**Tool Summary Sheet:**

**NIDCR Observational Protocol Template**

**Purpose**: To provide an instructional template for use in development of a protocol for observational studies

**Audience/User**

Principal Investigators and Study Staff

**Details**

This document is the National Institute of Dental and Craniofacial Research (NIDCR) protocol template for an observational study.

In an observational study, the investigator does not alter the care that people receive, but simply records observations and analyzes data. These studies may focus on risk factors, natural history, variations in disease progression or in disease treatment. They often assess specific health characteristics of the enrolled human subjects by collecting biospecimens (e.g., for biomarker or genomic analyses), obtaining photographic, radiographic or other images, and/or collecting medical history or exposure data from research subjects.

Observational studies that collect biospecimens, images, or other data involve human subjects, and require Institutional Review Board (IRB) approval. This protocol template is based on the essential protocol elements in Section 6 of the [*ICH E6 guidance on 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 a study protocol that meets NIDCR standards and includes all elements required for an IRB to assess study risks and benefits.

**Best Practice Recommendations**

* NIDCR considers many factors in the context of risk to human subjects and complexity of the study when determining the resources needed to meet the Institute’s study oversight responsibilities. Based on the potential risk for subjects and the complexity of the clinical study, the NIDCR Medical Monitor will provide guidance on the appropriate level of data and safety monitoring. Investigators should consult the NIDCR Program Official (and/or Project Scientist, when applicable) 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 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).
* 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** | **Version Date** | **Summary of Revisions Made:** |
| 2.0 | 11Feb2013 | Original version with Tool Summary Sheet |
| 3.0 | 06Jan2014 | Revised text regarding Safety Oversight method, Final Statistical Analysis, Data Sharing, and Clinical Site Monitoring; clarified instructional text and added text placeholders |
| 4.0 | 09Sep2019 | Edits made to improve clarity and utility, and align with NIH policies and current standards |

<Title>

NIDCR Protocol Number: <number provided by NIDCR>

NIH Grant Number:

Study Principal Investigator:

Institution:

NIDCR Program Official:

NIDCR Medical Monitor:

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 (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection 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:

Signed:  Date: 

Name: 

Title: 

{Include signature blocks for Clinical Site Investigator(s), when applicable. Duplicate as needed}

Clinical Site Investigator:

Signed:  Date: 

Name: 

Title: 

{End required text}

TABLE OF CONTENTS

{This table uses the Table of Contents function in Microsoft Word that will automatically update headings and page numbers used in the body of the report. To update the Table of Contents and all cross-references in the document, press CTRL-A to select the entire document, then press F9.}

Page

[STATEMENT OF COMPLIANCE i](#_Toc19111635)

[SIGNATURE PAGE ii](#_Toc19111636)

[TABLE OF CONTENTS iii](#_Toc19111637)

[LIST OF ABBREVIATIONS v](#_Toc19111638)

[PROTOCOL SUMMARY vii](#_Toc19111639)

[1 KEY ROLES AND CONTACT INFORMATION 1](#_Toc19111640)

[2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE 2](#_Toc19111641)

[2.1 Background Information 2](#_Toc19111642)

[2.2 Rationale 2](#_Toc19111643)

[2.3 Potential Risks and Benefits 2](#_Toc19111644)

[2.3.1 Potential Risks 2](#_Toc19111645)

[2.3.2 Potential Benefits 3](#_Toc19111646)

[3 OBJECTIVES AND OUTCOME MEASURES 4](#_Toc19111647)

[3.1 Primary 4](#_Toc19111648)

[3.2 Secondary 5](#_Toc19111649)

[3.3 Tertiary/Exploratory 5](#_Toc19111650)

[4 STUDY DESIGN 6](#_Toc19111651)

[5 STUDY POPULATION 7](#_Toc19111652)

[5.1 Participant Inclusion Criteria 7](#_Toc19111653)

[5.2 Participant Exclusion Criteria 8](#_Toc19111654)

[5.3 Strategies for Recruitment and Retention 8](#_Toc19111655)

[5.4 Participant Withdrawal 9](#_Toc19111656)

