PREFACE TO THIS PROTOCOL TEMPLATE

This preface contains clarification about the protocol template and its supporting materials. **Remove this Preface** before finalizing and distributing the clinical trial protocol.

Most Institutes and Centers (ICs) at the National Institutes of Health (NIH) fund behavioral and social clinical trials, although ICs vary in the specific planning activities and supporting documentation required to conduct such studies. The following template is a suggested general format for clinical trial protocols that are testing a behavioral or social intervention. Use of the template is optional. This clinical protocol template was created to guide investigators through the systematic development of a comprehensive clinical protocol, especially for investigators less familiar with the information and level of detail expected in a clinical protocol. Finally, this protocol template may be a useful tool for anticipating decision-points and potential challenges before a study launches, so that comprehensive planning ensures smooth and systematic study operations.

It is important to note that the clinical protocol is just one piece of information that may be required by NIH ICs. Please consult your IC contact for guidance about other required documents for NIH-funded behavioral or social intervention clinical trials.

This template is based on a previous one that resulted from collaboration between the NIH and the Food and Drug Administration (FDA) and that was specifically designed for Phase 2/3 drug and device studies. This template maintains much of the content and structure of the earlier template but has been tailored to behavioral and social research. The instructional text and examples tend to focus on traditional notions of clinical trials in which behavioral and social interventions are tested for prevention or treatment of a disease or condition. That said, this template is meant to be applicable to studies including basic behavioral and social science research (bBSSR) in which one or more independent variable(s) are manipulated for the purpose of understanding some health-related aspect of functioning. Efforts were made to include language befitting such bBSSR studies, e.g., the section header "Study Intervention(s)/Experimental Manipulation(s)", but additional translation of language or concepts may be necessary.

The goal of this template is to assist investigators in writing a comprehensive clinical trial protocol that meets the standards outlined in the *International Council on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (ICH-E6)*. These are international standards of good clinical practice that apply to all clinical trials, and their goals are to ensure research integrity and protect human subjects. For more detailed information about how these standards apply to social and behavioral clinical trials, readers are encouraged to access the recent NIH-sponsored Best Practices Training for Social and Behavioral Research, which has tailored Good Clinical Practice to social and behavioral clinical trials (*Good Clinical Practice for Social and Behavioral Research*).

How To Use This Template

It is important to incorporate all sections of the template into your protocol and to do so in the same order. If a particular section is not applicable to your trial, please retain it, but indicate that it is not applicable by writing "N/A" under the section heading. Where appropriate, use cross-references, rather than duplicating text. If it is necessary to add additional subheadings at the third or lower level, please use the available heading styles so that they will be included when the table of contents is updated. This template contains two types of text: instruction/explanatory text and example text.

Instruction/explanatory text is indicated by *italics* and should be deleted prior to finalizing the protocol. This text provides information on the content that should be included in the protocol. It also notes if a section should be left blank. For example, many headings include the instruction, "*No text is to be entered in this section; rather it should be included under the relevant subheadings below.*"

Example text is included to further aid in protocol writing and should be modified to suit the intervention, behavioral or social manipulation study, design, and conduct of the planned clinical trial, or it may be deleted if it is not relevant. Example text is indicated in [regular font]. Within example text, a need for insertion of specific information is notated by <angle brackets>.

Headers and footers: The header of this template should be updated with the specific information requested in the <angled brackets,> including the shortened protocol title. You can remove the reference to the protocol template from the footer. If you choose to leave the template reference in the footer, consider adding "Based on the" before "NIH Behavioral and Social Intervention Clinical Trial Protocol Template…"

Version control is important to track protocol development, revisions, and amendments. It is also necessary to ensure that the most recently updated and IRB approved version of a protocol is used by all staff conducting the study. **With each revision, the version number and date located in the header of each page should be updated**. When making changes to an approved and "final" protocol, the protocol amendment history should be maintained (see **Section 10.4, Protocol Amendment History**).

<Title*>

This title should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.

Protocol Number*: <Number>

National Clinical Trial (NCT) Identified Number: <Number, once assigned by CT.gov>

Principal Investigator*: <Principal investigator>

Sponsor: <Sponsor name, if applicable>

"Sponsor" indicates an institution, foundation, or individual who takes responsibility for and initiates a clinical investigation; often times this is the university with which the Principal Investigator is affiliated.

Grant Title: <Grant Title>

Grant Number*: <Grant Number>

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

Version Number: v.<x.x>

<Day Month Year>

All versions should have a version number and a date. Use an international date format (e.g.,YYYY-MM-DD [2017-12-21] or write out the month (e.g., 21 December 2017).

For the initial submission of a protocol to the IRB, indicate "Not applicable; this is the first version of the protocol." in the table below. For any subsequent amendment being submitted to the IRB, add details of the specific changes that are being implemented in the amendment. Please note that Section 10.4 is a high-level summary of <u>all</u> formal protocol versions/amendments.

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

Table of Contents

STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

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

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

OR

(2) [The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

For either option above, the following paragraph would be included:

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

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name*:

Title*:

Investigator Contact Information

Affiliation*:

Address:

Telephone:

Email:

[For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site.]

Signed: _____ Date: _____

Name:

Title:

Affiliation:

1 PROTOCOL SUMMARY

No text is to be entered in this section; rather it should be included under the relevant subheadings below. It may be useful to complete this section after the relevant sections in the protocol have been completed.

