Tool Summary Sheet:

NIDCR Interventional Protocol Template

**Purpose**: To provide an instructional template for use in development of a protocol for studies using an intervention (biomedical or behavioral)

NOTE: If the protocol is for a Phase 2 or 3 clinical trial funded by the National Institutes of Health (NIH) that is being conducted under a Food and Drug Administration (FDA) Investigational New Drug (IND) or Investigational Device Exemption (IDE) Application, investigators are encouraged to use the NIH protocol template found here: <https://osp.od.nih.gov/clinical-research/clinical-trials/>.

Audience/User

Principal Investigators and Study Staff

Details

This document is the National Institute of Dental and Craniofacial Research (NIDCR) protocol template for an interventional study that is NOT a phase 2 or 3 clinical trial being conducted under an IND or IDE Application.

The NIH defines a [clinical trial](https://grants.nih.gov/policy/clinical-trials/definition.htm) as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. However, researchers conducting studies with interventions that do not meet the NIH definition of a clinical trial may consider using this template. This protocol template is based on the essential protocol elements in Section 6 of the [ICH E6 guideline for Good Clinical Practice](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf). The template will assist investigators in preparing an interventional study protocol that meets NIDCR standards and includes all elements required for an Institutional Review Board (IRB) to assess study risks and benefits.

Best Practice Recommendations

* The IRB’s risk assessment and the complexity of the study are used by the NIDCR to determine the resources needed to meet the Institute’s study oversight responsibilities. Based on the potential risk for participants and the complexity of the study, the NIDCR Medical Monitor will provide guidance on the appropriate level of data and safety monitoring. Investigators should consult the NIDCR Program Official when writing the protocol template sections on Assessment of Safety, Study Oversight, and Clinical Site Monitoring.
* The Grantee Institution may have an IRB-specified protocol format. Use of that IRB format is acceptable to NIDCR, provided the necessary elements (the section headings included in the template table of contents) are included in the protocol. A grant application is generally not acceptable as a protocol. Pasting text from the grant application will not usually meet the requirements for an acceptable protocol.
* Changes to the protocol via an amendment cannot be implemented until IRB approval is received.
* Terminology has been consistently applied throughout this template but can be updated to reflect appropriate study-specific terminology (e.g., participant / subject, case report form / data collection form).
* The Study Intervention section (Section 6) of this template includes sub-sections for:
1. Study Product, such as an investigational or approved drug or device (Sections 6.1 - 6.6);
2. Behavioral Intervention (Sections 6.7 - 6.10) and;
3. Procedural Intervention (Section 6.11 - 6.14).

Choose the appropriate section that matches the type of study intervention planned and delete the other sections.

* Refer questions regarding use of this protocol template to the appropriate NIDCR Program Official or the NIDCR Office of Clinical Trials Operations and Management (OCTOM).

Technical/Formatting Notes

* In the template, instructions for each section are included in *{blue italics}* (“CROMS\_Instruction” style). Instructional text will also be enclosed in braces to signify this text for screen-readers used by the visually impaired. As you complete a section, **delete the instructions.**
* Where sample text is included in standard font, you may include it in your protocol as written or modify as needed for your study. Sample text is set off by the introductory instructional text *{Begin sample text}* and closing instructional text *{End sample text}*. Remove this instructional text if you use the sample text.
Note: Sample text may contain additional embedded instructional text. As you complete a section, **delete the embedded instructions.**
* Required protocol text is set off by the introductory instructional text *{Begin required text}* and the closing instructional text *{End required text}*. Remove this instructional text while maintaining the required text in the document.
Note: Required text may contain additional embedded instructional text. As you complete a section, **delete the embedded instructions.**
* Text enclosed with < > is a placeholder for a specific detail (e.g., <protocol title>); replace as appropriate, and remove < >.
* It is not necessary to include text under a major numbered heading (e.g., 1, 2) that is immediately followed by numbered subheadings, (e.g., 2.1, 2.2). That is because certain numbered headings are used only for organizational purposes. Text should be entered under all applicable numbered subheadings. Enter N/A in subsections that are not applicable to the study. See <Insert text> notations for guidance.
* It is easiest and cleanest to use the styles that are embedded in the document, rather than to create your own.
* Protocol version control: Refer to NIDCR Version Control Guidance. Primary author controls version number and date, which appear on title page and header/footer of each protocol page. Use 0.1, 0.2, 0.3, etc., for early drafts of the protocol. Once all NIDCR and study team comments have been resolved, re-label last draft version 0.x as final version 1.0 for IRB submission. When drafting an amendment to an IRB-approved protocol, use the protocol whole version number with draft numbers in the decimal. For example, version 2.1 is the first draft of an amendment to protocol version 2.0. When the final draft of this amended protocol is ready for IRB review, change the version number to Version 3.0 before IRB submission.
* Versioning includes both a version number and version date. When the version number and date change, be sure to update them in the header of each section of the protocol.
* Remove this Tool Summary Sheet before use.

Tool Revision History:

Version

| **Number** | **Date** | **Summary of Revisions Made:** |
| --- | --- | --- |
| 3.0 | 11Feb2013 | Original version with Tool Summary Sheet. |
| 4.0 | 03Jan2014 | Revised text regarding Safety Oversight method, Final Statistical Analysis, Data Sharing, and Clinical Site Monitoring; clarified instructional text and added text placeholders. |
| 5.0 | 11Mar2019 | Edits made to improve clarity and utility, and align with NIH policies and current standards |

<Title>

NIDCR Protocol Number: <number provided by NIDCR>

NIDCR Grant Number:

Principal Investigator:

**Grantee Institution:**

NIDCR Program Official:

NIDCR Medical Monitor:

****IND/IDE Sponsor:**** <sponsor name, if applicable; do not include IND/IDE number>

Draft or Version Number: <x.x>

<Day Month Year>

STATEMENT OF COMPLIANCE

{Begin required text}

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (GCP) (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). 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.

{End required text}

SIGNATURE PAGE

{Begin required text}

The signature below constitutes the approval of this protocol and the attachments, 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.

Principal Investigator or Clinical Site Investigator:

Signed: Date:

Name:

Title:

{End required text}

{For multi-site studies, the protocol should be signed by each of the clinical site investigators, i.e., the individual who is responsible for the day to day study implementation at his/her specific clinical site. For a clinical trial involving an Investigational New Drug (IND), this is the individual who signs the Form FDA 1572 for a drug or the investigator agreement for a device.}

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LIST OF ABBREVIATIONS

{In this section, please add all disease or study-specific abbreviations/acronyms that appear in the protocol document. Remove abbreviations that are not used in the document (deleting the table row in which they appear).}

|  |  |
| --- | --- |
| AE | Adverse Event/Adverse Experience |
| CFR | Code of Federal Regulations |
| CSI | Clinical Site Investigator |
| CIOMS | Council for International Organizations of Medical Sciences |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DMFS | Decayed, missing, and filled tooth surfaces |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| FFR | Federal Financial Report |
| FWA | Federalwide Assurance |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator’s Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ICMJE | International Committeeof Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| MOP | Manual of Procedures |
| N | Number (typically refers to participants) |
| NDA | New Drug Application |
| NIDCR | National Institute of Dental and Craniofacial Research, NIH, DHHS |
| NIH | National Institutes of Health |
| OCTOM | Office of Clinical Trials Operations and Management, NIDCR, NIH |
| OHRP | Office for Human Research Protections |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PO | Program Official, NIDCR, NIH |
| PS | Project Scientist, NIDCR, NIH |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| US | United States |
| WHO | World Health Organization |

PROTOCOL SUMMARY

{Limit to 1-2 pages; put key words in boldface in Protocol Summary.}

|  |  |
| --- | --- |
| **Title:** |  |
| **Précis:** | <A brief overview of the study design, including study groups, schedule of interventions, schedule for specimen or data collection, and analyses to be performed.> {The précis should be only a few sentences in length. A detailed schematic describing all visits and assessments (schedule of events) should be included as Appendix A.} |
| **Objectives:** | <Insert objectives copied from the body of the protocol. Include the primary objective and secondary objectives and specify outcome measures.>Primary: Secondary:  |
| **Population:** | <Population information, including sample size, gender, age, demographic group, general health status, geographic location.> |
| **Phase or Stage:** | <Enter Phase or Stage if applicable; consider FDAAA implications and consult with NIDCR Program Official if needed> |
| **Number of Sites:** | <Insert a list of sites if 3 or fewer sites; for more than 3 sites, insert the number of sites only, and list the sites in Section 1.>  |
| **Description of Intervention:** | <Describe the intervention. If intervention is a drug, include dose and route of administration. For a non-pharmaceutical study (device, procedure or behavioral intervention), provide brief description.> |
| **Study Duration:** | <Estimated time (in months) from when the study opens to enrollment until completion of data analyses.> |
| **Subject Participation Duration:** | <Time it will take to conduct the study for each individual participant.> |
| **Estimated Time to Complete Enrollment:** | <Estimated time from enrollment into study of the first participant to enrollment into study of the last participant.> |

**Schematic of Study Design:**

{The diagram below shows the preferred format and the level of detail needed to convey an overview of study design. Complete each text box 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). The time point(s) indicated in the schematic should correspond to the time point(s) in Section 7 of the protocol, Study Schedule (e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7).}

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

Perform baseline assessments.