[5.4.1 Reasons for Participant Withdrawal 9](#_Toc19111657)

[5.4.2 Handling of Participant Withdrawals 10](#_Toc19111658)

[5.5 Premature Termination or Suspension of Study 10](#_Toc19111659)

[6 STUDY SCHEDULE 11](#_Toc19111660)

[6.1 Screening 11](#_Toc19111661)

[6.2 Enrollment/Baseline 12](#_Toc19111662)

[6.3 Intermediate Visits 12](#_Toc19111663)

[6.4 Final Study Visit 13](#_Toc19111664)

[6.5 Withdrawal Visit 13](#_Toc19111665)

[6.6 Unscheduled Visit 13](#_Toc19111666)

[7 STUDY PROCEDURES/EVALUATIONS 14](#_Toc19111667)

[8 ASSESSMENT OF SAFETY 16](#_Toc19111668)

[8.1 Definitions of Safety Parameters 16](#_Toc19111669)

[8.1.1 Adverse Events 16](#_Toc19111670)

[8.1.2 Unanticipated Problems 17](#_Toc19111671)

[8.2 Specification of Safety Parameters 17](#_Toc19111672)

[8.3 Reporting Procedures 18](#_Toc19111673)

[8.3.1 Unanticipated Problem Reporting 18](#_Toc19111674)

[8.3.2 Serious Adverse Event Reporting to NIDCR 20](#_Toc19111675)

[9 STUDY OVERSIGHT 21](#_Toc19111676)

[10 CLINICAL SITE MONITORING 23](#_Toc19111677)

[11 STATISTICAL CONSIDERATIONS 25](#_Toc19111678)

[11.1 Study Hypotheses 25](#_Toc19111679)

[11.2 Sample Size Considerations 25](#_Toc19111680)

[11.3 Final Analysis Plan 26](#_Toc19111681)

[12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS 27](#_Toc19111682)

[13 QUALITY CONTROL AND QUALITY ASSURANCE 28](#_Toc19111683)

[14 ETHICS/PROTECTION OF HUMAN SUBJECTS 29](#_Toc19111684)

[14.1 Ethical Standard 29](#_Toc19111685)

[14.2 Institutional Review Board 29](#_Toc19111686)

[14.3 Informed Consent Process 29](#_Toc19111687)

[14.4 Exclusion of Women, Minorities, and Specific Age Groups 30](#_Toc19111688)

[14.5 Participant Confidentiality 31](#_Toc19111689)

[14.6 Future Use of Stored Specimens and Other Identifiable Data 32](#_Toc19111690)

[15 DATA HANDLING AND RECORD KEEPING 33](#_Toc19111691)

[15.1 Data Management Responsibilities 33](#_Toc19111692)

[15.2 Data Capture Methods 33](#_Toc19111693)

[15.3 Schedule and Content of Reports 34](#_Toc19111694)

[15.4 Study Records Retention 34](#_Toc19111695)

[15.5 Protocol Deviations 34](#_Toc19111696)

[16 PUBLICATION/DATA SHARING POLICY 36](#_Toc19111697)

[17 LITERATURE REFERENCES 37](#_Toc19111698)

[SUPPLEMENTAL MATERIALS 38](#_Toc19111699)

[APPENDICES 39](#_Toc19111700)

[APPENDIX A: Schedule of Events 40](#_Toc19111701)

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 |
| CIOMS | Council for International Organizations of Medical Sciences |
| CRF | Case Report Form |
| CROMS | Clinical Research Operations and Management Support |
| CSI | Clinical Site Investigator |
| CSOC | Clinical Study Oversight Committee |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data and Safety Monitoring Board |
| FFR | Federal Financial Report |
| FWA | Federalwide Assurance |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| MOP | Manual of Procedures |
| N | Number (typically refers to participants) |
| 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 |
| OHSR | Office of Human Subjects Research |
| PD | Protocol Deviation |
| 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 |

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 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 and Outcome Measures:** | <Insert objectives copied from the body of the protocol. Include the primary objective and secondary objectives and specify outcome measures.>  |
|  | Primary Objective(s) and Outcome Measure(s):  |
|  | Secondary Objective(s) and Outcome Measure(s):  |
| **Population:** | <State the sample size for each group/cohort and briefly define group/cohort characteristics> |
| **Number of Sites:** | <Insert a list of sites.> |
| **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 subject.> |
| **Estimated Time to Complete Enrollment:** | <Estimated time from enrollment into study of the first subject to enrollment into study of the last subject.> |

**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. The time point(s) indicated in the schematic should correspond to the time point(s) in Section 6 of the protocol, Study Schedule, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.}

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

Initial assessments

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

Follow-up assessments (in-person, phone, electronic, etc.)