1.1 SYNOPSIS

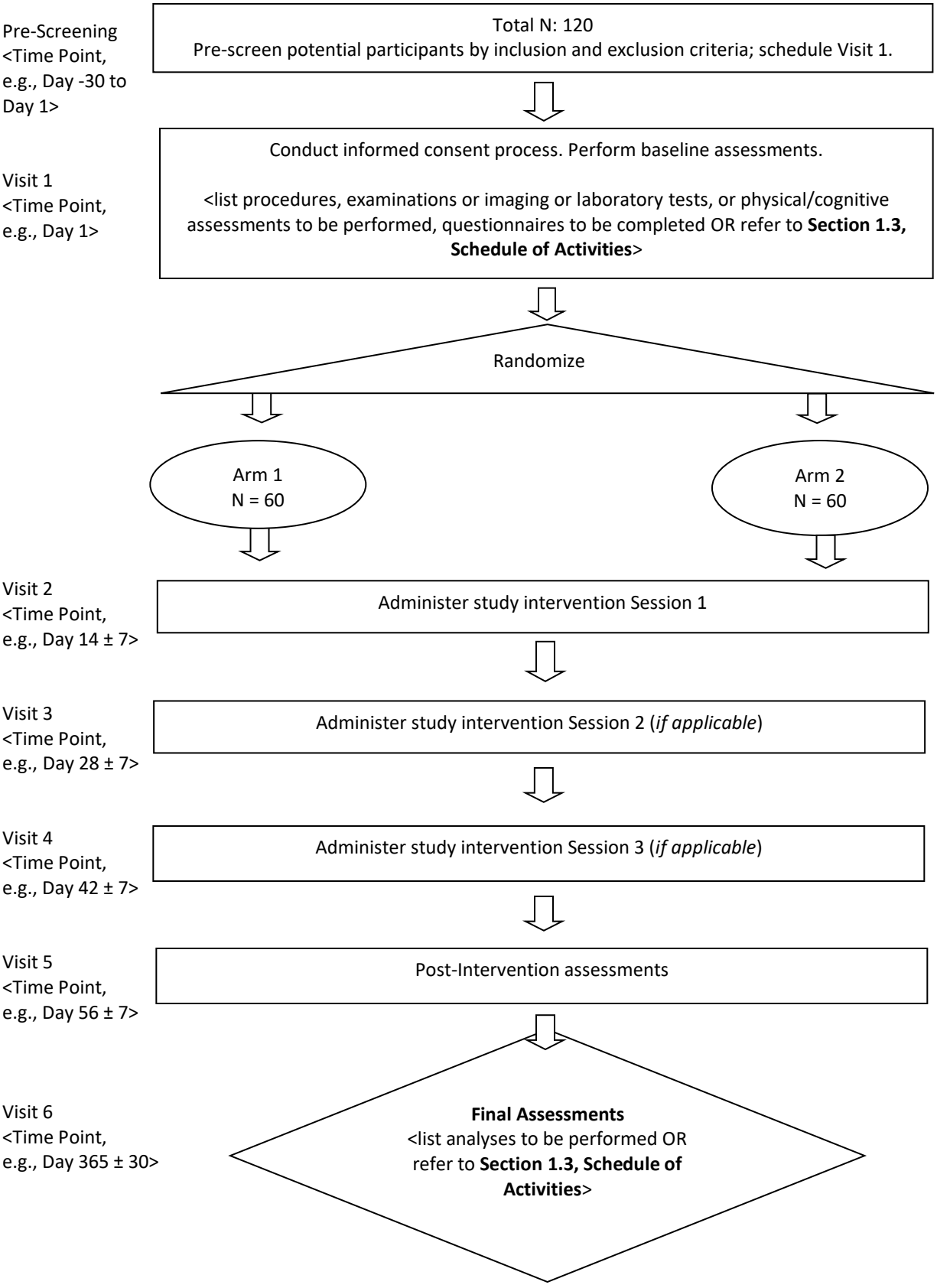
Title:	<Full Title>
Grant Number:	<Grant Number>
Study Description:	*Provide a short description of the protocol, including a brief statement of the study hypothesis(es). This should be only a few sentences in length. A detailed schematic describing all visits and a schedule of assessments should be included in **Section 1.2, Schema and Section 1.3, Schedule of Activities**.*
Objectives*:	*Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol.* <Primary Objective: Secondary Objectives: >
Endpoints*:	*Include the primary and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol.* <Primary Endpoint: Secondary Endpoints: >
Study Population:	*Specify the sample size, gender, age, demographic group, general health status, and geographic location.*
Phase* or Stage:	*Indicate Phase or Stage, as appropriate. Institutes and Centers may differ in their preferences for categorizing research. Consult with your Program Official (PO)*
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 indicate if the study is intended to include sites outside of the United States.*
Description of Study Intervention/Experimental Manipulation:	*Describe the study intervention (a.k.a, experimental manipulation; hereafter referred to as "study intervention"). Include intervention dose (length and frequency) and how it will be administered. Include method of delivery (e.g., group vs. individual, web-based, etc.).*
Study Duration*:	*Estimated time (in months) from when the study opens to enrollment until completion of data collection.*
Participant Duration:	*Time (e.g., in months) it will take for each individual participant to complete all study-related tasks.*

1.2 SCHEMA

*This section should include a diagram or flowchart that provides a quick "snapshot" of the study and ideally is limited to 1 page. Below is an example schematic that shows the level of detail needed to convey an overview of the study design. Revise with study-specific information and adapt the diagram to illustrate your study design (e.g., changing method of assignment to study group, adding study arms, visits, etc.). The time point(s) indicated in the schematic should correspond to the time point(s) in **Section***

***1.3, Schedule of Activities**, e.g., Visit 1, Day 1; Visit 2, Day 14 ± 7; etc. Although the convention is to call contacts with participants "Visit 1, Visit 2, etc.," participant contacts in which data will be collected remotely without an in-person visit should also be included in this schematic. One alternative is to use the term "Time 1, Time 2, etc.," to accommodate both in-person visits and assessments conducted remotely.*

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



1.3 SCHEDULE OF ACTIVITIES

The schedule below is provided as an example and should be modified or replaced as appropriate.

The schedule of activities (SOA) 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 screening procedures that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility, study objectives and endpoints. Other procedures should be done sparingly and with consideration, as they may add unnecessary complexity and participant burden. However, for feasibility or other studies that include an aspect of procedural refinement; those activities may be appropriate for inclusion herein and elsewhere in the protocol.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the visit time points to study endpoints (e.g., short-duration interventions and follow-up periods might require short outcome assessment windows, whereas longer follow-up periods of 6 months or longer might have a window of several weeks). In some cases, the protocol may include an unscheduled visit (e.g., if participants are asked to come to the clinic when they are experiencing specified symptoms). For unscheduled visits, specify all data that would be important to collect.

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 14 ±7	Visit 3 Day 28 ±7	Visit 4 Day 42 ±7	Visit 5 Day 56 ±7	Visit 6 Day 365 ±30	Unscheduled Visit
EMR Review Eligibility	X							
Informed Consent		X						
Demographics		X						
Clinical history		X					X	
Height & Weight		X	X				X	
Outcome Evaluation								
Pain Assessment (Brief Pain Inventory)		X			X		X	X
Quality of Life Questionnaire		X	X	X	X	X	X	
Randomization		X						
Control & Experimental Interventions – Occupational therapy		X	X	X	X			
Adverse Events Reporting		X	X	X	X	X	X	X

<Insert table>

2 INTRODUCTION

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

The following subsections should include relevant background information and rationale for the clinical trial. This should be a brief overview (e.g., approximately 3-7 pages). Referring to relevant intervention manuals for more detail is appropriate. Text for Sections 2.1 and 2.2 may come from the Background and Significance section of the grant application.

2.1 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), the reason for conducting the clinical trial and the rationale underlying the intervention. State the name and the nature of the intervention, the hypothesized target(s) of the intervention (i.e., the putative cognitive, affective, behavioral, social, community, organizational, etc., target necessary to produce the behavior change relevant to the clinical outcome), and the clinical outcome of interest.

<Insert text>

2.2 BACKGROUND

This section should include:

- *A summary of relevant basic and clinical research, including research conducted in other countries*
- *Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations should be listed in **Section 11, 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>

2.3 RISK/BENEFIT ASSESSMENT

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

The following subsections should include a discussion of known risks and benefits, if any, to human participants. Text from the corresponding sections of the Human Subjects section of the grant application, and/or IRB package may be used here.

2.3.1 KNOWN POTENTIAL RISKS

Include a discussion of known potential risks from either clinical or nonclinical studies. For behavioral or social intervention studies, relevant published literature should provide relevant risk information. For studies including a licensed or approved product, a package insert or device labeling should be used as a primary source of risk information. If the study includes an investigational product, the Investigator's Brochure (IB) should be a primary source of the risk information.

Describe any physical, psychological, social, legal, economic, or any other risks to participants by participating in the study that the Principal Investigator (PI) foresees, addressing each of the following:

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

<Insert text>

2.3.2 KNOWN POTENTIAL BENEFITS

Include a discussion of known potential benefits from either clinical or nonclinical studies. For behavioral or social intervention studies, relevant published literature should provide relevant benefits information. For studies including a licensed or approved product, a package insert or device labeling should be used as a primary source of benefits information. If the study includes an investigational product, the Investigator's Brochure (IB) should be a primary source of the benefits information.