(*list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed*)

Administer initial study intervention.

Follow-up assessments of outcome measures and safety

(*list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed*)

Follow-up assessments of outcome measures and safety

(*list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed*)

**Final Assessments**

*List analyses to be performed*

Randomize

Repeat study intervention (*if applicable*).

Prior to Enrollment

Visit 1
Time Point

Visit 2
Time Point

Visit 3
Time Point

Visit 4
Time Point

Visit X
Time Point

#

# KEY ROLES AND CONTACT INFORMATION

{Provide the following information for each individual:

Name, degree, title

Institution Name

Address

Phone Number

Fax Number

Email}

|  |  |
| --- | --- |
| **Principal Investigator:**  | <Site investigator responsible for conducting the study>  |
| **Medical Monitor:** | {Insert Medical Monitor name and contact information and indicate if he/she is the NIDCR Medical Monitor, appointed by the study or appointed by the NIDCR}  |
| **NIDCR Program Official:** |  |
| **Clinical Site Investigators:** | <if applicable, investigator name, institution> |
| **Institutions:** | {List study sites, clinical laboratory(ies), data coordinating centers, and other medical or technical departments and/or institutions, as applicable. Provide the following information for each organization or institution:Institution NameAddressContact Person/Local InvestigatorPhone NumberFax NumberEmail}  |
| **Other Key Personnel:** | {Consider listing, for example:* For a study with a non-clinically trained PI, the qualified individual responsible for study clinical examinations and safety assessments
* Collaborating Program Officials from other National Institutes of Health Institutes or Centers
* Major international collaborators, if not included as site investigators
* Protocol data manager
* Epidemiologist
* Statistician}
 |

# INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## Background Information

<Insert text>

{This section should include brief background information for this study. It should not be a copy of the background information from a grant application. In a protocol, the tone of the text should be informative, not persuasive as in a grant application. Avoid expressing bias or assumptions about study outcomes.

Include:

* A brief description of the health problem that the study will address
* The name and description of the study intervention/study product(s)
* Discussion of important research relevant to the study that provides background and scientific justification for the study (include findings from in vitro studies, preclinical in vivo studies, and relevant clinical studies)
* Applicable clinical, epidemiological, or public health background or context of the study
* Importance of the study and any relevant treatment issues or controversies}

## Rationale

<Insert text>

{State the reason for conducting the study. Include, as applicable, information about the population, disease or condition, current standard of care (if one exists), and limitations of knowledge or available therapy. Include a statement of the study hypothesis.}

## Potential Risks and Benefits

{No text is to be entered under this section heading; include text in the relevant subsections below. Include in subsections 2.3.1 and 2.3.2 a discussion of known risks and benefits, if any, to human subjects. Be sure that information in these subsections is consistent with your consent document.

NOTE: This information will be used to determine whether an event is “Expected” and therefore not an unanticipated problem requiring expedited reporting.}

### Potential Risks

<Insert text>

{Describe in detail any physical, psychological, social, legal, economic, or any other anticipated risks to study participants. Include risks of study intervention and other study procedures. Briefly describe procedures that will be followed to help mitigate risks.

One or more of the following may serve as the source of risk information:

* Package insert for a licensed product
* Investigator’s Brochure (IB) for an investigational product
* Preclinical data reports
* Literature search and review (include references)}

### Potential Benefits

<Insert text>

{If the research is beneficial, describe any physical, psychological, social, legal, or any other anticipated benefits to participants. While it may not provide direct benefit to participants, the importance of the knowledge that may result from the study may be mentioned.

Note: Compensation to participants is not considered a “benefit.” See Strategies for Recruitment and Retention, Section 5.3.}

# OBJECTIVES AND OUTCOME MEASURES

{In the subsection tables that follow, provide a detailed description of the one primary objective and any secondary or tertiary objectives of the study. An objective is the reason for performing the study in terms of the scientific question to be answered. The primary objective is the main question. This objective generally drives statistical planning for the study (e.g., calculation of the sample size to provide the appropriate power for statistical testing). Secondary objectives are goals that will provide further information on the use of the intervention.

For behavioral and social intervention studies, common primary objectives are to determine the efficacy or effectiveness of an intervention, or to test a proposed mechanism of action of an intervention. Common secondary objectives are to identify mediators or moderators of an intervention effect.

Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include:

* General purpose (e.g., feasibility, acceptability, efficacy, safety, tolerability, pharmacokinetics) and/or specific purpose (e.g., dose-response, superiority to placebo, mechanisms of action, effect of an intervention on disease incidence, disease severity, or health behavior)
* Name(s) of intervention (e.g., procedure, drug, biologic, behavioral intervention) being evaluated, specification of doses or dose ranges to be studied, dose regimens, intervention frequency}

In the tables, give succinct but precise definitions of the outcome measures used to address the study’s primary objective and key secondary or tertiary objectives. An outcome measure is a specific measurement or observation used to assess the effect of the study intervention (e.g., safety as defined by specific laboratory tests or occurrence of adverse events, or efficacy, as defined by laboratory tests, clinical assessments of disease status, assessments of psychological characteristics, assessments of individual or group oral health behaviors, assessments of healthcare visit attendance). Outcome measures should be prioritized and should correspond to the study objectives and hypotheses being tested. Include the study visits or time points at which each outcome will be assessed. Additional subsections may be added to accommodate tertiary/exploratory objectives, if applicable. Delete tables that do not apply (i.e., secondary and/or tertiary outcome measure table(s)).}

## Primary

| **Objective** | **Brief Description/Justification of Outcome Measure** | **Outcome Measured By**  | **Time Frame** |
| --- | --- | --- | --- |
| <Insert text>{The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).}. | <Insert text>*{Briefly explain why the outcome measure was chosen. The primary outcome measure’s importance and role in the analysis and interpretation of study results should be clear. The primary outcome measure is the basis for concluding that the study met its objective. Generally, there should be just one primary outcome that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary outcomes may require an adjustment to the sample size calculations and p-value threshold. However, this is not always the case. For example, in many trials of medical devices there are primary outcomes for both safety and effectiveness.* In a trial designed to establish efficacy, a primary outcome measure should represent a clinically meaningful effect or should have demonstrated ability to predict clinical benefit. For behavioral or social intervention studies testing for efficacy or effectiveness, there may be several indicators of a primary outcome of interest (e.g., pain, parenting, oral hygiene). For behavioral or social intervention studies testing something other than efficacy or effectiveness, describe the outcome measures to be included in the analysis that are most central to the primary study objective. Identify the hypothesized role that each outcome measure plays in the study hypotheses (e.g., moderator, mediator, covariate).} | <Insert text>{Briefly state how the primary outcome measure will be assessed (e.g., instrument name, biomarker assay, radiograph).} | <Insert text>{Include the study visits or time points at which each primary outcome measure will be assessed.} |

## Secondary

| **Objective** | **Brief Description/ Justification of Outcome Measure** | **Outcome Measured By**  | **Time Frame** |
| --- | --- | --- | --- |
| <Insert text>{Briefly state the secondary objective(s). The secondary objective(s) are goals that will provide further information on the use of the intervention.} | <Insert text>{Briefly explain why the outcome measure was chosen. Secondary outcomes may include, for example, outcomes related to efficacy, safety, or both. Secondary outcomes are those that may provide supportive information about the study intervention’s effect on the primary outcome or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary outcomes be short, because the chance of demonstrating an effect on any secondary outcome after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases.}  | <Insert text>{Briefly state how the secondary outcome measure(s) will be assessed (e.g., instrument name, biomarker assay, radiograph).} | <Insert text>{Include the study visits or time points at which each secondary outcome measure will be assessed.} |
| <Insert text> | <Insert text> | <Insert text> | <Insert text> |

## Tertiary/Exploratory

| **Objective** | **Brief Description/Justification of Outcome Measure** | **Outcome Measured By**  | **Time Frame** |
| --- | --- | --- | --- |
| <Insert text>{Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.} | <Insert text>{Briefly explain why the outcome measure was chosen. Tertiary/exploratory outcomes 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.Outcomes that are not listed in an alpha conserving plan will be considered exploratory.} | <Insert text>{Briefly state how the tertiary/exploratory outcome measure(s) will be assessed (e.g., instrument name, biomarker assay, radiograph).} | <Insert text>{Include the study visits or time points at which each tertiary/exploratory outcome measure will be assessed.} |
| <Insert text> | <Insert text> | <Insert text> | <Insert text> |

# STUDY DESIGN

<Insert text>

{The scientific integrity of the study and the credibility of the data from the study depend substantially on the study design. Include a brief paragraph or bulleted text describing the study design. This section should include:

* A brief description of the type/design of study to be conducted, including:
	+ intervention model (e.g., dose escalation, single group, parallel, cross-over, factorial, sequential)
	+ masking (open label or masked and those who will remain masked throughout the study duration – e.g., participant, care provider, investigator, outcomes assessor)
	+ Allocation (e.g., randomized, non-randomized)
* A description of the study population and the rationale for selection of the population (e.g., healthy/sick, inpatient/outpatient, demographic groups). Do not list inclusion/exclusion criteria here, as these will be listed in Sections 5.1 and 5.2.
* A brief discussion of the rationale for design features
* Phase of trial, if applicable
* Single or multicenter
* The number of study groups/arms
* Description of study groups/arms including sample size (including a table, if appropriate); stratifications that will affect enrollment
* Approximate time to complete study enrollment
* The expected duration of subject participation
* Identification and specifics of administration of the study intervention and its control or comparison, which may be placebo or current standard of care (e.g., drug (including placebo); device (including sham); biological/vaccine; procedure/surgery; radiation; behavioral (e.g. psychotherapy, lifestyle counseling); genetic (including gene transfer, stem cell and recombinant DNA); dietary supplement (e.g., vitamins, minerals)).
* Rationale for the dosage, dose regimen, route of administration, behavioral intervention method
* A brief description of the sequence and duration of all study periods, including follow-up (specify individual participants vs. entire study). Details of study visit schedules will be included in Section 7, Study Schedule.
* Planned variation in intervention dose or schedule (e.g., dose escalation)
* A brief summary of methods for collecting data for assessment of study objectives (detailed methods will be included in Section 8)
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)}

## Substudies (if applicable)

<Insert text>

{A substudy asks a separate research question from that of the parent protocol. It may or may not contribute to the parent protocol’s objectives but uses all or a subset of study participants or specimens from the main protocol.

A concept for a proposed substudy must be approved by the NIDCR Program Official. A substudy may be included in the main protocol or in a stand-alone protocol. If a substudy is added to the protocol for an ongoing study, a protocol amendment is required. List with brief description:

* Description of the substudy and its objectives
* Impact on main study
* Potential participating sites}

# STUDY POPULATION

{No text is to be entered under this section heading; include text in the relevant subsections below. In subsections 5.1 to 5.6, define the study population, describe participant recruitment, and discuss issues related to study intervention discontinuation, participant withdrawal and/or loss to follow-up. The study population should be appropriate for the stage of the study and the development stage of the study product or other intervention.

Use the following guidelines when developing participant eligibility criteria to be listed in subsections 5.1 and 5.2:

* The eligibility criteria should provide a definition of participant characteristics required for study entry.
* The risks of the intervention should be considered in the development of the inclusion/exclusion criteria so that risk is minimized.
* The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >32 years old as an inclusion criterion and age ≤32 years old as an exclusion criterion).
* Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment.
* If reproductive status (i.e., pregnancy, lactation, reproductive potential) is an eligibility criterion, provide specific contraception requirements (e.g., licensed hormonal methods).}

## Participant Inclusion Criteria

{Provide a statement that individuals must meet all of the inclusion criteria to be eligible to participate in the study and then list each criterion.}

{Begin sample text, adapt as needed for the study}

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

* Provide signed and dated informed consent form
* Willing to comply with all study procedures and be available for the duration of the study
* Male or female, aged <XX to XX>
* In good general health as evidenced by medical history *or* Diagnosed with specific condition/disease *or* Exhibits specific clinical signs or symptoms or physical/oral examination findings
* Laboratory results within a specific range
* Women of reproductive potential must use highly effective contraception *{specify methods of contraception acceptable for the study, e.g., licensed hormonal methods. See* [ICH M3 Guidance](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002941.pdf) *for information on highly effective contraception.}*
* Men of reproductive potential must use condoms *{if appropriate for study}*.

{End sample text}

## Participant Exclusion Criteria

{Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.}

{Begin sample text, adapt as needed for the study}

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

* Medical condition, laboratory finding, or physical exam finding *{specify, e.g., vital signs outside of specific range}* that precludes participation
* Use of disallowed concomitant medications *{specify medication and period of use that is exclusionary, if applicable}*
* Presence of <specific devices (e.g., orthodontic appliances, dentures)>
* Recent febrile illness that precludes or delays participation *{specify time frame}*
* Pregnancy or lactation
* Known allergic reactions to components of the study product(s)
* Treatment with another investigational drug or other intervention *{within a specified time frame}*
* History of or current tobacco, drug or alcohol use *{define parameters for exclusion}*
* Characteristics of household or close contacts *{e.g., household contacts who are immunocompromised, residence in same household as a participant already participating in study, if blinding or compliance could potentially be compromised}*
* Anything that would place the individual at increased risk or preclude the individual’s full compliance with or completion of the study.

{End sample text}

## Strategies for Recruitment and Retention

<Insert text>

{Identify strategies for participant recruitment and retention, addressing the following:

* Provide the target sample size by gender, race and ethnicity, and age; identify anticipated number to be screened in order to reach the target enrollment.
* Indicate from where the study population will be drawn (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public), and provide information about the availability of the study population in the identified setting(s). Where appropriate (single center studies), include names of hospitals, clinics, etc.
* Specify approach(es) for conforming with NIH policy on inclusion of individuals of all ages, and inclusion of women and minorities. Include information on the age of participants to be recruited and provide ethical or scientific justification for any age-related exclusion criteria. Also include information on the numbers of women and minorities to be recruited and provide justification if women and/or minorities will not be recruited.
* If appropriate, include justification for inclusion of vulnerable participants as defined in the Common Rule (45 CFR Part 46) and describe related recruitment strategies. Include safeguards for protecting vulnerable populations. Note that special protections apply if any participants are members of a vulnerable population, even if it that population is not specifically targeted for the study (e.g., if a participant becomes a prisoner during the study).
* Provide general information about recruitment strategies (e.g., flyers, newspaper advertising, social media, recruiting through patient advocacy groups).
* If participants will be compensated for study participation, describe amount and schedule of payments.
* If the study requires long-term subject participation, describe procedures that will be used to enhance subject retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).
* Describe the plans to minimize loss to follow-up and missing data. Participants are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures. The description should include when a participant will be considered lost to follow-up (e.g., if he or she fails to return for specified number of scheduled visits and is unable to be contacted by the study site staff) and whether the study design will accommodate replacing lost/withdrawn participants.}

## Treatment Assignment Procedures

<Insert text>

{This section should describe the methods of assigning participants to study groups, including randomization procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that masking or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not).}

### Randomization Procedures (if applicable)

<Insert text>

{Include plans for the maintenance of study randomization codes. The timing and procedures for planned and unplanned breaking of randomization codes should be included.}

### Masking Procedures (if applicable)

<Insert text>

{State whether the intervention arms will be masked if the study includes more than one intervention. Plans for maintaining appropriate masking for the study should be discussed. Refer to unmasking procedures described in the Manual of Procedures (MOP).}

## Participant Withdrawal or Discontinuation from Study Procedures/Intervention

{No text is to be entered under this section heading; include text in the relevant subsections below. Participants may voluntarily discontinue from the study intervention or withdraw consent for all participation in the study. The PI may also discontinue a participant from the study intervention or withdraw a participant from the study. If the participant does not withdraw consent, all attempts should be made to follow the participant, especially for safety and efficacy study endpoints (if applicable). The subsections below should state which adverse events would result in discontinuation of study intervention, how information about discontinuation of intervention or study withdrawal will be documented, and whether withdrawn study subjects will be replaced.}

### Reasons for Participant Withdrawal or Discontinuation from Study Procedures/Intervention

{Provide a list of reasons a participant may withdraw or an investigator may discontinue/withdraw participants from the study. It may be appropriate to provide distinct discontinuation criteria for participants/cohorts. If so, each set of criteria should be listed separately and the distinction between the criteria must be stated clearly. Also note that participants may withdraw or discontinue voluntarily from participation in the study at any time}

{Begin sample text, adapt as needed for the study}

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

Subjects may choose to discontinue the intervention or study procedure but continue to be followed.

An investigator may discontinue an individual’s participation in an intervention or withdraw an individual from the study if:

* Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
* The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

{End sample text}

### Handling of Participant Withdrawals from Study or Participant Discontinuation of Study Intervention

<Insert text>

{Describe efforts that will be made to capture reasons for participant withdrawal of consent or discontinuation from the study intervention/procedures. Consider requiring separate documentation for discontinuation of study intervention/procedures or participant withdrawal from the study. Describe the use of a dedicated Case Report Form (CRF) to capture the date and the specific underlying reason for discontinuation of study intervention, procedures or participant withdrawal. Also describe efforts that will be made to provide information or referral for care (if applicable). For participants who discontinue from the study intervention, describe efforts that will be made to continue follow-up, especially for safety and efficacy outcome measures (if applicable). Every effort must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (UPs).