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

Follow-up assessments (in-person, phone, electronic, etc.)

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

**Final Assessments**

**(in person, phone, electronic, etc.)**

Screening and
Enrollment
Day XX±YY

Visit 1

Day XX±YY

Visit 2

Day XX±YY

Visit 3

Day XX±YY

Visit X

Day XX±YY

# 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:** | {If applicable, 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:**  | <Program Official name> |
| **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:* The qualified individual(s) responsible for study clinical examinations and safety assessments
* Major collaborators (e.g., epidemiologist, statistician)
* Key study staff}
 |

# 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
* Discussion of important research relevant to the study that provides background and scientific justification for the study
* Applicable clinical, epidemiological, or public health background or context of the study}

## Rationale

<Insert text>

{State the reason for conducting the study. Include, as applicable, information about the population, disease or condition, and limitations of knowledge.}

## 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 procedures. If study data are obtained from standard of care procedures, the protocol generally should not need to list risks of those procedures, which would be performed even if the participant was not enrolled in the study. Consider describing inconveniences to the participant, if relevant. Briefly describe procedures that will be followed to help mitigate risks.}

### 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 health condition that is the focus of the study.

Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general or specific purpose (e.g., to evaluate biomarkers as physiologic correlates of disease, to determine genomic factors affecting oral health conditions, to determine risk factors for disease or condition).

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/exploratory objectives. An outcome measure is a specific measurement or observation used to describe the patterns of diseases or traits or associations with exposures, risk factors, or treatment. Outcome measures should be prioritized and should correspond to the study objectives and hypotheses being tested. Include the study visits at which the biospecimens, images or other data will be obtained and the specific laboratory tests or other analytical measures to be used. 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 study (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(s) 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.} | <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 health condition that is the focus of the study.} | <insert text>{Briefly explain why the outcome measure was chosen. It is recommended that the list of secondary outcome measures be short, because the chance of demonstrating an effect on any secondary outcome measures 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. Outcomes measures 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 [e.g., cross-sectional, cohort, case-control, case-only, case-crossover, ecological or community study, family-based or other (explain)]
* A brief description of the clinical sites and rationale for inclusion of these sites
* A brief description of the study population and the rationale for selection of the population (e.g., healthy/sick, inpatient/outpatient, demographic groups), sample size and characteristics of different study groups, if applicable. Do not list inclusion/exclusion criteria here, as these will be listed in Sections 5.1 and 5.2. Specify approach(es) for conforming with NIH policy on inclusion of individuals of all ages, and inclusion of women and minorities. Provide justification for the populations that will be excluded.
* A brief discussion of the rationale for design features
* A brief description of the study timeline, including approximate time to complete enrollment and expected duration of subject participation (details of study visit schedule will be included in Section 6, Study Schedule)
* A brief description of the biospecimens, imaging data, survey data, or other data to be collected for assessment of study objectives (detailed methods for collecting specimens or data will be included in Section 7, Study Procedures)
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical images)
* If the study requires that study staff (investigator, examiner, laboratory personnel, etc.) be masked with respect to the study group of a research participant, specimen, or image, state how masking will be maintained.}

# STUDY POPULATION

{No text is to be entered under this section heading; include text in the relevant subsections below. In subsections 5.1 to 5.5, define the study population, describe participant recruitment and discuss issues related to participant withdrawal.

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 being in the study 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 also 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.