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

- *Immediate potential benefits*
- *Long-term potential benefits*

Note that payment to participants, whether as a non-coercive inducement to participate or as compensation for time and inconvenience, is not considered a "benefit." Provision of incidental care is also not to be considered a benefit. For details of compensation see ***Section 5.5, Strategies for Recruitment and Retention****.*

<Insert text>

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

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

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

<Insert text>

3 OBJECTIVES AND ENDPOINTS

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

*An **objective** is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., feasibility, acceptability, engagement of the intervention target, identifying mechanisms of action, mediation, moderation, efficacy, effectiveness, dissemination, implementation).*

*A study **endpoint** is a specific measurement or observation to assess the effect of the study intervention. Study endpoints should be prioritized and should correspond to the study objectives and hypotheses being tested. Give succinct and precise definitions of the study endpoints used to address the study's primary objective and secondary objectives (e.g., specific diagnostic tests that define safety or efficacy, clinical assessments of disease status, assessments of psychosocial characteristics, patient reported outcomes, behaviors or health outcomes). A full description of study endpoints, including administration, scoring, psychometrics, adjudication of endpoints, etc., belongs in **Section 8**, **Study Assessments and Procedures**.*

A putative mechanism of action is the theorized explanation for how the intervention functions.

*Consider whether primary and secondary endpoints should be adjusted for multiple comparisons, family-wise error rates, alpha inflation, etc. Details of any such adjustments should be included in **Section 9.4.2, Analysis of the Primary Endpoint(s)** and **Section 9.4.3, Analysis of the Secondary Endpoint(s)**.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).	*The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of*	*Briefly identify the hypothesized role that each measure plays in the study objectives, e.g., moderator, mediator, causal mechanisms, covariate.*	*This column is optional and can be included when appropriate.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective. *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.*		
Secondary			
The secondary objective(s) are goals that will provide further information on the use of the intervention.	*Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention's effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is*	*Briefly identify the hypothesized role that each measure plays in the study objectives, e.g., moderator, mediator, causal mechanisms, covariate.*	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiple comparisons becomes increasingly small as the number of endpoints increases.		
Tertiary/Exploratory			
Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.	*If exploratory endpoints will be examined, they should be specified. Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.*	Briefly identify the hypothesized role that each measure plays in the study objectives, e.g., moderator, mediator, causal mechanisms, covariate.	

4 STUDY DESIGN

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

4.1 OVERALL DESIGN

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should be consistent with the ***Section 1.1, Synopsis*** *and* ***Section 1.2, Schema*** *and include:*

- *A statement of the hypothesis (es) associated with the objectives and the endpoints (i.e., outcomes to be assessed)*
- *A description of the Phase or Stage of the trial (confer with your Program Official for guidance)*
- *A description of the type/design of trial to be conducted (e.g., randomized, attention-control, multiple baseline, A-B-A design, dismantling, adaptive, SMART design, optimization trials, repeated measures, group- or cluster-randomized, superiority or non-inferiority design, within-subjects)*
- *Specification of the method for assigning participants to study groups/arms (i.e., randomized, non-randomized (single-arm design), or N/A). If randomization is used, specify the following:*
  - *Randomization method*
  - *Specify allocation ratio, unit of randomization, allocation concealment, and when in the study timeline randomization will occur (e.g., after baseline assessment)*
  - *Who (i.e., what role) will generate and implement the randomization schema*
  - *How randomization errors be handled*
- *Specification of the number of study groups/arms and duration of the study intervention and follow-up period(s)*
- *Indication if this will be a single site or multi-site trial. A multi-site trial is defined as the implementation of the same study protocol at two or more independent investigational sites where participants are seen for an intervention and/or assessment of outcomes*
- *Name and brief description of study intervention(s)*
- *If appropriate, description of control group(s) used; attention-control or other comparison conditions. Provide a rationale for the selection of control group(s) and discuss limitations associated with it. Selection of control groups should be based on how best to address the research question. In some cases, subjects can serve as their own controls.*
- *If applicable, a statement that an interim analysis is planned and refer to details in* ***Section 9.4.6, Planned Interim Analysis***
- *If applicable, a statement that the study includes any stratifications and if so, identify the stratification planned (e.g. sex, race/ethnicity, age, dose) and refer to details* ***in Section 9.4.7, Sub-Group Analyses***
- *Name of sub-studies, if any, included in this protocol. For instance, a sub-study might entail performing one or more assessments on a subset of the sample included in the study (e.g., conducting a cognitive interview on a 10% of the study subjects).*

- *If there are multiple studies associated with the grant, confer with your PO to determine the best approach for protocol development (e.g.., detail all studies included in one protocol, or develop individual protocols for each study).*

<Insert text>

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Describe the rationale for the type and selection of control or comparison condition(s) and study design. Discuss known or potential problems associated with the control group chosen in light of the specific disease, health behavior, and intervention(s) being studied.

<Insert text>

4.3 JUSTIFICATION FOR INTERVENTION

Provide a justification for the mode of intervention delivery, and for the length, number, and frequency of intervention contacts. If an intervention has been adapted for other cultures, provide justification for these adaptations being culturally relevant. Briefly describe the minimum-acceptable participation in, or exposure to, the intervention in order to have evaluable data.

<Insert text>

4.4 END-OF-STUDY DEFINITION

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

Example text provided as a guide, customize as needed:

[A participant is considered to have completed the study if he or she has completed the baseline assessment, at least 4 intervention sessions, and the 6-month and 12-month follow-up assessments.

The end of the study is defined as completion of the 12-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.]

<Insert text>

5 STUDY POPULATION

*If the study design requires clarification of various groups of study participants, that clarification can be included directly under **Section 5**. For example, for a feasibility study that includes therapist-participants*

and patient-participants, clarify the distinction of those populations here. Subsequent subsections should also differentiate by participant type, where relevant.

The following subsections should include a description of the study population(s) and participant recruitment. The study population should be appropriate for clinical trial phase/stage of the study intervention. It is essential that the population's characteristics be considered during the trial planning phase to ensure the trial can adequately meet its objectives and provide evidence for the total population that will potentially utilize the study intervention under evaluation (e.g., elderly and pediatric populations, women, and minorities).

Behavioral studies often have unique units of measurement. For example, the study may evaluate at the clinic or classroom level, rather than at a patient or student level. In other cases, the care provider could be the subject of the intervention. It may even evaluate at multiple levels within the same protocol. The description of the study population should match the unit of measurement or level of analysis; there is no expectation that characteristics of individual participants be described if inclusion/exclusion criteria are based on group characteristics.

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

- *The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment*
- *For population-based interventions, indicate if study "participant" is at a broader level, such as schools, hospitals, churches, community organizations, or other, as appropriate*
- *If participants require screening, distinguish between screening participants vs when a participant is considered enrolled/entered/randomized*
- *Indicate if screening procedures will be performed under a separate screening consent form*
- *Consider the risks of the study intervention 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, behavioral or other participant characteristics that will be used as criteria for enrollment or exclusion*
- *If reproductive status (e.g., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide study requirements (e.g., contraception methods, pregnancy testing)*
- *If the study involves more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation*

5.1 INCLUSION CRITERIA

Inclusion criteria are characteristics that define the population under study, e.g., those criteria that every potential participant must satisfy, to qualify for study entry. Provide a statement that individuals must*

meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion. Women and members of minority groups must be included in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. Beginning in 2019, participants of all ages must be included in accordance with the NIH Policy on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects.

Some criteria to consider for inclusion are: provision of appropriate consent and assent, willingness and ability to participate in study procedures, age range, health status, specific clinical or psychological diagnosis, and symptoms, background medical or psychosocial treatment, laboratory ranges, and use of appropriate contraception. Additional criteria should be included as appropriate for the study design and risk with the goal of being broadly inclusive while still supporting the science and protecting subjects' safety.