This section should include a discussion of replacement of participants who withdraw consent or discontinue the intervention early, if replacement is allowed.}

## Premature Termination or Suspension of Study

{List possible reasons for termination or suspension of the study, e.g., study closure based on principal investigator (PI) decision, or NIDCR decision. For any study that is prematurely terminated or suspended, the PI will promptly inform the IRB and NIDCR and provide the reason(s) for the termination or suspension.}

{Begin sample text, adapt as needed for the study}

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency (NIDCR), the Investigational New Drug (IND) /Investigational Device Exemption (IDE) sponsor, and regulatory authorities>. The principal investigator will also promptly inform the IRB and NIDCR and will provide the reason(s) for the termination or suspension.

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

* Determination of unexpected, significant, or unacceptable risk to participants.
* Insufficient adherence to protocol requirements.
* Data that are not sufficiently complete and/or evaluable.
* Determination of futility.

{End sample text}

# STUDY INTERVENTION

{An interventional study may involve an investigational drug or device or an approved drug or device (Section 6.1), and/or a behavioral intervention (Section 6.7), and/or a surgical or other intervention (Section 6.11). Depending on the type of intervention(s) in your study, some of the sections below may not apply. Complete applicable sections and delete sections and subsections that do not apply (including headings). For example, if your study involves only a behavioral intervention, delete Sections 6.1 to 6.6 and 6.11 to 6.14; numbering of behavioral section headers will then automatically update, so that the first behavioral section becomes Section 6.1, etc. Include additional subsections, if necessary.}

## Study Product Description

<Insert text>

{**If the study does not use a study product, delete this section, including the heading and associated subheadings.**

Product information can usually be obtained from:

* Investigator’s Brochure, if available, for investigational drug or biologic
* package insert, for licensed drug or biologic
* proposed labeling and material safety data sheet (MSDS) for investigational device
* final labeling for a marketed device.

Provide this study product information to all investigators and NIDCR.

If multiple products are to be evaluated, this section and the following sections should be repeated for each product and the sections should be renumbered accordingly. Include sections to describe placebo or control product.}

### Acquisition

<Insert text>

{Describe how the study product will be acquired (e.g., an investigational product may be supplied by the manufacturer or IND/IDE sponsor, an approved product may be acquired from the hospital pharmacy).}

### Formulation, Packaging, and Labeling

<Insert text>

{Describe the formulation, packaging, and labeling of the study product as supplied.}

### Product Storage and Stability

<Insert text>

{Describe product’s storage needs. Include storage requirements and stability (temperature, humidity, security, and container).

For studies in which multidose vials are used, provide additional information regarding stability and product expiration time after initial use.}

## Dosage, Preparation and Administration of Study Product

<Insert text>

{List study product(s), route, doses, and frequency of administration. Include thawing, diluting, mixing, and reconstitution or other preparation instructions, as appropriate. Include any specific instructions or safety precautions for administration of study products, masking of the product, or the study staff administering it. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc.}

## Modification of Study Product Administration for a Participant

<Insert text>

{Clearly explain instructions for modification of dose due to toxicity or any other reason. Address dose modifications for specific abnormal laboratory values of concern or other AEs that are known to be associated with the planned intervention regimen. Do not restate reasons for withdrawal of participants. Cross-reference relevant sections, as appropriate.}

## Accountability Procedures for the Study Product

<Insert text>

{Provide plans for how the study product will be distributed, including participation of a drug repository, frequency of product distribution, amount of product shipped, device tracking procedures, and plans for return of unused product.}

## Assessment of Participant Compliance with Study Product Administration

<Insert text>

{If applicable, include in this section plans for compliance assessment (e.g., questionnaires, direct observation, pill counts).}

## Concomitant Medications/Treatments

<Insert text>

{This section should be consistent with the medications restrictions in the inclusion/exclusion criteria.

Describe the data that will be recorded related to permitted concomitant medications and/or treatments. Include details about when the information will be collected (at screening, at all study visits, etc.). Discuss any rescue treatments or medications that are included in the study design.}

## Study Behavioral or Social Intervention(s) Description

<Insert text>

{**If the study does not use a behavioral or social intervention, delete this section, including the heading and associated subheadings.**

Provide a general description of the behavioral and social intervention(s) included in this study. If one or more intervention(s) will be compared to a control intervention or to treatment as usual, include a general description of these. Detailed descriptions of behavioral or social intervention(s), including any intervention manuals, scripts, participant hand-outs, etc., can be provided in a separate Manual of Procedures (MOP).}

{Begin sample text, adapt as needed for the study}

This study will compare 3 behavioral interventions, each using a different approach to behavior change. The study intervention called “Coping Moments” teaches problem-solving skills, including anticipating challenging situations and developing strategies for coping with these. Coping Moments is a cognitive-behavioral intervention. The study intervention called “Motivating Moments” makes salient the participant’s ambivalence about behavior change, and empowers the participant to make behavior-change decisions. Motivating Moments is a motivation-based intervention. The control intervention called “Teaching Moments” provides participants information about the connection between daily tooth brushing and oral health. Teaching Moments is a psycho-educational intervention.

{End sample text}

## Administration of Intervention

<Insert text>

{Describe whether the intervention will be delivered in-person or in some other modality. If in-person, describe who will administer the intervention. If not in-person, describe how participants will access the intervention. Describe the number of sessions to be delivered, the frequency of session delivery, and the approximate duration of each session.}

## Procedures for Training Interventionists and Monitoring Intervention Fidelity

<Insert text>

{Describe the training and supervision of staff who will administer the intervention, or of staff who will facilitate participants’ accessing the intervention. Describe the procedures for monitoring intervention fidelity, including how interventionists’ fidelity to the intervention manual will be documented and assessed, what criteria will signal inadequate fidelity, and how re-training or replacement of interventionists will be managed. If audio or video recordings of sessions will be used to monitor intervention fidelity, describe the coding system to be used to extract fidelity data from these recordings, and how fidelity coders will be selected and trained.}

## Assessment of Participant Compliance with Study Intervention

<Insert text>

{If applicable, include in this section plans for compliance assessment (e.g., questionnaires, telephone follow-up contacts, direct observation).}

## Study Procedural Intervention(s) Description

<Insert text>

{**If the study does not use a procedural intervention, delete this section, including the heading and associated subheadings.**

Describe the dental, surgical, or other medical procedural intervention(s) that will be tested in the study. If one or more intervention(s) will be compared to a control intervention or to treatment as usual, include a general description of these. Detailed descriptions of the intervention(s), including any intervention manuals, detailed procedures, participant handouts, etc., can be provided in a separate Manual of Procedures.}

## Administration of Procedural Intervention

<Insert text>

{Include information about who will administer the intervention and how the intervention will be administered. In addition, describe the schedule of the intervention procedure(s), including the number of interventions, frequency of the intervention delivery, and the approximate duration of each intervention.}

## Procedures for Training of Clinicians on Procedural Intervention

<Insert text>

{Describe any means used to standardize the surgical or procedural intervention (e.g., single operator, calibration, images, minimal time of therapy required, specialized required instruments and/or materials, required measurements). Describe any re-standardization or re-evaluation procedures and time intervals between reassessments.}

## Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

<Insert text>

{If applicable, include in this section plans for compliance assessment (e.g., questionnaires, research record review, medical record review, laboratory result review, telephone follow-up contacts, direct observation).}

# STUDY SCHEDULE

{Information outlined in this section should refer to and be consistent with the information in the Schedule of Events in Appendix A and in Section 8.

Provide a schedule of initial, intermediate, and final study visits, and include all contacts with participants, e.g., telephone contacts. State permissible time windows for study visits, e.g., Day 7 ± 1 day (weekly visits will have a small window, whereas a 6-month follow-up visit might have a window of several weeks). When establishing visit intervals and windows, consider feasibility and relevance to study outcome measures, and take into account how weekends and holidays will affect the windows.

For each visit, identify the purpose and describe what will occur at the visit. If any of the procedures occurring at a visit are completed as part of standard clinical care rather than as study procedures, identify them as such.}

## Screening

{Include any evaluations necessary to assess whether an individual meets eligibility criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the time frame prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment).

This section must include instructions for obtaining signed informed consent. If screening procedures are required for eligibility (e.g., review of medical records, clinical examination, or laboratory tests), they may be performed under a separate screening consent form. State if a separate screening consent will be used. If a separate screening consent form will not be used, the study consent form must be signed prior to screening.