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

Participation in a clinical study that may interfere with participation in this study *{within a specified time frame}*

History of or current tobacco, drug, or alcohol use *{define parameters for exclusion}*

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.
* If appropriate, describe recruitment strategies for vulnerable participants as defined in the Common Rule (45 CFR Part 46). 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 retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance, etc.
* Describe the plans to minimize loss to follow-up and missing data. 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.}

## Participant Withdrawal

{No text is to be entered under this section heading; include text in the relevant subsections below. Participants may withdraw consent for study participation. The PI may also withdraw a participant from the study. The subsections below should state which events would result in withdrawal, how information about withdrawal will be documented, and whether withdrawn study participants will be replaced.}

### Reasons for Participant Withdrawal

{Provide a list of reasons a participant may withdraw or an investigator may withdraw participants from the study. It may be appropriate to provide distinct withdrawal 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 from participation in the study at any time.}

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

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

An investigator may withdraw a participant from the study if:

Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.

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

<Insert text>

{Describe efforts that will be made to capture reasons for participant withdrawal of consent. Describe the use of a dedicated Case Report Form (CRF) to capture the date and the specific underlying reason for participant withdrawal. Also describe efforts that will be made to provide information or referral for care (if applicable). It may be appropriate to collect safety data if participant withdrawal occurs because of an unanticipated problem (UP) or serious adverse event (SAE).

This section should include a statement of whether participants who withdraw or discontinue early will be replaced, and the time frame for which this will occur (e.g., throughout enrollment phase, for the first year of data collection).}

## Premature Termination or Suspension of Study

{List possible reasons for termination or suspension of the study in this section, e.g., study closure based on principal investigator (PI) decision, IRB decision, or NIDCR decision. For any study that is prematurely terminated or suspended, the PI will promptly inform all parties 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. The Principal Investigator is responsible for promptly notifying all parties and providing 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 subjects.

Insufficient adherence to protocol requirements.

Data that are not sufficiently complete and/or evaluable.

Determination of futility.

{End sample text}

# 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 7.

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 may have a small window, whereas a 6-month follow-up visit may have a larger window). When establishing visit intervals and windows, consider scientific appropriateness, logistical feasibility (such as taking into account weekends and holidays), and relevance to study outcome measures. If a study visit occurs outside of a study window, state whether assessments need to be repeated and the time frame for which they would need to be repeated. State the method of contact for each visit (in-person, by phone, electronically, etc.)

For each visit, identify the purpose and briefly describe what will occur at the visit. If any data/samples from standard clinical care procedures will be used for this study (e.g., dental radiographs are clinically indicated as part of a dental visit, and the same radiographs will also be analyzed by the researchers to record study data), clearly identify the procedure as being performed as part of standard clinical care.}

## 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 comparison with later assessments. Discuss the sequence of events that should occur during the enrollment visit. List any special conditions (e.g., negative pregnancy test must be available prior to initiating study procedures).

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.

{End sample text}

## Intermediate Visits

{List each visit, including visit number and visit window. For each visit, list the evaluations/procedures/specimen collections 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/other specimen.

{End sample text}

## Final Study Visit

{Define when the final study visit should occur and describe any special procedures/evaluations or instructions to the participant. Describe provisions for follow-up of ongoing Adverse Events (AEs)/Serious Adverse Events (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/other specimen.

Provide final instructions to participant *{e.g., follow-up of ongoing adverse events, oral hygiene instructions.}*

{End sample text}

## Withdrawal Visit

<Insert text>

{If a 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 this section, describe general procedures for collection of all study data including clinical observations, laboratory results, biospecimens, images, and/or questionnaire responses. Indicate where appropriate, that procedures/evaluations will be performed by qualified personnel, and identify by role the study personnel who will perform the procedure or evaluation. Specify which procedures are required (for primary outcome or safety assessments) and which are optional. Consider creating subsections (e.g., Medical History Collection, Clinical and Laboratory Evaluations, Biological Specimen Collection, Questionnaires, Focus Groups) for organization and ease of reading.

If study data will be obtained from a procedure performed as part of standard clinical care, clearly identify the standard of care procedure, specifying the information that will be collected from that procedure (e.g., dental radiographs are clinically indicated as part of a dental visit, and the same radiographs will also be analyzed by the researchers to record study data), and indicate how the data from that procedure will be obtained.