Example text provided as a guide, customize as needed:

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

1. Provision of signed and dated informed consent form
2. For children, informed assent and parental informed consent to participate in the study
3. Stated willingness to comply with all study procedures and lifestyle considerations (see **Section 5.3, Lifestyle Considerations**) and availability for the duration of the study
4. Males and females; Age <specify range>
5. Self-reported diagnosis of <condition under study>, or documented diagnosis of <condition under study>
6. Willingness to adhere to the <study intervention> regimen
7. Enrolled at <school name> school during the <year-year> school year
8. Score between <numerical range> on the <validated scale or measure>
9. BMI at or above <value> percentile
10. Access to necessary resources for participating in a technology-based intervention (i.e., computer, smartphone, internet access)
11. Not currently practicing <behavior> and have not participated in a class or program on <behavior> within the last 12 months]

<Insert text>

5.2 EXCLUSION CRITERIA

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

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

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

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

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

1. Current use of medications or dietary supplements for weight or appetite control, whether prescribed or not
2. Participation in another treatment or intervention study within <specify time frame>
3. Presence of a condition(s) or diagnosis, either physical or psychological, or physical exam finding that precludes participation <examples>
4. Activity restrictions that limit one's ability to engage in intense physical activity

<Insert text>

5.3 LIFESTYLE CONSIDERATIONS

Include content in this section if applicable, otherwise note as "N/A."

Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, intake of caffeine, alcohol, or tobacco, or limits on activity). Describe what action will be taken if a participant has used prohibited medications, treatments or procedures (e.g., early withdrawal by study Investigator).

Example text provided as a guide, customize as needed:

[During this study, participants are asked to:

- Refrain from starting medications or dietary supplements for weight or appetite control
- Refrain from brushing teeth, eating, or drinking 30 min prior to salivary cortisol collection
- Fast on the morning(s) that blood samples will be collected for <assay>
- Avoid caffeine and nicotine for 24 hours prior to study assessment visits]

<Insert text>

5.4 SCREEN FAILURES

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

Example text provided as a guide, customize as needed:

[Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a previous affective disorder, and the lifting of physical activity restrictions previously in place. Rescreened participants will be assigned the same participant number as for the initial screening.]

<Insert text>

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Identify general strategies for participant recruitment and retention. This section may refer to a separate detailed recruitment and retention plan in the Manual of Procedures (MOP) and site specific plans could be included in a site-specific Standard Operating Procedures (SOP) document. Consider inclusion of the information below either in this section or the MOP.

- *Anticipated number to be screened, including women, minorities, and participants across the lifespan, in order to reach the target enrollment size (should be consistent with information contained in **Section 9.2, Sample Size Determination**)*
- *Anticipated enrollment sample size by gender, race and ethnicity, and age*
- *The anticipated accrual rate over the course of the study including accrual rate by any key subject characteristics such as by sex, age, or racial or ethnic minority group (e.g., 5 parent-child dyads per month over 24 months)*
- *Planned recruitment strategies (e.g. university student research pool, patient advocacy groups, online recruitment services, community advisors, national newspaper, local flyers). Include rationale for why the strategy will be appropriate for reaching the targeted study population.*
- *When applicable, consider and include strategies adapted to the cultural context of the study or population*
- *If recruitment or data collection procedures occur in a public setting, community-based outreach, or other similar settings, describe a plan for ensuring participants' and study staff's safety.*
- *For multi-site studies, description and number of recruitment sites (e.g., inpatient hospital setting, student health service, community center), and anticipated number of participants to be recruited from each site*
- *Procedure of how potential screening participants will be identified and approached*
- *Indicate whether an interview or a run-in period will be used to identify eligibility*
- *Specific strategies that will be used to recruit and retain historically under-represented populations in order to target sample size and conform with the NIH Policy on Inclusion of Women and Minorities and Inclusion of Individuals Across the Lifespan as Participants in Research Involving*

Human Subjects. Include the number of women, minorities, and participants representing ages across the lifespan expected to be recruited, or provide justification on those rare occasions where women and/or minorities will not be recruited, and/or where age restrictions are justified.

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

Include a section to address participant incentives:

- *Specify if participants will be compensated or provided any incentives (e.g. vouchers, gift cards,) for study participation. Describe the type of incentive, amount, and timing of such compensation in relation to study activities (include financial and non-financial incentives).*
- *Describe steps to minimize coercion or undue influence, i.e., whether appropriate level of incentive is used so not to be viewed as coercive*
- *Describe who will receive incentives (if not the participant). For example, if participants are minors, state whether the minor or the parent/guardian will receive the incentive. If participants are incapacitated adults, state if payment will be provided to the participant or to a legally authorized representative or guardian.*

If appropriate, in a section for vulnerable participants include:

- *Justification for inclusion of vulnerable participants and recruitment strategy. Include safeguards for protecting vulnerable populations. Please refer to OHRP guidelines when choosing the study population. Note that these regulations apply if any participants are members of the designated population, even if it is not the target population (e.g., if a participant becomes a prisoner during the study).*

<Insert text>

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

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

The following subsections should describe the study intervention that is being tested in the clinical trial, and any control or comparison conditions being used in the trial. The study intervention(s) may be one or more experimental manipulations meant to cause short-term change in functioning, or behavioral or social interventions or treatments meant to improve clinical outcomes or endpoints, either in the short-term or long-term.

If multiple study interventions are to be evaluated in the trial, ***Section 6.1, Study Intervention(s) Administration*** *and* ***Section 6.2, Fidelity*** *and their accompanying subsections, should clearly differentiate between each intervention using distinct subsection headings. Address attention-control and comparison conditions within each part of* ***Section 6.1*** *and* ***Section 6.2****. If the control or comparison condition(s) is/are handled differently (e.g., frequency of intervention delivery within a subject) than the study intervention, be sure to state how they are each handled, separately. If the control or comparison condition(s) are handled the same as the study intervention, state as such. In addition, not all sections may be relevant for the trial. If not relevant, note as "N/A" in that section.*

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

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

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Describe the study intervention(s)/experimental manipulation(s), including any control or comparison interventions or conditions. This description should include the theory/theories on which the intervention(s) is/are based, and the intended mechanistic target(s) of the intervention(s), as well as the targeted clinical endpoints. The intervention manual(s) may be included in the appendices, and can be referenced here. If multiple interventions will be described, use separate subsections for each.

<Insert text>

6.1.2 ADMINISTRATION AND/OR DOSING

Describe how the study intervention(s)/experimental manipulation(s) will be administered, including frequency or schedule; whether there will be interventionists (i.e., a specified individual who administers the intervention); the setting in which the intervention will be delivered; and the number of sessions constituting a complete or "full-dose" intervention. Include the parameters that are relevant to delivery of the intervention and control/comparison condition, as relevant (e.g., intensity, duration, and/or frequency/number of sessions; number, difficulty level and/or intervals between trials in computer-administered intervention applications). Specify whether participants will interact with other participants or with a shared interventionist after assignment to study arms, and whether face-to-face or virtually. Such interactions are common in group- or cluster-randomized trials and in individually randomized group-treatment trials. For cases in which tracking dose or exposure is difficult, or for which standard metrics are still being developed, it may be necessary to include multiple metrics, e.g., technology-based interventions where metrics could include hits on the study webpage, number of texts received by the participant, number of responses to scheduled prompts to engage in an activity, etc.