Confirm that the procedures listed are consistent with those included in the Schedule of Events (Appendix A).}

{Begin sample text, adapt as needed for the study}

**Screening Visit (Day -28 to -1)** *{include a window that is appropriate for the study}*

* Obtain and document consent from potential participant on screening consent form.
* Review medical/dental history to determine eligibility based on inclusion/exclusion criteria.
* Review medications history to determine eligibility based on inclusion/exclusion criteria.
* Perform medical/dental examinations needed to determine eligibility.
* Collect blood/urine/saliva.
* Schedule study visits for individuals who are eligible and available for the duration of the study.
* Provide potential participants with instructions needed to prepare for first study visit *{specify instructions to be provided}.*

{End sample text}

## Enrollment/Baseline

{Discuss evaluations/procedures necessary to assess or confirm whether an individual still meets the eligibility criteria and may be enrolled, and specify what will be recorded at baseline for later outcome measure comparison after study intervention (e.g., baseline signs and symptoms prior to treatment). Discuss the sequence of events that should occur during enrollment and/or initial administration of study product or intervention. List any special conditions (e.g., results of the pregnancy test must be negative and available prior to administration of study product or intervention). List the procedures for administering the study product or intervention and follow-up procedures after administration.

Confirm that the procedures listed are consistent with those included in the Schedule of Events (Appendix A).}

{Begin sample text, adapt as needed for the study}

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

* Obtain and document consent from participant on study consent form.
* Verify inclusion/exclusion criteria.
* Obtain demographic information, medical/dental history, medication history, alcohol, and tobacco use history.
* Record results of physical and dental examinations.
* Collect blood/urine/saliva/other specimen.
* Administer the intervention. Following administration of <intervention>
	+ Assess pain on visual analog scale
	+ Administer Symptoms Questionnaire

{End sample text}

## Intermediate Visits

{List each intervention or evaluation visit, including visit number and visit window. For each visit, list the procedures to be completed (in chronological order, if applicable).

Confirm that the procedures listed are consistent with those included in the Schedule of Events (Appendix A).}

{Begin sample text, adapt as needed for the study}

**Visit 2, Day X ± Y**

{Repeat for each visit, providing a study-appropriate window for the visit.}

* Record adverse events as reported by participant or observed by investigator.
* Record results of physical and dental examinations.
* Collect blood/urine/saliva.
* Administer the <intervention>.
* Record participant’s compliance with <intervention>.
* Following administration of <intervention>
	+ Assess vital signs
	+ Administer Symptoms Questionnaire

{End sample text}

## Final Study Visit

{Define when the final study visit should occur and if any special procedures/evaluations or instructions will be given to the participant. Describe provisions for follow-up of ongoing AEs/SAEs. If study results will be shared with participants, discuss when and how participants will receive this information.

Confirm that the procedures listed are consistent with those included in the Schedule of Events (Appendix A).}

{Begin sample text, adapt as needed for the study}

**Final Study Visit** **(Final Visit, Day X ± Y)**

* Record adverse events as reported by participant or observed by investigator.
* Record results of physical and dental examinations.
* Collect blood/urine/saliva.
* Record participant’s compliance with <intervention>.
* Provide final instructions to participant *{e.g., follow-up of ongoing adverse events, oral hygiene instructions}*.

{End sample text}

## Withdrawal Visit

<Insert text>

{If participant withdraws early or investigator terminates subject participation, specify which of the evaluations required for the final study visit should be offered to the participant.}

## Unscheduled Visit

<Insert text>

{Specify how unscheduled visits will be handled and documented.}

# STUDY PROCEDURES/EVALUATIONS

{Information outlined in the Procedures/Evaluations section should refer to and be consistent with the information in the Schedule of Events in Appendix A.

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

All procedures listed here should be specific to the study and not part of standard clinical care. Procedures completed during the study as part of normal standard of clinical care should be identified as such and summarized in a separate section.}

## Study Procedures/Evaluations

<Insert text>

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

* Medical history (describe what is included for history, e.g., time-frame considerations, whether history will be obtained by interview or from medical records).
* Medications history (e.g., describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter). Assessment of eligibility should include a review of permitted and prohibited medications.
* Physical examination (list the vital signs [including height and weight] and organ systems to be assessed. Address details in the MOP.); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur.
* Oral exams, including caries assessments or periodontal measurements.
* Radiographic or other imaging assessments.
* Biological specimen collection.
* Administration of questionnaires or other instruments for subject-reported outcomes, (e.g., daily diary). Describe the purpose and content of questionnaires. Specify by whom and how each questionnaire will be administered and who will be the respondents. State whether the questionnaire has been previously validated. Questionnaires may be provided to NIDCR in protocol appendices or as separate documents.
* Observation and coding of subject behaviors.}

## Laboratory Procedures/Evaluations

### Clinical Laboratory Evaluations

<Insert text>

{List all laboratory evaluations to be done as part of the study (e.g., hematology, clinical chemistry, urinalysis, pregnancy testing). Differentiate screening laboratories from those taken after treatment. Include specific test components and estimated volume and type of specimens needed for each test (or refer to the study’s MOP). Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory.}

### Special Assays or Procedures

<Insert text>

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

### Specimen Preparation, Handling, and Storage

<Insert text>

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

### Specimen Shipment

<Insert text>

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

# ASSESSMENT OF SAFETY

{Develop this section in consultation with the NIDCR Program Official and NIDCR Medical Monitor. To establish a meaningful safety system for the study, consider the risks of the study intervention and other study procedures as well as the characteristics of the study population (healthy individuals, individuals with disease, vulnerable populations such as children, etc.). This section should be tailored for specific study characteristics, including but not limited to the following:

* the study involves an investigational new drug or investigational device;
* the study procedures have risks separate from those related to the intervention;
* the study requires selection of an appropriate toxicity grading scale;
* the study involves risks to individuals other than research subjects (e.g., study interventionists, other study staff, family members or associates of study subjects, communities);
* reporting of certain events (e.g., suspected child abuse or substance abuse) is mandatory because of the study population or study design characteristics;
* the study is conducted at multiple sites, and will require centralized safety oversight.}

## Specification of Safety Parameters

<Insert text>

{Describe safety parameters that will be recorded in the study. “Recording” refers to documenting data in the study database. Recording events is critical for assessing whether an event must be reported. Define what data will require reporting to the IRB or to other individuals or groups (including NIDCR, IND sponsor, etc.) that are responsible for study oversight and protection of human subjects.

Unanticipated problems (UPs) must be recorded in the data collection system, and must be reported to the IRB and NIDCR in accordance with IRB-defined timelines. UPs include incidents, experiences, and outcomes that are not adverse events, as well as a subset of adverse events. Follow IRB policy for reporting other events to the IRB.

Include in this section a statement that all serious adverse events (SAEs) and all events determined to be UPs will be promptly reported to NIDCR, for assessment by the NIDCR Medical Monitor. Determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all subjects enrolled in the research. If the investigator determines that an adverse event is not an unanticipated problem, but the NIDCR Medical Monitor subsequently determines that the adverse event does represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the NIDCR Medical Monitor will report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

Describe any disease-related events common in the study population (i.e., expected events) that will not be reported as study safety events. Describe how these events will be recorded and monitored.}

### Unanticipated Problems

{Per the definition, only a subset of adverse events would be characterized as unanticipated problems. There are other types of incidents, experiences, and outcomes that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).}

{Begin sample text}

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

* unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

{End sample text}

### Adverse Events

{Consult the NIDCR Program Official/NIDCR Medical Monitor about this section. The definition of adverse event here is drawn from the OHRP guidance; for some studies, the definition from ICH E6 or 21 CRF 312.32 for IND safety reporting may be more appropriate.}

{Begin sample text, adapt as needed for the study}

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

{End sample text}

### Serious Adverse Events

{SAEs are a subset of all AEs.}

{Begin sample text, adapt as needed for the study}

A serious adverse event (SAE) is one that meets one or more of the following criteria:

* Results in death
* Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
* Results in inpatient hospitalization or prolongation of existing hospitalization
* Results in a persistent or significant disability or incapacity
* Results in a congenital anomaly or birth defect
* An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

{End sample text}

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

{Describe how AEs and SAEs will be identified and followed until resolved or considered stable. Specify procedures for soliciting (if applicable), recording, and follow-up of AEs and SAEs, consistent with the study procedures and time frames in the Schedule of Events. Include duration of follow-up after appearance of events (e.g., 1 week, 2 months).}

{Begin sample text, adapt as needed for the study}

The PI will record all 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.

{End sample text}

## Characteristics of an Adverse Event

{Begin sample text, adapt as needed for the study}

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event’s occurrence, will be considered in determining if the event is a UP.

{End sample text}

### Relationship to Study Intervention

{All adverse events must have their relationship to study intervention assessed. Describe the method of determining the relationship of an AE to a study intervention. 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 an interventional study, the study intervention must always be suspect.}

{Begin sample text, adapt as needed for the study}

To assess relationship of an event to study intervention the following guidelines are used:

1. Related (Possible, Probable, Definite)
	1. The event is known to occur with the study intervention, and/or
	2. There is a temporal relationship between the intervention and event onset and/or
	3. The event abates when the intervention is discontinued, and/or
	4. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
	1. There is no temporal relationship between the intervention and event onset, and/or
	2. An alternate etiology has been established.