Possible content for this section 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 (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.
* Laboratory evaluations (e.g., hematology, clinical chemistry, urinalysis, pregnancy testing). Differentiate screening laboratories from evaluations required for study outcomes. Include specific test components and approximate volume and type of specimens needed for each test (or refer to the study’s MOP). Describe approaches to provide for appropriate longitudinal and cross-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.
* Oral exams, including caries assessments or periodontal measurements (describe the caries assessment system, the specific periodontal measurements, or other oral exam assessments to be recorded).
* Radiographic or other imaging assessments.
* Functional evaluations (e.g., salivary flow, speech production).
* Observation and coding of participant behaviors.
* Biological specimen collection. Describe the general procedures for specimen collection. Include in this section information about the specimen source (enrolled study subjects or biorepository), pre-collection procedures for participants, mode of collection, amount of specimen (e.g., blood or saliva volume), frequency of collection, participant time required for collection, and procedures to ascertain specimen quality. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP.
* Administration of questionnaires or other instruments for subject-reported outcomes, (e.g., daily diary, pain questionnaire, quality of life questionnaire). Describe the purpose and content of questionnaires. Specify by whom and how each questionnaire will be administered and who will be the respondents. Describe the source of all questions, whether the questions have been modified from their original source, and whether the questionnaire has been previously validated in its current form with the study population. Questionnaires may be provided to NIDCR in protocol appendices or as separate documents.
* Conduct of focus groups and/or interviews.}

# ASSESSMENT OF SAFETY

{Develop this section in consultation with the NIDCR Program Official (and/or NIDCR Project Scientist, if applicable), NIDCR Office of Clinical Trials Operations and Management (OCTOM), and NIDCR Medical Monitor. To establish a meaningful safety system for the study, consider any risks of the study procedures and 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:

* whether the study procedures (e.g., radiographs, biopsies) involve known risks;
* whether the study is conducted at multiple sites, and will require centralized safety oversight;
* whether the study involves risks to individuals other than research subjects (e.g., 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}

## Definitions of Safety Parameters

{The Office for Human Research Protections (OHRP) specifies that “the Health and Human Services (HHS) regulations at 45 CFR part 46 do not define or use the term adverse event, nor is there a common definition of this term across government and non-government entities.” However, its guidance on Unanticipated Problems Involving Risk and Adverse Events provides the following definitions for consideration}.

### Adverse Events

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

An adverse event (AE) 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 Event

{Serious Adverse Events 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

Based upon appropriate medical judgment, the event may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

{End sample text}

### 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 if they meet all three of the listed criteria (e.g., a breach of confidentiality could place participants at risk of 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}

## Specification of Safety Parameters

*{Describe whether events will be actively solicited from participants and recorded during planned visits, and the safety parameters that will be recorded. “Recording” refers to documenting data in the study database. Recording events is critical for assessing whether an event must be reported to the entities responsible for study oversight. Define what data will require reporting to the IRB or to other individuals or groups (including NIDCR) 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. If SAEs are required to be reported to the NIDCR, SAEs should be recorded in the data collection system and must be reported to NIDCR in accordance with IRB-defined timelines. Follow IRB policy for reporting other events to the IRB.

Include in this section a statement that describes which events will be promptly reported to NIDCR, for assessment by the NIDCR Medical Monitor.}

{Begin sample text, add study-specific details as noted above, adapt in consultation with NIDCR}

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

{End sample text}

## Reporting Procedures

{In the following subsections, describe procedures and time frames for reporting events to the IRB and to NIDCR. Consult with NIDCR Program and OCTOM to determine which events will require reporting to NIDCR.

Describe the protocol-specific reporting procedures, including the individual responsible for each step (e.g., the investigator, the Data Coordinating Center), which forms should be completed, time frames for reporting, how reports will be distributed and who they will be distributed to (e.g., NIDCR, IRB), and what follow-up is required.

Include specific details of reporting procedures for each type of event.

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, or NIDCR.}

### Unanticipated Problem Reporting

{In a federally-funded study, institutions engaged in human subjects research 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.}

{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 the Clinical Research Operations and Management Support (CROMS) contractor. Additional reporting instructions can be found in the <insert document name, such as MOP or DSMP>.