<Insert text>

6.2 FIDELITY

No text is to be entered in this section; rather it should be included under the relevant subheadings below. This section refers to efforts made to confirm that the intervention is appropriately conducted by the interventionist(s). It is distinct from the content of ***Section 6.4, Study Intervention Adherence****, which is intended to capture a study participant's adherence to an intervention.*

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

If the protocol objectives depend on consistent administration of the study intervention(s) or experimental manipulation(s), then a plan for monitoring and ensuring consistent administration (fidelity of delivery) is expected. If the protocol objectives relate to understanding variability in delivery (e.g., an objective of comparing different intensities of an intervention or an objective of examining effects of intervention delivered by a person versus internet-based), a plan for how variability will be monitored is expected. Detailed information may be provided in a MOP or a separate SOP. If one or more study interventions will be delivered by interventionists, state how success of training will be assessed (e.g., will supervisors be used for quality assurance of the interventionists?). The degree to which subjects adhere to the intervention is addressed in ***Section 6.4, Study Intervention Adherence****. For group- or cluster-randomized trials and individually randomized group-treatment trials, describe the plan to track changes in the structure of the groups or clusters over the course of the study.*

<Insert text>

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This section should contain a description of randomization and blinding[*] (also referred to as "masking") procedures (if applicable to the study design). It should include a description or a table that describes how study participants (at the individual or group level) will be assigned to study arms, without being so specific that blinding or randomization might be compromised (e.g., the ratio between intervention and control or comparison groups may be stated). If adaptive randomization or other methods of covariate balancing/minimization are employed, embed a cross-reference to the methods of analysis in ***Section 9, Statistical Considerations****. In addition, details regarding the implementation of procedures to minimize bias should be included in this section. Do not include details that might compromise these strategies.*

Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse events). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

Sometimes blinding is attempted but is known to be imperfect because of obvious differences between study interventions. Such problems or potential problems should be identified and, if there are plans to assess the magnitude of the problem or manage it, these should be described (e.g., having endpoint measurements carried out by study staff shielded from information that might reveal study group assignment).

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

Include a description of your plans to manage and report inadvertent unblinding. If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained (e.g., computer-delivered tasks capturing reaction times, and Holter tapes with automated ECG read-outs are presumably immune to observer bias). If blinding is considered desirable but not feasible, the reasons and implications should be discussed.

<Insert text>

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

This section refers to efforts made to confirm that the subject of the intervention/experimental manipulation is appropriately adhering to the intervention (e.g., regularly completing a food diary, attending weekly therapy visits). It is distinct from the content of ***Section 6.2****,* ***Fidelity****, which captures the interventionist's quality of intervention/experimental manipulation administration. This section should describe how participants' adherence with study procedures will be tracked, (e.g., attendance at intervention visits, exposure to intervention materials). Include a discussion of what documents/activities are mandatory versus optional to complete (e.g., participant questionnaires or laboratory assessments) in order to remain an active participant and what source documents/records will be used to calculate study intervention adherence.*

This section may not be applicable to some studies (e.g., studies involving a single visit, delivering a single set of laboratory tasks).

<Insert text>

6.5 CONCOMITANT THERAPY

Include content in this section if applicable, otherwise note as "N/A."

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

Example text provided as a guide, customize as needed:

[For this protocol, participants may use non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and prescribed medications. Medication usage will be assessed at each study visit and documented in the relevant Case Report Form (CRF).]

<Insert text>

6.5.1 RESCUE THERAPY

Include content in this section if applicable, otherwise note as "N/A."

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

Example text provided as a guide, customize as needed:

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

The study team may use rescue therapy. However, the use of rescue medications will be delayed, if possible, for at least <insert timeframe> following the administration of <study intervention>. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, will be recorded in <location>.]

<Insert text>

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

Participants may withdraw voluntarily from the study or the PI may discontinue— a participant from the study. In some cases, a participant may withdraw from the study intervention—or be discontinued from the study intervention by the PI(s)—and still continue to participate in other aspects of the study. This section should state which events, adverse or otherwise (e.g. move from the area) would result in discontinuation of the study intervention for a specific subject, or would result in a subject being fully discontinued/withdrawn from the study. ***Consider requiring separate documentation for participant discontinuation/withdrawal from the study intervention and from the study****. In addition, a dedicated Case Report Form (CRF) page should capture the date and the specific underlying reason for participant discontinuation/withdrawal.*

This section may not be applicable to some studies (e.g., studies involving a single visit, delivering a single set of laboratory tasks).

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Describe the criteria for discontinuing the study intervention, including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., details and quantity of specific adverse events/serious adverse events or clinical worsening), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation. Identify individuals responsible for determining whether study interventions should be discontinued (e.g., independent clinician or ombudsman) and the specific instruments used to make these determinations. Also describe any approaches for restarting administration of study intervention(s).

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems (UPs). If applicable, include references to ***Section 8.3, Adverse Events and Serious Adverse Events*** *and* ***Section 8.4, Unanticipated Problems****.*

This section may not be applicable to some studies (e.g., studies involving a single visit, delivering a single set of laboratory tasks).

Example text provided as a guide, customize as needed:

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

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.]

<Insert text>

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

*Provide a list of reasons participation may be fully discontinued from the study (as compared to reasons a participant may be discontinued from the intervention as covered in **Section 7.1, Discontinuation of Study Intervention/Experimental Manipulation**). It may be appropriate to provide distinct discontinuation criteria for participants and cohorts (e.g., an individual subject may be withdrawn if the subject demonstrates a substantial increase in violence). If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also, note that participants may withdraw voluntarily from the study or the study intervention at any time. But, investigators should seek to minimize participant discontinuation/withdrawal from the study except for safety reasons.*

*This section should include a discussion of replacement of participants who withdraw or are discontinued early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data. This should be captured in **Section 9, Statistical Considerations.***

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 a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

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

<Insert text>

7.3 LOST TO FOLLOW-UP

The protocol should state when a participant will be considered lost to follow-up (e.g., after missing a certain number of study visits, after a certain number of failed attempts to contact the participant). Also, describe the plans to minimize loss to follow-up and missing data. This section may not be applicable to some studies (e.g., studies involving a single visit, delivering a single set of laboratory tasks).

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 study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit <specify time frame>, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up]

<Insert text>

8 STUDY ASSESSMENTS AND PROCEDURES

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

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

*List and describe study procedures, measures, and assessments to be done to fulfill all but the safety objectives of the study (see **Section 8.2, Safety Assessments**). This section will include any non-safety baseline assessments (e.g., screening, eligibility, enrollment), even though they would not be affected by the intervention per se.*

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.

In certain cases, it is the intention of the intervention, combined with the objective of the outcome measure that determines whether it should be included in this section or in the safety section. For example, in one study body weight may be an efficacy outcome and in other cases it may be a safety outcome (e.g., increase in body weight as a secondary result of a smoking cessation intervention).

Note if a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments. Include any definitions used to characterize outcomes (e.g., diagnostic criteria, sub-clinical symptoms, and change in health behaviors considered clinically-significant).

Note that the protocol should provide a high-level overview of all procedures, including administration, scoring, and psychometrics. When applicable, discuss any cultural adaptations that will be implemented and provide support for the validity of these adaptations. Additional relevant details can be provided in a MOP or SOP. Provide justification for any sensitive procedures (e.g., provocative testing, deception). In addition, note where approaches to decrease variability, such as centralized laboratory assessments or observational coding, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in ***Section 1.3, Schedule of Activities (SoA)*** *and the time points of these procedures do not need to be included here. In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.*

This section may include (but is not limited to) a list and description of the following (example) categories:

- ***Physical examination-based assessments*** *(e.g., height and weight, organ systems, motor or visual acuity assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
- ***Performance-based assessments*** *(e.g., physical function – gait, balance; sensory testing – pain perception, proprioception; neuropsychological/cognitive assessments – dementia assessment, executive function, memory performance tests)*
- ***Administration of questionnaires, interviews,*** *or other instruments for patient (or other, e.g., family, caregiver-) reported outcomes, such as a daily diary*
- ***Ecological momentary assessment*** *(real-time repeat sampling of a person's behaviors, symptoms, or experiences typically outside of the clinic setting often using an application or other device, physical activity/sleep monitor or other sensor)*
- ***Radiographic or other imaging assessments*** *State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study's MOP or a separate SOP.*
- ***Biological specimen collection and laboratory evaluations*** *Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study's MOP.*
- ***Special assays or procedures required*** *(e.g., 3-D image capture of facial emotional expression, video recording of standardized family interaction tasks, a food choice task after laboratory intervention). Special instructions for the preparation, handling, storage, and shipment of raw data and/or specimens should be briefly explained in this section with detailed discussion in the study's MOP.*

- ***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 participants (e.g., radiographic or other imaging or laboratory evaluations). Address when endpoints will be assessed with respect to timing of rescue medication/therapy, if applicable.

