention per the sponsor’s requirements. Describe who would have access to records, including the investigator and other study staff, the clinical monitor, funding institutions, representatives of the NIH Institute or Center (IC), IND/IDE sponsor, representatives from the IRB, regulatory agencies, and representatives of the pharmaceutical company supplying product to be tested. In addition, consider inclusion of the following information:*

* Describe whether identifiers will be attached to data/samples, or whether data will be coded or unlinked.
* If unlinked or coded, and additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.
* If research data/samples will be coded, describe how access to the “key” for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.
* *Include a discussion of the circumstances in which data or samples will be shared with other researchers.*
* *Include a discussion of plans to publish participant’s family pedigrees, with a description of measures to minimize the chance of identifying specific families.*
* *Describe any situations in which personally identifiable information will be released to third parties.*
* *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).*
* *Approaches to ensure privacy of study participants*

*For some studies, a Certificate of Confidentiality (CoC) may be necessary. A CoC provides protection to researchers and research institutions from being forced to provide identifying information on study participants to any federal, state or local authority. Authorization comes from NIH through section 301 (d) of the Public Health Service Act (42 U.S.C. 241 (d)) which provides the Secretary of Health and Human Services the authority to protect the privacy of study participants. Refer to the NIH Certificate of Confidentiality Kiosk, for more details.*

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

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

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

Certificate of Confidentiality (if applicable)

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.]

<Insert text>

### Future Use of Stored Specimens and Data

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

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

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

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

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

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

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

<Insert text>

### Key Roles and Study Governance

*Provide the name and contact information of the Principal Investigator and the Medical Monitor.*

|  |  |
| --- | --- |
| **Principal Investigator** | **Medical Monitor** |
| *Name, degree, title* | *Name, degree, title* |
| *Institution Name* | *Institution Name* |
| *Address* | *Address* |
| *Phone Number* | *Phone Number* |
| *Email* | *Email* |

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

<Insert text>

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

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator 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 Data Coordinating Center or sponsor>. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.]

<Insert text>

## Abbreviations

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

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

## Protocol Amendment History

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Description of Change** | **Brief Rationale** |
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# APPENDIX II: ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

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

## AdversE Events

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

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

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

### Definition of Adverse Events (AE)

*Provide the definition of an AE being used for the clinical trial. The FDA definition of an AE is used in this template 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 GCP definition may be more appropriate. However, it is important to note that FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a) for studies performed under an IND, regardless of the definition of AE used in the protocol.*

*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>

### 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. It is important to note that FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a) for studies performed under an IND, regardless of the definition of SAE used in the protocol. Note that the example text provided is from the drug regulations (21 CFR 312.32 (a)). 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:*

[An adverse event (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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.]

<Insert text>

### Classification of an Adverse Event

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

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

#### Severity of Event

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

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

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

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

<Insert text>

#### Relationship to Study INTERVENTION

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

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

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

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

*OR*

* **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
* **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
* **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
* **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
* **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

<Insert text>

#### Expectedness

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

*An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or device labeling 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 protocol, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB or package insert 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 or package insert 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, package insert, or device labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the study intervention, but are not specifically mentioned as occurring with the particular study intervention under investigation.*

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

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

<Insert text>

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

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

*An unsolicited AE would 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 intervention, 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 adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. 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.

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

<Insert role or name> will record all reportable events with start dates occurring any time after 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>

### Adverse Event Reporting

*This section addresses responsibilities of investigators for reporting of AEs. However, it is important to recognize that sponsors have additional responsibilities under regulations that are not described in this template and should be incorporated into relevant SOPs.*

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

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

<Insert text>

### Serious Adverse Event Reporting

*This section addresses responsibilities of investigators for reporting of SAEs. However, it is important to recognize that sponsors have additional responsibilities under regulations that are not described in this template and should be incorporated into relevant SOPs.*

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

*Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in* ***Section 8.3.2, Definition of Serious Adverse Events*** *must be submitted on an SAE form to the Data Coordinating Center (DCC) if one exists for the study. Studies overseen by a DSMB or other independent oversight body (e.g., safety monitoring committee, independent safety monitor), may be required to submit expedited notification of all SAEs or only SAEs thought to be related to study intervention.*

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

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

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

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

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

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

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

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

*Example 1, applicable for a drug or biologic protocol:*

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

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (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. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (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.]