{End sample text}

### Serious Adverse Event Reporting to NIDCR

{Consult with NIDCR Program and OCTOM to determine if SAEs (other than SAEs that are considered UPs) will be reported to NIDCR for this study. If SAEs that are not considered UPs will not be reported to NIDCR, delete this section.}

{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 the CROMS contractor. Additional reporting instructions can be found in the <insert document name, such as MOP or DSMP>.

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 NIDCR’s centralized safety system 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 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.}

# 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 subjects and the complexity of the clinical study. The NIDCR Medical Monitor will determine the appropriate level of data and safety monitoring, which may include additional oversight by one or more of the following: Data and Safety Monitoring Board (DSMB), Clinical Study Oversight Committee (CSOC), Independent Safety Monitor (ISM), or NIDCR Medical Monitor.

After consulting with the NIDCR Program Official (and/or NIDCR Project Scientist, if applicable) and Medical Monitor, describe in this section the type of oversight for the study. Identify who is responsible (e.g., DSMB, CSOC, ISM, NIDCR MM), 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 required text, modify as needed}

The investigator will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The PI will review the data for safety concerns and data trends at regular intervals, and will promptly submit reportable events to the IRB and NIDCR that arise during the conduct of the study.

{End required text}

{Begin sample text for DSMB}

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, 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 CSOC}

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of a Clinical Study Oversight Committee (CSOC) composed of members with expertise in <in consultation with NIDCR, appropriate clinical, statistical, scientific, ethical disciplines will be inserted>. The CSOC will meet <insert time interval> to assess unanticipated problems, study conduct, and progress. If major concerns arise, more frequent meetings may be held. The CSOC will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the CSOC. At this time, most data elements that the CSOC needs to assess will be clearly defined. The CSOC will provide recommendations to the NIDCR.

{End sample text for CSOC}

{Begin sample text for ISM}

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}

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of the NIDCR Medical Monitor. The PI will generally 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. A separate quality management report may also be expected. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

{End sample text for NIDCR Medical Monitor}

# CLINICAL SITE MONITORING

{Consult with the NIDCR Program Official (and/or NIDCR Project Scientist) and the NIDCR Office of Clinical Trials Operations and Management (OCTOM) about this section.

It is the Principal Investigator’s responsibility to ensure that institutional or other regulatory requirements for clinical site monitoring are met. NIDCR may also require independent clinical site monitoring through the NIDCR Clinical Research Operations and Management Support (CROMS) contractor.

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 standards and ICH E6.

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 a specific 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 subject 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 the 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.

Some studies may be conducted to obtain preliminary qualitative data. The statistical section should describe this approach, including frequency reporting of variables, confidence intervals, etc.}

## Study Hypotheses

<Insert text>

{State the formal 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 number of subjects.

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), justified and referenced by historical data as much as possible
	+ Assumed dropout rates, withdrawal, missing data, etc., also justified
	+ Approach to handling withdrawals, missing data, etc., e.g., to what extent data from withdrawn subjects will be evaluable, whether withdrawn subjects 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.}

## Final Analysis Plan

<Insert text>

{Describe analyses for assessing the primary and secondary objectives.

Plans must clearly identify the analyses, data stratifications, and methods to account for missing or unused data. Discuss how outcome measures will be assessed and transformed, if relevant, before analysis (e.g., Is the primary variable binary, categorical, or continuous?).

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 research 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, recorded data from automated instruments, audio recordings of 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 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; list the 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 subjects. 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.

The source documents for this study are:

<insert bulleted list of source documents>

{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>).

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.

In this section, address each of the following bullets and refer to a separate quality management plan, if applicable:

* 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, 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 (e.g., correcting procedures that are not in compliance with protocol) and quality control issues (e.g., correcting errors in data entry).
* Staff training 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/>.}

# 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 material 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: <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

<Insert text>

{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 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 whether a translated consent document will be available and state that an appropriate person will conduct the consent process.