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

<Insert text>

8.2 SAFETY 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. Consider matching the framework and language that is requested by your Institutional Review Board (IRB). Some studies may not include safety assessments. If your study does not include safety assessments, indicate as "N/A" and delete all instructional and example text associated with this section.

Note that the protocol should provide a high-level overview of all safety procedures, and detailed information can be further provided in a MOP or SOP. In addition, note where approaches to decrease variability, such as centralized laboratory assessments, are being employed. The specific timing of procedures/evaluations to be done at each study visit are captured in ***Section 1.3, Schedule of Activities (SoA)*** *and the time points of these procedures do not need to be included here. In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.*

This section may include a list and description of the following safety procedures/evaluations, as applicable and how safety will be protected:

- ***Physical examination***
- ***Performance-based assessments***
- ***Ecological momentary assessment***
- ***Physical activity/sleep monitor or other sensor***
- ***Radiographic or other imaging assessments***
- ***Biological specimen collection and laboratory evaluations***
- ***Special assays or procedures required***
- ***Administration of questionnaires or other instruments*** *for patient-reported outcomes, such as self-reported symptoms or satisfaction ratings*
- ***Assessment of adverse events*** *Describe provisions for identification and follow-up of ongoing AEs/SAE. If support staff will have contact with individuals, indicate how they should report identified AEs/SAE to the study team.*

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

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

<Insert text>

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

*Depending on the nature of the intervention, it may not be necessary to collect adverse events, except those that are considered to be unanticipated problems (UPs; see **Section 8.4, Unanticipated Problems** for clarification). If the protocol limits safety reporting to UPs, indicate "N/A" in this section and remove the remaining contents prior to **Section 8.4**.*

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 a professional with experience in the clinical care of your population. Consider the risks of the study intervention(s) and other study procedures and the characteristics of the study. This section should be tailored for specific study characteristics, including but not limited to the following:

- *The study involves risks to individuals other than research participants (e.g., household or intimate contacts, communities, study clinicians, pharmacists or interventionists, etc.)*
- *Reporting of certain events (e.g., suspected child abuse or substance abuse) is mandatory and may be discovered because of the study population or study design characteristics*
- *The study is conducted at multiple sites, and will require centralized safety oversight*
- *The study involves a population at heightened risk of serious adverse events (e.g., participants at heightened risk of suicide, clinical deterioration, etc.)*

*In developing this section, consider the risks of the study intervention. Review and reference the applicable sources of information, such as literature and other sources that describe the study intervention. Text provided in the package submitted to your IRB may be useful in completing **Sections 8.3 and 8.4**.*

8.3.1 DEFINITION OF ADVERSE EVENTS

Provide the definition of an Adverse Event (AE) being used for the clinical trial. Refer to your institutional review board for definitions and guidance (please note that the FDA definition of an AE is used in this template. However, 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. If your study is being conducted under an IND, FDA regulations require reporting based on the definition included in 21 CFR 312.32 (a)). In the event that a study is considered to carry a low risk to subjects (e.g., studies labeled under the "no more than minimal risk" designation), specify which AEs will be recorded and/or which will not. These decisions should be based on the nature of the study and intervention as well as the subject population.

Example text provided as a guide, customize as needed:

[This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

<Insert text>

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Refer to your institutional review board for the latest guidance and definition of Serious Adverse Events (SAE). In some cases, it may be appropriate to create a list of expected events that do not need to be reported to the IRB.

<Insert text>

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

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

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

8.3.3.1 SEVERITY OF EVENT

All AEs should be assessed by the principal investigator, and if necessary, another professional with clinical experience in the study population using a protocol defined grading system. Describe the method of grading an AE for severity.

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>

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

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, behavioral) is part of the documentation process, but it is not a factor in determining what is or is not recorded 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 recorded. 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) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures 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 procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- **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 procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). 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 procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) 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 procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

<Insert text>

8.3.3.3 EXPECTEDNESS

Expected adverse reactions are AEs that are known to occur for the study procedures 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. 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 unlikely to occur in the study population, or it is unlikely to occur at the severity that has been observed.

Example text provided as a guide, customize as needed:

[A clinician with appropriate expertise in <insert condition> 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 procedures.]

<Insert text>

8.3.4 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). This section clarifies how and which events will be recorded in the study record/case report form.* ***Sections 8.3.5, Adverse Event Reporting*** *through* ***Section 8.3.9, Reporting of Pregnancy,*** *discuss how and when events will be reported beyond the study record/case report form.*

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?" 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, not otherwise precluded per the protocol, 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 procedures (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 will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric 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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

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

<Insert text>

8.3.5 ADVERSE EVENT REPORTING

This section addresses responsibilities of investigators for reporting of AEs outside of the study team and the clinical database. However, it is important to recognize that sponsors and/or funding agencies 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 (some institutions may require that AEs be reported within a pre-specified amount of time). 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. If reporting is required to more than one entity (e.g., IRB and funding agency), PIs should submit reports to both entities using the earliest required reporting timeframe.

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>

8.3.6 SERIOUS ADVERSE EVENT REPORTING

This section addresses responsibilities of investigators for reporting of SAEs outside of the study team and the clinical database. However, it is important to recognize that sponsors and/or funding agencies 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.*

For studies regulated by the FDA, see 21 CFR 312.64(b), 21 CFR 312.32(c)(1) and (c)(2). For IDE studies, see 21 CFR 812.150(a)(1),(b)(1), and 812.46(b).

Example:

[In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and 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 event.]

<Insert text>

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Include content in this section if applicable, otherwise note as "N/A."

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>

8.3.8 EVENTS OF SPECIAL INTEREST

Include content in this section if applicable, otherwise note as "N/A."

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 psychiatric hospitalization, and significant changes in behavior (e.g., interpersonal violence, substance abuse)..

<Insert text>

8.3.9 REPORTING OF PREGNANCY

Include content in this section if applicable, otherwise note as "N/A."

Pregnancy is not reported as an adverse event, but some studies will require unique considerations if pregnancy was to occur during the study (e.g., discontinuation of a diet-based intervention or imaging assessments).

State the study's pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to the NIH, other oversight committee, 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>

8.4 UNANTICIPATED PROBLEMS

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

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

The reporting of Unanticipated Problems (UPs) applies to non-exempt human subjects research conducted or supported by DHHS. Provide the definition of an UP being used for this clinical trial. UPs include situations that arise during the course of a study but are not directly related to study procedures (e.g., subject information stored on an encrypted laptop is compromised when the laptop is stolen; receipt of wrong dose or contaminated **study** medication; complaint from a participant or family member of a participant*). 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 consenting/enrollment of new participants or halting of study procedures for consented/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 consented/enrolled participants*.

[This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). 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.]