*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 Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (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>

### Reporting Events to Participants

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

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

<Insert text>

### 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.*

*Include any other reportable events not already included in the previous sections, such as cardiovascular and death events, medical device incidents (including malfunctions), laboratory test abnormalities, and study intervention overdose.*

<Insert text>

### Reporting of Pregnancy

*Include content in this section if applicable, otherwise note as not-applicable. Pregnancy is not an adverse event, but some studies will require unique considerations if pregnancy was to occur during the study.*

*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 study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).*

<Insert text>

## Unanticipated Problems

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

### Definition of Unanticipated Problems (UP)

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

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

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

[The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

*Additional example text, applicable for device protocols:*

[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>

### Unanticipated Problem Reporting

*This section addresses responsibilities of investigators for reporting of UPs. Describe the UP reporting procedures, including timeframes. Further details should be included in a MOP or SOP including a description and a flow chart of when events are reported to various oversight (e.g., DSMB, safety monitoring committee, independent safety monitor) and regulatory groups, and what study staff are responsible for completing and signing off on the UP report forms.*

*Institutions engaged in human subjects research conducted or supported by Department of Health and Human Services (DHHS) must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)). Furthermore, for research covered by an assurance approved for federal wide use by OHRP, DHHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.*

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

[The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

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

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

* UPs that are serious adverse events (SAEs) will be reported 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 the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB’s receipt of the report of the problem from the investigator.]

*Additional example text, applicable for device protocol:*

[An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (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 the Food and Drug Administration (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>

### Reporting Unanticipated Problems to Participants

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

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

<Insert text>

# APPENDIX IV: NOVEL IMAGING OR NOVEL DEVICE MANUAL

*No text needed here*

## Imaging Manual

*Imaging manual is intended to be used as a step-by-step description of the hardware, image acquisition, reader study and quality assurance for novel imaging. Content varies with the novel imaging to be performed but possible applicable content includes:*

* *Scanner specifications*
* *Scanner qualification procedures*
* *Novel tracer – preparation, dose*
* *Image acquisition protocol for each scanner type*
  + *Radiation dose*
  + *Contrast dose*
* *Ongoing site quality control procedures (dose monitoring, calibration, etc.)*
* *Reader study description – number of readers, images reviewed, blinding, etc.*
* *Reader forms*

*In general, standard-of-care clinical imaging for participant followup does not need to be described in the Imaging Manual.*

<Insert text>

## Device Manual

*Medical Device is defined, in part, as any health care product that does not achieve its primary intended purpose by chemical action or by being metabolized.*

*Provide the following Device Information:*

* *Device Name*
  + *Intended Use*
  + *Sponsor*
  + *Name*
  + *Address*
  + *Contact Person*
  + *Contact Information*
* *Manufacturer Information*
  + *Name*
  + *Address*
  + *Contact Person*
  + *Contact Information*

*Is the device a*

* *Therapeutic Device (Intended to treat a specific condition or disease), or a*
* *Diagnostic Device (Provides information when used alone or in the context of other information to help assess a subject’s condition)?*

*Which FDA Category applies to this device?*

* *Significant Risk Device (SR) is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; or (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject.*
* *Non-significant Risk Device (NSR) is an investigational device that does not meet the definition for significant risk.*

*Provide IDE Number, if applicable.*

*If device is commercially available, provide copy of the FDA-approved labeling information.*

*Provide all relevant information about the device, including*

* *a description of each important component, ingredient and property*
* *the principle of operation of the device*
* *a description of the mechanism of action, instructions for use, storage, handling, preparation, or pre-use checks,*
* *preclinical testing including (where appropriate) design calculations, in vitro tests, mechanical and electrical tests, reliability test, software validation, performance tests, ex vivo tests, biological safety tests,*
* *risks/harms that may result from use of the device,*
* *existing clinical data,*
* *clinical adverse events observed in previous clinical trials,*
* *risk management*
* *regulatory or other relevant references, if any.*

<Insert text>

# INFORMED CONSENT TEMPLATE

**Template For**

**Basic Elements of Informed Consent   
45 CFR Part 46.116 (A)**

Your Informed Consent document must address the 8 basic elements listed in Section a below. The first 4 elements will be specific to your protocol. Text approved by your local IRB for the last 4 elements should be available from your institution.

Your Informed Consent document should also address the 6 additional elements listed in Section b below, if they are relevant to your clinical trial.

**For purposes of the RSNA CTMW, please write a few sentences for each of the 8 basic elements, and any of the 6 additional elements that are relevant, in language understandable by the potential subjects for your clinical trial.**

“§46.116 General requirements for informed consent.

No investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Section (a):

1. Statement that study involves research; explanation of purpose(s) and expected duration of participation; description of procedures and identification of experimental procedures.

2. Description of risks or discomforts to subject. For studies involving research-related radiation exposure, information regarding radiation dose and risks should be included.

3. Description of benefits to subject or to others.

4. Disclosure of alternative procedures, if appropriate.

5. Description of the extent to which confidentiality will be maintained.

6. For research involving more than minimal risk, explanation as to whether compensation and medical treatments are available if injury occurs.

7. Explanation of whom to contact if questions arise about the research or the subjects' rights or whom to contact if research-related injury occurs.

8. Statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits, and that subject may discontinue at any time.

Section (b):

Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects to be involved in the study.”

1. From ClinicalTrials.gov Protocol Data Element Definitions available at: <https://prsinfo.clinicaltrials.gov/definitions.html>. Accessed March 2017. [↑](#footnote-ref-2)