Consider other special circumstances such as low literacy, braille, or web-based consenting.}

{Begin sample text; adapt as needed for a specific 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 sample text}

## Exclusion of Women, Minorities, and Specific Age Groups

<Insert text>

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

## Participant 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 study monitor, representatives of NIDCR or other funding institutions, the study sponsor (grantee institution), and IRB representatives}

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

Participant 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 the <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.

Confidentiality of Data Sharing

As described in section 16, 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 sample text}

## Future Use of Stored Specimens and Other Identifiable Data

<Insert text>

{Refer to Human Subject Regulations Decision Chart 5:
<https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html#c5>.

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 or video recordings). Specify the location(s), if other than the clinical site, where specimens or other data will be maintained, how long specimens or other data will be stored, if the site's IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens or data (e.g., specimens will be coded, bar-coded, de-identified, identifying information will be redacted from audio recording transcripts). Include a statement that genomic testing will or will not be performed.}

# DATA HANDLING AND RECORD KEEPING

{Include instructions for data handling or record-keeping procedures required for maintaining subject 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/>.}

{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 Principal 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 must be reviewed by the Principal Investigator or designee.

{End sample text}

## Data Capture Methods

<Insert text>

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

## 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 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

<Insert text>

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

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

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

{End sample text}

## Protocol Deviations

<Insert text>

{Departures from the study procedures described in the IRB-approved protocol occur in many studies. Some protocol deviations may be intentional to protect participant safety, while others are only discovered to have occurred after the fact. Examples of deviations include a missed or out-of-window visit (such as due to external/environmental factors), incomplete procedure/assessment at a visit, or a change in a procedure made to protect participant safety. All protocol deviations should be tracked for safety, scientific, and operational reasons. IRBs vary in their reporting requirements for protocol deviations.}

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

A protocol deviation is any change, divergence, or departure from the study procedures described in the IRB-approved clinical study protocol. The deviation may be on the part of the participant, the investigator, or study staff.

Consistent with the investigator obligations in the ICH E6 Guideline for Good Clinical Practice, the Principal Investigator will document in study source documents and explain any deviation from the IRB-approved protocol. The PI will report to the IRB any deviations or changes made to eliminate immediate hazards to participants and any changes that increase risk to participants and/or significantly affect the conduct of the study.

<Insert additional IRB requirements and timelines for reporting protocol deviations.>

<Based on consultation with the NIDCR Program Official, NIDCR Project Scientist (if applicable), and/or Medical Monitor, describe reporting to NIDCR and/or an NIDCR oversight entity.>

Protocol deviations will be assessed for their impact on safety, study operations, and data integrity. Appropriate corrective and preventive actions will be implemented if warranted.

{End sample text}

# PUBLICATION/DATA SHARING POLICY

{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, and provide study-specific policies on publication and authorship policies, and compliance with applicable federal regulations and NIH Data Sharing Policies.}

{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 if 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.

{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>.}

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
* 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, CSOC, 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 number 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 6)
* 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 6 and 7.}

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Procedures** | **Screening** **(Day –X to –Y)** | **Study Visit 1** **(Day 0)** | **Study Visit 2****(Day X ± Y)** | **Study Visit 3****(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 |  |  |  |  |
| Physical Examination: Complete | X |  |  |  | X | X |
| Physical Examination: Symptom-Directed |  | X | (X) | (X) |  |  |
| Physical Examination: Vital Signs |  | (X) | (X) | (X) |  |  |
| Physical Examination: Oral Exam | X | X | (X) | (X) | X | X |
| Clinical Lab: Urine Pregnancy Test | X |  |  |  |  |  |
| Research Laboratory: Immunology \_\_mL whole blood |  | X |  | (X) | X | X |
| Research Laboratory: Biomarkers \_\_mL saliva (or blood) |  | X |  |  | X |  |
| Research Laboratory: Sample for Genetic Analysis |  | X |  |  | X |  |
| Other Procedures: Caries Assessment or Periodontal Measurements |  | X |  |  | X |  |
| Other Procedures: Pain Assessment or Other Questionnaire |  | X |  | (X) | X | (X) |
| Other Procedures: Photograph or Other Imaging | X | X |  |  | (X) | (X) |

{End sample text}

{Specify time points for study procedures 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

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).}