8.4.2 UNANTICIPATED PROBLEMS 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 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/funding agency 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/funding agency 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]

*See **CD Section 8.4.1** for additional example text applicable for devices.*

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Include content in this section if applicable, otherwise note as "N/A." Describe how participants will be informed about UPs on an individual or aggregate level.

<Insert text>

9 STATISTICAL CONSIDERATIONS

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

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

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

State whether the statistical plan will be posted publicly or registered before the study begins. If pre-registration is planned, describe where the analysis plan will be posted or registered, and what information will be provided at the time of analysis registration.

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of analysis (e.g., feasibility/acceptability, efficacy, effectiveness, implementation) and time period for which each endpoint will be analyzed. Include this information for each hypothesis being tested, if multiple hypotheses are present. If the study is intended as a feasibility or pilot study, please consider that a formal hypothesis may not be available at the time of protocol writing. If so, include a statement indicating that hypotheses will be generated or that descriptive statistics only will be calculated.

- Primary Endpoint(s):

[We hypothesize that, compared to patients who receive a psychoeducation control intervention, patients who receive Cognitive Behavioral Therapy for dental fear will have reduced dental fear after completing the therapy which, in turn, will lead to better oral health one year after treatment.

Alternatively, our null hypothesis is that there will be no difference in the effects of Cognitive Behavior Therapy for dental fear and psychoeducation at one year post-therapy.]

<Insert text>

- Secondary Endpoint(s):

<Insert text>

9.2 SAMPLE SIZE DETERMINATION

Include number of participants to have adequate power to test the primary hypothesis for the study. Provide all information needed to support the proposed calculations and judge the feasibility of enrolling and following the necessary number of participants. In particular, specify all of the following, including for secondary hypotheses, as appropriate to your planned relevant analysis:

- *Outcome measure used for calculations (almost always the primary endpoint variable)*
- *Test statistic and statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Null and alternative hypotheses*
- *Type I error rate (alpha) and any adjustments for multiple outcomes tested*
- *Power level (e.g., 90% power) based on effect size of "X" and attrition rate of Y*
- *For group- or cluster-randomized study trials and individually randomized group-treatment trials, report estimates of intraclass correlation, kappa, or equivalent, with justification, and document methods for sample size calculation. Include a sensitivity analysis reflecting the impact of potential differences between the estimate and the realized value of the intraclass correlation or equivalent, the number of clusters per arm, and the size and variability in the size of those clusters.*
- *Effect size (outcome mean and variance) or range of effect sizes to detect with justification for the validity of this effect size from previous research (include citations)*
- *Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*
- *Anticipated impact of dropout rates, withdrawal, cross-over to other study arms, missing data, etc. on study power (see also **Section 9.4.2, Analysis of the Primary Efficacy Endpoint(s)** and **Section 9.4.3, Analysis of the Secondary Endpoint(s)**)*
- *Method for adjusting calculations for planned interim analyses, if any (see **Section 9.4.6, Planned Interim Analyses**)*
- *For a qualitative analysis include a sampling plan that addresses participant selection (e.g., theoretical sampling or purposive sampling), as well as how the determination that adequate sample data has been attained (for example, theoretical saturation). Specific criteria should be provided for determining when this sample size is achieved (e.g., when three successive interviews are conducted with no new themes detected and all the key demographic characteristic variations have been represented). Cite support for these decisions.*
- *For a cluster-randomized or individually randomized group-treatment trial, report estimates of intraclass correlation, kappa or equivalent, with justification, and document methods for sample*

size calculation. Include a sensitivity analysis reflecting the impact of potential differences between the estimate and the realized value of the intraclass correlation or equivalent, the number of clusters per arm or condition, and the size and variability in the size of those clusters.

- *For a Bayesian (non-frequentist) approach, include any simulation results as appendices and describe the choice of priors. For fixed-N designs, provide the expected distribution of Bayes factors or a justification for not using these factors. For sequential designs, describe the desired strength of evidence or stopping rule, what range of sample sizes are expected, and what is the probability of misleading evidence.*

In some cases, it may be useful to perform a sensitivity analysis to establish the smallest effect size that could be detected given the computed sample size and to indicate what the anticipated effect size might be.

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

Discuss whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term, ***Section 9.4.9, Exploratory Analyses****). Whenever possible, report the power for all secondary endpoints, using the computed sample size and data in the literature to guide those estimates.*

<Insert text>

9.3 POPULATIONS FOR ANALYSES

Clearly identify and describe the analysis populations (e.g., which participants will be included in each). As a guide, this may include, but is not limited to, any or all of the following:

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

<Insert text>

9.4 STATISTICAL ANALYSES

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

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

9.4.1 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 qualitative research, describe how procedural and interpretive rigor will be monitored and maintained*
- *For inferential tests, indicate the p-value and confidence intervals for statistical significance (Type I error) and whether one or two-tailed*
- *Indicate whether covariates will be pre-specified in the sections below or later in a SAP*
- *State whether checks of assumptions (e.g., normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests)*

<Insert text>

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

For each primary endpoint:

- *Describe how the primary endpoint is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure*
- *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide a rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here.*
- *For cluster-randomized or individually randomized group-treatment trials describe a) how the analyses will reflect the expected positive within-group correlation and b) how the analyses will account for any heterogeneity in that correlation that may be expected among study arms or conditions as a function of the study design*
- *If fitting a repeated measures model, describe how the variance and covariance across repeated measures will be calculated*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
- *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)*
- *Describe the Populations for which the analysis will be conducted, as discussed in* ***Section 9.3, Populations for Analyses***

- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, non-adherence and lost to follow-up*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary*

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

<Insert text>

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint*
- *Describe how each secondary endpoint is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure*
- *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, mediation or moderation analyses, multilevel modeling, MANOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors or effect size*
- *For group- or cluster- randomized trials and individually randomized group-treatment trials, describe how the analyses will reflect the expected positive within-group correlation and how any heterogeneity in that correlation that may be expected among study arms as a function of the study design*
- *Describe details to check assumptions required for certain types of analyses (e.g., checks on assumptions of normality, transformations or, when appropriate, nonparametric tests)*
- *Describe the Populations for which the analysis will be conducted as discussed in* ***Section 9.3, Populations for Analyses***
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, non-adherence and lost to follow-up*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary*

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

<Insert text>

9.4.4 SAFETY ANALYSES

This section is not applicable for most behavioral clinical trials.

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 the 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., expectedness, 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 Assessments****.*

<Insert text>

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Include content in this section if applicable, otherwise note as "N/A."

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

<Insert text>

9.4.6 PLANNED INTERIM ANALYSES

Include content in this section if applicable, otherwise note as "N/A."

Protocols should specify a priori whether there are plans for conducting any analyses of primary and secondary outcome data before the study is completed. This clarification is required for all studies in order to verify that, if such analyses are planned, they are fully integrated into the sample size and analyses plans. Therefore, 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, futility or efficacy), 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 intervention for safety, including whether they pertain to the entire study, specific study arms or participant subgroups, or other components of the study. 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.

State how endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed halting guidelines.

Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

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

<Insert text>

9.4.7 SUB-GROUP ANALYSES

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

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

For group- or cluster randomized trials and individually randomized group-treatment trials, describe how sub-group analyses will reflect the expected positive within-group correlation and how any heterogeneity in that correlation may be expected among study arms as a function of the study design.

<Insert text>

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

<Insert text>

9.4.9 EXPLORATORY ANALYSES

All planned exploratory analyses should be specified in the protocol.

<Insert text>

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

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

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

10.1.1 INFORMED CONSENT PROCESS

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

The following subsections should describe the procedures for obtaining and documenting informed consent of study participants. State if a separate screening consent will be used. If a separate screening consent will not be used, the study consent must be signed prior to conducting study screening procedures.