{End sample text}

### Expectedness

{The risk information to assess expectedness can be obtained from preclinical studies, the package insert, device labeling or investigator’s brochure, published medical literature, or the intervention risks described in this protocol or the informed consent document.}

{Begin sample text, adapt as needed for the study}

The Study PI and/or study-appointed, clinically/medically responsible individual will determine whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

{End sample text}

### Severity of Event

{Describe the method of grading an adverse event for severity. Many toxicity tables are available for use and are adaptable to various study designs. Select an appropriate grading scale for the study population, the type of intervention, and the intervention risks. The IRB may provide guidance, or you may consult NIDCR if needed.}

{Begin sample text, adapt as needed for the study}

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

{End sample text}

## Reporting Procedures

{Institutions engaged in human subjects research conducted or supported by the Department of Health and Human Services (DHHS) must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others [45 CFR 46.103(b)(5)]. In a federally-funded study, institutions are required to promptly report unanticipated problems to OHRP. The regulations do not define prompt. OHRP guidance indicates that the appropriate time frame for prompt reporting will vary, and recommends the following general guidelines:

* Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
* Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
* All unanticipated problems should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB’s receipt of the report of the problem from the investigator.

In the following subsections, describe the protocol-specific reporting procedures, including the individual responsible for each step (e.g., the investigator, the Data Coordinating Center, the study-appointed clinically/medically responsible individual), which forms should be completed, time frames for reporting, how reports will be distributed, and what follow-up is required.

Include specific details of reporting procedures for:

* Deaths and life-threatening events
* Other SAEs
* Other adverse events

The OHRP provides guidance on reporting time frames, but each IRB may establish its own criteria and time frames for reporting events. The sample text in the following sections should be customized by including IRB-specified reporting time frames or protocol-specific parameters (safety issues) that need to be reported in an expedited fashion to the IRB, other oversight body, IND/IDE sponsor, or NIDCR. Discuss this section with NIDCR Office of Clinical Trials Operations and Management (OCTOM) and/or NIDCR program staff.}

### Unanticipated Problem Reporting

{Begin sample text. Adapt as needed for the study, in consultation with NIDCR.}

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

* appropriate identifying information for the research protocol, such as the title, investigator’s name, and the IRB project number;
* a detailed description of the adverse event, incident, experience, or outcome;
* an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
* a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

* Unanticipated problems that are serious adverse events will be reported to the IRB within <insert timeline in accordance with IRB policy> of the investigator becoming aware of the event.
* Any other unanticipated problem will be reported to the IRB within <insert timeline in accordance with IRB policy> of the investigator becoming aware of the problem.
* All unanticipated problems should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB’s receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR’s centralized reporting system via Rho Product Safety:

* Product Safety Fax Line (US):  1-888-746-3293
* Product Safety Fax Line (International):  919-287-3998
* Product Safety Email: rho\_productsafety@rhoworld.com

General questions about UP reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

* US: 1-888-746-7231
* International: 919-595-6486

{End sample text}

### Serious Adverse Event Reporting

{Begin sample text. Adapt as needed for the study, in consultation with NIDCR.}

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NIDCR’s centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

* Product Safety Fax Line (US):  1-888-746-3293
* Product Safety Fax Line (International):  919-287-3998
* Product Safety Email: rho\_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

* US: 1-888-746-7231
* International: 919-595-6486

The study’s clinically responsible individual will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

* All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within <insert timeline in accordance with IRB policy> of site awareness.
* Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within <insert timeline in accordance with IRB policy> of site awareness.

All SAEs will be followed until resolution or stabilization.

{End sample text}

{Other supporting documentation of the event may be requested and should be provided as soon as possible.}

### Reporting of Safety Events to FDA

<Insert text>

{If the study is conducted under an IND or IDE, describe in this section the process and time frames for investigators to report events to the IND/IDE sponsor, and state that the IND or IDE sponsor will comply with requirements for reporting to FDA. Consult the NIDCR Program Official and NIDCR Medical Monitor for assistance with this section. State in the protocol that NIDCR will be copied on any reports.

The IND or IDE sponsor must comply with mandatory reporting of safety events to the Food and Drug Administration (FDA). The IND or IDE sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. Regulations for drugs and biologics are found in [*21 CFR 312.32*](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32) and regulations for medical devices are found in [*21 CFR 812.150*](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150). For IND studies, according to [*21 CFR 312.64(b)*](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64), an investigator must immediately report to the IND sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure, and must include an assessment of whether there is a reasonable possibility that the drug caused the event. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol. For IDE studies, according to *[21 CFR 812.150(a)(1)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=812.150" \o "21 CFR 812.150(a)(1))*, an investigator must submit to the IDE sponsor and to the reviewing IRB a report of an unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

If the study intervention includes a regulated product but the study is not conducted under an IND or IDE, it may be appropriate to name alternative means for voluntary reporting of events (e.g., MedWatch). State in the protocol that NIDCR will be copied on any reports.}

### Events of Special Interest

<Insert text>

{Describe any other events that merit reporting to NIDCR, the IND/IDE sponsor, study leadership, IRB, and regulatory agencies.}

### Reporting of Pregnancy

<Insert text>

{State the study’s pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to NIDCR, an IND or IDE sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of treatment while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).}

## Halting Rules

<Insert text>

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

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

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.}

# STUDY OVERSIGHT

{NIDCR clinical research studies must be monitored for subject safety, protocol compliance, and data integrity. The method and degree of monitoring required varies, depending on the potential risk for participants and the complexity of the clinical study. For clinical research deemed to be more than minimal risk or for clinical research where the nature or complexity of the study merits additional oversight, independent data and safety monitoring will usually be required. Such clinical research may include clinical studies of investigational drugs, devices, or biologics; clinical studies of licensed products; clinical studies of surgical interventions including dental restorative and periodontal procedures; or clinical studies of behavioral interventions. Based on both study risk and complexity, the NIDCR Medical Monitor will determine the appropriate level of data and safety monitoring, which may include oversight by one or more of the following: Data and Safety Monitoring Board (DSMB), Independent Safety Monitor (ISM), or NIDCR Medical Monitor.

After consulting with the NIDCR Program Official and NIDCR Medical Monitor, describe in this section the type of oversight for the study. Identify who is responsible (e.g., DSMB, ISM, NIDCR Medical Monitor), and note the expertise represented. State what outcomes will be monitored and the frequency of data and safety monitoring. Use sample text provided below for the applicable oversight type, and delete inapplicable sample text.}

{Begin sample text for DSMB, adapt as needed for the study}

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in <in consultation with NIDCR, appropriate clinical, statistical, scientific, ethical disciplines will be inserted>. The DSMB will meet <insert time interval> to assess safety and efficacy data (if applicable), study progress, and data integrity for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDCR.

{End sample text for DSMB}

{Begin sample text for ISM, adapt as needed for the study}

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of an Independent Safety Monitor (ISM), <in consultation with NIDCR, name the individual, and describe his/her expertise>. The ISM is independent of the study and will be available in real time to review and recommend appropriate action regarding adverse events and other safety issues.

{End sample text for ISM}

{Begin sample text for NIDCR Medical Monitor, adapt as needed for the study}

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of the NIDCR Medical Monitor. The PI will submit a report every 6 months to the NIDCR Medical Monitor for review. This report will include data regarding enrollment and retention, unanticipated problems and protocol deviations, disposition of biospecimens, outcome measures, quality management findings and other relevant parameters. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

*{End sample text for NIDCR Medical Monitor}*

# CLINICAL SITE MONITORING

{It is the Principal Investigator’s responsibility to ensure that institutional or other regulatory requirements for clinical site monitoring are met. Based on a determination of study oversight requirements, NIDCR may also require independent clinical site monitoring through the NIDCR Clinical Research Operations and Management Support (CROMS) contractor. Consult the NIDCR Program Official and the NIDCR Office of Clinical Trials Operations and Management (OCTOM) about this section.

Site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on NIDCR, study sponsor standards, ICH E6 and, when appropriate, regulatory guidelines.

Include in this section a general description of the site monitoring planned for the study. State who will conduct the monitoring. Indicate the frequency of monitoring visits. This section may refer to a separate detailed monitoring plan document developed by or provided to OCTOM. The separate monitoring plan will describe in detail who will conduct the monitoring, the frequency of monitoring, the level of detail of monitoring (e.g., the number of subject data forms to be reviewed, the percentage of particular data fields to be monitored) and who is responsible for addressing findings in the monitoring report. If the NIDCR conducts clinical site monitoring, OCTOM will develop a clinical monitoring plan (CMP).