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

This section should demonstrate that the consent form contains all required regulatory elements. List all consent 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 will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol <insert list>.]

<Insert text>

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of language other than English. Any procedures for determining competency and assessing comprehension/understanding should be included here as well as 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 are emancipated during a study.*

<Insert text>

10.1.2 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 ongoing study participants, the IRB, and sponsor/funding agency and provide the reason(s) for the termination or temporary suspension.

When a study is prematurely terminated, refer to ***Section 7, Study Intervention/Experimental Manipulation Discontinuation and Participant Discontinuation/Withdrawal****, for handling of consented/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, 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/funding

agency 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 of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).]

<Insert text>

10.1.3 CONFIDENTIALITY AND PRIVACY

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

Include procedures for maintaining participant confidentiality, privacy protections, any special data security requirements, and record retention per the sponsor's and/or funding agency requirements. Describe who will 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 companies or organizations supplying the product or device 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*
- *Indicate who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access*

- *Discuss any additional features to protect confidentiality (e.g., use of a certificate of confidentiality)*

For some studies, 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. If the researcher obtains informed consent for research covered by a Certificate of Confidentiality (automatically granted to NIH funded clinical research), NIH expects that the researcher will tell participants about the protections afforded by the Certificate and any exceptions to that protection. Refer to the NIH Certificate of Confidentiality Kiosk for more details and suggested consent language.

Example text provided as a guide, customize as needed:

[Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

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

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the 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/funding agency 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>.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.]

<Insert text>

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

If specimens or data 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 questionnaires/assessment data, specimens, images, audio or video recordings, and other individual level participant data. 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). Describe how long these data will be used by the investigative team and if/when these data will be made publicly available on a data repository or data enclave. 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>

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor or Independent Safety Monitor. Update table heading to remove non-relevant role.

Principal Investigator	**Medical Monitor or Independent Safety 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.

Consider clarifying the process for how study staff and participants can report study misconduct. Consider the institution(s) guidelines when developing a plan. When applicable, clarification of the study participant reporting would be included in the informed consent document.

<Insert text>

10.1.6 SAFETY OVERSIGHT

Every trial must have appropriate safety oversight. This could include study team self-assessments, usually guided by sub-components of a Quality Management Plan (see Section 10.1.8) or assessments conducted by an independent monitor, committee or board. Examples of independent safety oversight include a Safety Monitoring Committee (SMC), Data Safety Monitoring Board (DSMB), Safety Assessment Committee (SAC), and/or an Independent Safety Monitor (ISM)[1]. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety and data integrity in the study. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB.

Example text provided as a guide, customize as needed:

[Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB)/Safety Monitoring Committee (SMC) composed of individuals with the appropriate expertise, including <list expertise>. Members of the SMC will be independent from the study conduct and free of conflict of interest. The SMC will meet at least semiannually to assess safety and efficacy data from each arm of the study. The SMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the SMC needs to assess will be clearly defined. The DSMB will provide its input to <specify the study sponsor/National Institutes of Health staff/other>.]

<Insert text>

10.1.7 CLINICAL MONITORING

Clinical monitoring refers to activities of an independent party or group to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved

[1] An Independent Safety Monitor (ISM) is a physician, nurse, or other individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s). Not all studies will involve clinical monitoring by an independent party (e.g., a clinical research organization). For studies for which monitoring responsibilities will be handled internally, mark this section N/A, and describe self-monitoring activities in ***Section 10.1.8, Quality Assurance and Quality Control****.*

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

If a separate CMP exists, it should cover the following detail. Otherwise this detail should be included in the protocol. Consider the prevention and/or mitigation of important and likely risks, identified by a risk assessment, to critical data and processes. The types (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification)) of monitoring activities will depend on a range of factors, considered during the risk assessment, including the complexity of the study design, types of study endpoints, clinical complexity of the study population, geography, relative experience of the PI and of the sponsor with the PI, electronic data capture, relative safety of the study intervention, stage of the study, and quantity of data.
Example text provided as a guide, customize as needed:

[Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be as follows:]

If a separate CMP will be created, use the following example text as a guide; customize as needed:

[

- Monitoring for this study will be performed by <insert text>
- <Insert brief description of type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables)>
- <Insert text> will be provided copies of monitoring reports within <x> days of visit
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP]

OR

If a separate CMP will not be created, use the following example text as a guide; customize as needed: The following text can be used when an independent, external group is monitoring the site. If a site is conducting its own monitoring activities, those activities should be described in ***Section 10.1.8, Quality Assurance and Quality Control*** *and/or in a separate Quality Management Plan.*

[

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

<Insert text>

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

This section should briefly describe the plans for quality management, which encompasses quality assurance (QA)[2] and quality control (QC). Confer with your Program Official as to whether a separate Quality Management Plan is required.

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

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

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

*Regular monitoring and an independent audit, if conducted, must be performed according to ICH GCP. See also **Section 10.1.7, Clinical Monitoring**.*

Example text provided as a guide, customize as needed:

[Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.]

<Insert text>

10.1.9 DATA HANDLING AND RECORD KEEPING

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

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored or NIH-affiliated study, each site will permit

authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Indicate who will have access to records.

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

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Provide details regarding the type(s) of paper and electronic data capture that will be used for the study and any relevant data standards or common data elements that are being utilized as a part of the trial. Consider a brief note if there are data quality checks included in the data management system. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs. Further details should be provided in the MOP or the Data Management Plan (DMP), including detailed descriptions of source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring.

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

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

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

Provide a list of planned data standards, formats, terminologies and their versions, used for the collection, tabulation, and analysis of study data.

Example text provided as a guide, customize as needed:

[Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

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

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.]

<Insert text>

10.1.9.2 STUDY RECORDS RETENTION

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

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

Study intervention records may be described here if not addressed elsewhere in the protocol.

Example text provided as a guide, customize as needed:

[Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the

formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.]

<Insert text>

10.1.10 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. Protocol deviations are expected in some studies, and procedures for identifying and tracking expected deviations should be included in this section.

Example text provided as a guide, customize as needed:

[This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council 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 will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It will be 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 will be addressed in study source documents, reported to <specify NIH Institute or Center (IC)> Program Official and <specify Data Coordinating Center or sponsor>. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be 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>

10.1.11 PUBLICATION AND DATA SHARING POLICY

The publication and data sharing policies should be described in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for*

developing publication procedures and resolving authorship issues. Please refer to your specific contract, grant, and/or Clinical Trials Agreements. If details of the publication policy will be described in the study's MOP, refer to it here. The study must comply with:

- *The NIH Public Access Policy, the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, The Food and Drug Administration Amendments Act of 2007 (FDAAA), Clinical Trials Registration and Results Information Submission,*
- *The NIH Data Sharing Policy (if applicable),*
- *The NIH Genomic Data Sharing Policy, (if applicable), and*
- *The NIH Data Sharing Policy and Implementation Guidance,*
- *Any other relevant policies (e.g., NIH IC-specific data sharing or publication policy)*

Example text provided as a guide, customize as needed:

[This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.]

<Insert text>

10.1.12 CONFLICT OF INTEREST POLICY

This section should include a description of how the study will manage actual or perceived conflicts of interest.

Example text provided as a guide, customize as needed:

[The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the <specify NIH Institute or Center (IC)> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.]

<Insert text>

10.2 ADDITIONAL CONSIDERATIONS

This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or IRB-related requirements.

<Insert text>

10.3 ABBREVIATIONS AND SPECIAL TERMS

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). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

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 Council 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
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
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

10.4 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

11 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE).

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.