State that NIDCR will receive monitoring reports from the organization that conducts monitoring. NIDCR reserves the right to conduct independent clinical site monitoring as necessary.}

{Begin sample text if clinical site monitoring will be conducted, adapt as needed for the study.}

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by <insert>. The monitor will evaluate study processes and documentation based on the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP). The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from <insert> will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, NIDCR-OCTOM, and NIDCR Program staff. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

{End sample text}

{Begin sample text if no clinical site monitoring will be conducted, adapt as needed for the study}

No outside clinical site monitoring will be employed for this study. The Principal Investigator(s) and staff will closely monitor the subjects as they progress through the study. They will monitor and evaluate study processes and documentation based on the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP), and internal quality management plans. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

{End sample text}

# STATISTICAL CONSIDERATIONS

{The following subsections describing statistical considerations should be “self-contained” for coherence and ready reference. The analysis plans described should be directly aligned with the study objectives and outcome measures described in Section 3. The statistical plan should show how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH guidance document E9 (Statistical Principles for Clinical Trials) and the CONSORT statement ([*http://www.consort-statement.org/*](http://www.consort-statement.org/)), which describes standards for improving the quality of reporting randomized controlled trials.}

## Study Hypotheses

<Insert text>

{State the formal, testable, null, and alternate hypotheses for the primary objective and key secondary objectives.}

## Sample Size Considerations

<Insert text>

{Provide all information needed to validate your calculations, and also to judge the feasibility of enrolling and following the necessary numbers of participants.

Consider applicable items from the following list when describing sample size determination:

* Statistical method used to calculate the sample size
* Outcome measure used for calculations (almost always the primary variable)
* Test statistic
* Type I error rate
* Type II error rate
* Method for adjusting calculations for planned interim analyses, if any
* Assumptions used in calculations:
* Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible
* Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., also justified
* Approach to handling withdrawals and protocol violations, i.e., to what extent data from withdrawn participants will be evaluable (e.g., whether participants will be included in the “intent-to-treat” population), whether withdrawn participants will be replaced

Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size. Most assumptions are not accurate as point estimates.

When applicable, discuss whether the sample size also provides sufficient power for analysis of secondary and tertiary objectives in key subgroup populations.}

## Planned Interim Analyses (if applicable)

<Insert text>

{Describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing.}

### Safety Review

<Insert text>

{If statistical rules will be used to halt enrollment into all or a portion of the study (see Section 9.5), describe the statistical techniques and their operating characteristics, e.g., the probability of stopping under different safety event rates and the associated number of participants that would be enrolled.}

### Efficacy Review

<Insert text>

{Provide the same information as in Section 12.3.1, but for efficacy outcome measures. Also discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

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

## Final Analysis Plan

<Insert text>

{Describe analyses for assessing the primary and secondary objectives.

Plans must clearly identify the analyses cohorts (e.g., “Per Protocol” or “Intent to Treat,” as well as subsets of interest) and methods to account for missing, unused, or spurious data.

Discuss how outcome measures will be assessed and transformed, if relevant, before analysis. (Examples: Is the primary variable binary, categorical, or continuous? Will a series of measurements within a participant be summarized, such as by calculating the area under the curve? For survival outcome measures, what are the competing risks and censoring variables?)

For complex data analyses (e.g., multiple secondary objectives), an overview of the statistical analyses may be provided here, with more details in a separate statistical analysis plan written prior to performing any analyses.}

# SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

{Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants’ memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, audio recordings of counseling sessions or other data collection events, copies or transcriptions certified after verification as being accurate and complete, photographs or digital photo files, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study. It may be acceptable to use case report forms (CRFs) as source documents, but plans should be discussed with OCTOM before this process is finalized to ensure that source documentation is adequate. If CRFs are used as source documents, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

Describe how source documents will be managed in the study. Specify what will be considered source documents, how they will be maintained, and who will have access to records.}

{Begin required text; adapt as needed to specify what will be source documents for your study}

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

{End required text}

# QUALITY CONTROL AND QUALITY ASSURANCE

<Insert text>

{This section will address the plans for local quality assurance and quality control.
([*http://www.ich.org/fileadmin/Public\_Web\_Site/ICH\_Products/Guidelines/Efficacy/E6/E6\_R2\_\_Step\_4\_2016\_1109.pdf*](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf))**.**

Quality Management is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC) and quality assurance (QA) activities. All studies and each site in a multi-site study are expected to have a plan in place for assuring the quality of the research being conducted.

This section should describe the standard operating procedures (SOPs) relevant to quality management and/or refer to a separate quality management plan that describes:

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

Quality management tools designed for clinical site use are available on the NIDCR Toolkit for Clinical Researchers at [*http://www.nidcr.nih.gov/Research/toolkit/*](http://www.nidcr.nih.gov/Research/toolkit/).}

# ETHICS/PROTECTION OF HUMAN SUBJECTS

## Ethical Standard

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

{Begin required text}

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

{End required text}

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

## Institutional Review Board

{Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment materials by an appropriate IRB registered with the OHRP. For studies funded with applications with due dates on or after January 25, 2018, and contract solicitations published on or after January 25, 2018, NIH expects that all sites participating in multi-site studies which involve non-exempt human subjects research, will use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects. Indicate whether this study has a sIRB of record. Any amendments to the protocol or consent materials must also be approved before they are placed into use. Only institutions holding a current US Federalwide Assurance issued by OHRP may receive HHS support for research involving human subjects. Refer to: [*https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm*](https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm) *and*[*http://www.hhs.gov/ohrp/assurances/*](http://www.hhs.gov/ohrp/assurances/).}

{Begin required text; modify as appropriate for a multi-site study}

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 enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

{End required text}

## Informed Consent Process

{Identify different consent forms that are needed for the study (e.g., screening, study participation, future use of specimens, assent form for minors).

When a study includes participants who may be enrolled in the study only with the consent of the participant’s legally authorized representative (e.g., minors or participants whose cognitive impairment is such that they are unable to give informed consent), the participant should be informed about the study to the extent compatible with the participant’s understanding. If capable, the participant should assent and sign and personally date the written consent form. A separate IRB-approved assent form, describing (in simplified terms) the details of the study intervention, study procedures, and risks may be used. Assent forms do not substitute for the consent form signed by the participant’s legally authorized representative.

If non-English speakers will be enrolled, state that a translated consent document will be available and an appropriate person will conduct the consent process. Consider other special circumstances such as low literacy, braille, or web-based consenting.

For a multi-site study, each participating institution will be provided with a model informed consent form. Each institution may revise or add information to comply with institution consent templates, but may not remove procedural or risk content from the model consent form.}

{Begin required text; adapt as needed for the study}

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

{End required text}

## Exclusion of Women, Minorities, and Children (Special Populations)

<Insert text>

{Explain why any of these populations are excluded from study participation, or state that individuals of any age, gender or racial/ethnic group may participate.}

## Subject Confidentiality

*{Include as written or adapt sample text below and include required text, adding information about any study-specific procedures for maintaining subject confidentiality and any special data security requirements. Describe who would have access to records, including the investigator and other study staff, the clinical monitor, representatives of NIDCR or other funding institutions, study sponsor (grantee institution or IND/IDE holder), IRB representatives, and regulatory representatives.}*

{Begin sample text, adapt as needed for the study}

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the study sponsor.

The study monitor or other authorized representatives of <NIDCR or the study sponsor> may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

{End sample text}

{Begin required text}

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 (<https://humansubjects.nih.gov/coc/index>). As set forth in [45 CFR Part 75.303(a)](https://www.ecfr.gov/cgi-bin/text-idx?SID=f3e9328bbbd5aabe8e639ca48dcbcc7f&mc=true&node=se45.1.75_1303&rgn=div8) and [NIHGPS Chapter 8.3](https://grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.3_management_systems_and_procedures.htm), 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.

NIH Data Sharing Policies

As described in section 17, 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>). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

{End required text}

## Future Use of Stored Specimens and Other Identifiable Data

<Insert text>

{Refer to Human Subject Regulations Decision Charts 2 and 5: [*http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html*](http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html).

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

# DATA HANDLING AND RECORD KEEPING

{Include instructions for data handling or record-keeping procedures required for maintaining participant confidentiality, any special data security or data transfer requirements, and record retention.

Briefly describe steps to be taken to ensure that the data collected are accurate, consistent, complete, reliable, and in accordance with ICH E6. The description should include reference to source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring. Details may be provided in a MOP, a data management plan, or other citable reference document. Data management tools are available on the NIDCR Toolkit for Clinical Researchers at [*http://www.nidcr.nih.gov/Research/toolkit/*](http://www.nidcr.nih.gov/Research/toolkit/).}

{Begin sample text, adapt as needed for the study}

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

{End sample text}

## Data Management Responsibilities

{Include a general description (as in the sample text below) and add study-specific details and information about the role of a data coordinating center, if applicable.}

{Begin sample text, adapt as needed for the study}

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

{End sample text}

## Data Capture Methods

<Insert text>

{Provide details regarding the type of data capture that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and specify any related requirements (e.g., password protection and data quality checks for an electronic data system). Indicate expectations for time for submission of CRFs to a data coordinating center, if applicable.}

## Types of Data

<Insert text>

{Indicate the types of data that will be collected, such as safety, laboratory (clinical, immunology, pharmacokinetic, other study specific), and outcome measure data (e.g., periodontal measurements, caries assessments, physical measurements, questionnaire responses). Specify if safety data are collected in a separate database.}

## Schedule and Content of Reports

<Insert text>

{Indicate, as applicable, the schedule and content for data review and reports. Examples include reports to monitor enrollment, reports to the study oversight committee, reports of study conduct, and reports for interim data analysis and study progress. Identify plans for data analysis and interim and final study reports, steps for locking the database prior to analysis, and precautions related to masked data. Indicate whether and when coding is to occur.}

## Study Records Retention

{Specify the length of time for the investigator to maintain all records pertaining to this study. Consideration should be given to NIH grant and ICH guidance, federal and state and local regulations.}

{Begin sample text, adapt as needed for the study}

Study records will be maintained for at least three years from the date that the last grant federal financial report (FFR) is submitted to the NIH.

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

{End sample text}

## Protocol Deviations

{Begin sample text, adapt as needed for the study}

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

These practices are consistent with investigator and sponsor obligations in ICH E6.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to NIDCR and the IRB, according to their requirements.

{End sample text}

# PUBLICATION/DATA SHARING

{The publication and authorship policies should be established and briefly outlined in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. If details of the publication policy will be described in the study’s MOP, refer to it here.

Include the required text below; add study-specific information on publication and authorship policies, and compliance with applicable federal regulations and NIH Data Sharing Policies.

In addition to FDAAA and NIH policies, the International Committeeof Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. For more information, refer to <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>.}

{Begin required text}

This study will comply with all applicable NIH Data Sharing Policies. See <https://grants.nih.gov/policy/sharing.htm> for policies and resources.

NIH Public Access Policy

The NIH [*Public Access Policy*](https://publicaccess.nih.gov/index.htm) requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to [*PubMed Central*](https://www.ncbi.nlm.nih.gov/pmc/) immediately upon acceptance for publication. This ensures that the public has access to the published results of NIH funded research.

{End required text}

{Begin sample text; include text below for each policy that is applicable to your study}

NIH Genomic Data Sharing Policy

This study is a genomic study and will comply with the NIH Genomic Data Sharing Policy (<https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing/>), which calls for investigators funded by the NIH for genomic research to 1) share de-identified genomic and phenotypic data through an NIH-approved data repository and 2) submit documentation that describes how the institutions have considered the interests of the research participants, such as privacy and confidentiality. Submission of data to either the Database of Genotypes and Phenotypes (dbGaP) or another NIH-approved repository will be consistent with the permissions and limitations delineated on the study consent signed by study participants.

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

The study is a clinical trial and will comply with the NIH policy that establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results of these trials are submitted to ClinicalTrials.gov.

Food and Drug Administration Amendments Act of 2007 (FDAAA) and the Final Rule for Clinical Trials Registration and Results Information Submission

This study is an applicable clinical trial and will comply with [U.S. Public Law 110-85](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf) (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 and [42 CFR Part 11](https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission) (HHS Final Rule for Clinical Trials Registration and Results Information Submission), which mandate that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of "applicable clinical trials."

{End sample text}

# LITERATURE REFERENCES

<Insert text>

{Include a list of relevant literature references in this section. 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). The preferred format is ICMJE.}

{Begin examples}

“Journal citation:
Davis JT, Allen HD, Powers JD, Cohen DM. Population requirements for capitation planning in pediatric cardiac surgery. Arch Pediatr Adolesc Med. 1996;150(1):257-9.

Whole book citation:
Sherlock S, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford (England): Blackwell Scientific Publications; 1993.

Chapter in a book citation:
Cole BR. Cystinosis and cystinuria. In: Jacobson HR, Striker GE, Klarh S, editors. The principles and practice of nephrology. Philadelphia (PA): BC Decker Inc.; 1991. p.396-403.”

{End examples}

{A full listing of ICMJE style guidelines can be found at:
International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. JAMA. 1997;277:927-34.

You may also refer to:
[*http://www.nlm.nih.gov/bsd/uniform\_requirements.html*](http://www.nlm.nih.gov/bsd/uniform_requirements.html).*}*

SUPPLEMENTAL MATERIALS

{These documents are relevant to the protocol, but they are not considered part of the protocol and should not be attached or appended to the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

These are examples of documents that you may want to include as Supplemental Materials. If there are no supplemental materials to be referenced, this section should be deleted.

* Site Roster
* Manual of Procedures
* Behavioral Intervention Manual (if applicable)
* Calibration protocol (if applicable)
* Repository Instructions (if applicable)
* Biosafety Precautions (if applicable)
* Ionizing Radiation safety (if applicable)
* Laboratory Handling (if applicable)
* Case report forms
* Quality Management Plan
* Data Management Plan
* Clinical Monitoring Plan
* Statistical Analysis Plan
* DSMB or Oversight Committee Charter}

APPENDICES

{Documents that are officially affiliated with the protocol and will be submitted to the IRB with the protocol may be attached to the protocol as appendices or submitted to the IRB and to NIDCR as separate files. Changes to these items require IRB approval. When including items in this section, it is useful to label them (e.g., “Appendix A: Schedule of Events”).

These are examples of documents you may want to include as Appendices:

* Schedule of Events diagram or table (must match with Section 7)
* Key Study Questionnaires (validated and/or are not likely to change during the course of the study)
* Observational Coding Schemes (if applicable)
* Consent Form(s) sample/template (if applicable)

Include a cover page for each listed Appendix. The following page includes an example.}

APPENDIX A: SCHEDULE OF EVENTS

{Create a detailed schematic describing all visits and assessments, consistent with those listed in Sections 7 and 8.}

{Begin sample text, adapt as needed for the study}

| Procedures | Screening (Day –X to –Y) | Baseline (Day 0) | Study Visit 1 (Day X ± Y) | Study Visit 2 (Day X ± Y) | Study Visit 3 (Day X ± Y) | Study Visit 4 (Day X ± Y) | Study Completion (Day X ± Y) | Premature Discontinuation |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Signed Consent Form | X | X |  |  |  |  |  |  |
| Assessment of Eligibility Criteria | X | X |  |  |  |  |  |  |
| Review of Medical/Dental History | X | X |  |  |  |  |  |  |
| Review of Concomitant Medications  | X | X | X | X | X | X | X | X |
| Study Intervention |  | X | X | X | X | X |  |  |
| Physical Examination: Complete | X |  |  |  |  |  | X | X |
| Physical Examination: Symptom-Directed |  | X | (X) | (X) | (X) | (X) |  |  |
| Physical Examination: Vital Signs |  | (X) | (X) | (X) | (X) | (X) |  |  |
| Behavioral Assessment | X | X |  |  |  |  | X |  |
| Assessment of Adverse Events |  |  | (X) | (X) | (X) | (X) | X | X |
| Clinical Laboratory: Pregnancy test | X | X |  |  |  |  |  |  |
| Clinical Laboratory: Chemistry | X | X | (X) | (X) | (X) | (X) | X | X |
| Clinical Laboratory: Hematology | X | X | (X) | (X) | (X) | (X) | X | X |
| Clinical Laboratory: Urinalysis | X | X | (X) | (X) | (X) | (X) | X | X |
| Research Laboratory: Immunology \_\_mL whole blood |  | X |  | (X) |  | (X) | X | X |
| Research Laboratory: Biomarkers \_\_mL saliva |  | X |  |  |  |  | X |  |
| Research Laboratory: Sample for Genetic Analysis |  | X |  |  |  |  | X |  |
| Other Procedures: Periodontal Measurements |  | X |  |  |  |  | X |  |
| Other Procedures: Pain Assessment |  | (X) |  | (X) |  | (X) | (X) | (X) |

{End sample text}

{Specify time points for intervention or intermediate visits in days, weeks, or months, as appropriate for protocol. For each visit, provide a window during which the visit can occur. The window should be appropriate for the parameters to be assessed at the visit.

(X) – As indicated/appropriate.

Note: List the tests applicable to your specific protocol.

Provide a list of Clinical Laboratory tests, e.g.:

* **Pregnancy Test** – urine or serum test to establish eligibility
* **Hematology** – Hemoglobin, hematocrit, WBC and differential count, platelet count.
* **Biochemistry** – Sodium, potassium, chloride, urea, creatinine, glucose, uric acid, bicarbonate, amylase, lipase, albumin, total bilirubin, cholesterol, triglycerides, and creatine phosphokinase, as appropriate for the study.
* **Urinalysis** (protein and glucose), as appropriate for the study.

Provide a list of Research Laboratory tests and the required specimen types, e.g.:

* **Gene sequencing, Immunology** – X mL blood
* **Biomarkers** – X mL saliva or blood

Provide a list of other procedures done to evaluate outcome measures (e.g., caries assessments, periodontal measurements, photographs, x-rays, questionnaires, pain assessments).

Study intervention – Modify as appropriate if intervention is administered more than once throughout the study.}