Protocol Template

for

Interventional Studies and Observational Studies

**Guidance**

Please remove these Guidance pages (i, ii, iii) before finalizing and distributing the protocol.As you complete the protocol, please delete instructions/guidance text, also. The guidance text is GRAY.

This template is appropriate for both experimental studies and observational studies.

This template is a tool to help facilitate the preparation of a protocol document for your clinical research study.

If your study is FDA-regulated or NIH-funded, you may optionally choose to use the “*NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Template*”; note that doing so is not required by FDA and NIH.

Please retain major section headings to facilitate the review process; insert "Not applicable" in sections that are not appropriate for your protocol. But do modify or delete sub-section headings as needed.

**What Is A Protocol And How Is It Used In Research And Review?**

[The following guidance was excerpted from "Designing your Research for Speedy IRB Approval", a 2018 seminar by Paul W. Stewart, PhD, Professor of Biostatistics,

UNC Gillings School of Global Public Health. (<https://tracs.unc.edu/docs/biostatistics/Designing_Your_Research_for_Speedy_IRB_Approval_20181102.pdf>). ]

1. A Master Protocol Document (MPD or ‘protocol’) is a completely detailed blueprint for the research study. It is a working document that serves as a repository for accumulated ideas, information, literature review, procedures, strategies, algorithms, and plans for study conduct. The protocol should be a master source of text used for reference and guidance. Beginning in the early stages of study planning, it is highly efficient to use a MPD template as a tool for formulating plans, collecting ideas, reference, information, and evolving text for subsequent use in grant proposals, IRB applications, and publications.
2. Increasingly, funders, IRBs, and journals are requiring submission of a protocol as part of their review processes. For example: “The Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH E3 GCP 6) require a MPD for any study that involves human participants. In addition, Title 21 Part 312 of the Code of Federal Regulations (21 CFR 312) describes both a research protocol and protocol amendments for studies conducted under an Investigational New Drug (IND) application.”(<https://gcp.nidatraining.org>) A well-written MPD facilitates compliance with ClinicalTrials.gov reporting requirements.
3. The MPD should be as simple or complex as needed. All studies should have a MPD that specifies the essential details of the project: background, rationale, specific aims, study design, target population, recruitment and sampling strategy, a rationale for the chosen sample size, details of all procedures, plans for data collection and management, safety monitoring plans, and a complete and adequately detailed statistical analysis plan for each specific aim.
4. A grant proposal or IRB application is not a substitute for a MPD because they do not provide comprehensive details. A grant *proposal* is a persuasive document meant to convince funders of the need, relevance, and innovation of a research concept as well as the suitability of the research setting and investigators. An *IRB application* is intended to describe the planned study procedures, related risks and benefits, how participants' identities and data will be protected, the informed consent process, and other issues related to protection of human participants. A study specifies all these aspects of the research project, with special focus on clearly stated aims, specification of outcome measures and other variables of interest along with their units of measure (or the range of valid values if the variable is categorical), comprehensive description of the data to be collected, a rationale for the chosen sample size, and aim-specific statistical analysis strategies and methods to be used to analyze data.
5. In the MPD, the specific aims, study design, variables of interest, and aim-specific statistical analysis plans should be well-aligned; for example, if investigating feasibility issues is a specific aim, then the protocol should specify outcome measures addressing feasibility and plans for statistical analysis of feasibility data.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table: Examples of Alignment of the Specific Aims with Measures and Aim-Specific Analysis Plans** | | | |
| **Specific**  **Aim** | **Outcomes**  **Measures** | **Population Parameters to be Estimated (“Estimands”)** | **Statistical**  **Estimators** |
| Investigate feasibility  of using a wearable monitoring device | questionnaire score  for tolerability (ordinal) | proportion of the patients in the target population expected to have adequately‑high tolerability. | observed proportion and 95% C.I. |
| duration of wearing device (days:hours) | proportion of the patients in the target population expected to wear the device per protocol. | observed proportion and 95% C.I. |
| binary indicator of drop‑out (Y,N) | proportion of the patients expected to drop out in samples from the target population. | observed proportion and 95% C.I. |
| Obtain information  needed to plan a  future full-scale study | periodic measures  of salivary cortisol (mg/dL) | (1) mean concentrations in the target population,  (2) standard deviations in the target population,  (3) intra-class correlation in the target population,  (4) proportion of values expected to be missing in samples from the target population. | (1,2,3) model-based estimates.  (4) observed proportion of enrollees with complete data,  all with 95% C.I. estimates. |
| Evaluate the relative efficacy of a treatment regimens A and B | post-treatment viral burden (log10 copies/mL) | (1) expected mean levels for regimens A and B,  (2) proportions of patients with undetectable levels for regimens A and B, and  (3) differences thereof in the target population. | model-based estimates of the means and the proportions of values observed to be undetectable, all with 95% C.I. estimates. |
| Investigate the accuracy  of established predictive models  for FEV1. | FEV1 and predicted FEV1 | mean differences between FEV1 and  predicted values expressed as a function of  height and age in the target population. | model-based point- and interval-estimates of mean differences, regression coefficients, and components of variance. |

1. Protocol reviewers are tasked with assuring that studies involving human participants are founded on good science, are reasonable in terms of participant burden, and will yield valuable information to better understand, diagnose, treat or manage a disease, condition, or behavior. A comprehensive and carefully constructed MPD is a sign to others that the investigative team takes seriously their scientific and ethical responsibility to participants, funders, and their institution.
2. It is HIGHLY RECOMMENDED that investigators include a professional statistician on the research team as a co-investigator to collaborate on the development and execution of all aspects of the study protocol; e.g., study design, specific aims, measures of interest, statistical analysis strategies and methods, and justification of the choice of sample size in terms of anticipated precision of estimators and anticipated power levels of test procedures.
3. Statistical consultation through NC TraCS (tracs.unc.edu) can be extremely helpful and is highly recommended; however, a brief statistical consultation does not necessarily guarantee that scientific review will be free of substantial concerns. In contrast to comprehensive scientific review, a brief statistical consultation has the potential to address only the delimited specific questions you ask. To arrange a TraCS consultation, first logon to <https://tracs.unc.edu/> then request a consult at <https://tracs.unc.edu/index.php/consultation>]
4. For those studies that are not subject to FDA regulations, it is recommended that investigators use the HIPAA-compliant online REDCap software system available from NC TraCS Institute at UNC. Use of REDCap and REDCap training sessions are available at no charge to UNC investigators. Fees are charged by TraCS only for assistance provided by TraCS Biomedical Informatics Core. For collection and management of human research data, spreadsheet software such as MS Excel is not recommended. Use of REDCap and REDCap training sessions are available at no charge to UNC investigators. Fees are charged by TraCS only for assistance provided by TraCS Biomedical Informatics Core. For collection and management of human research data, spreadsheet software such as MS Excel is not recommended.

Advantages of using REDCap:

* Reliability. REDCap is in use in over 1500 institutions worldwide. Developed at Vanderbilt University, REDCap is hosted and supported locally at UNC by NC TraCS Institute. UNC REDCap is hosted on sophisticated IT infrastructure and is backed up multiple times per day.
* Security. Users access REDCap online through a secure login page. Traffic between the web browser and the database is encrypted. Data storage complies with UNC’s encryption policy. User-rights management gives you full control authorizations. Audit trails provide accountability.
* Ease of Use. The user interface is intuitive allowing simple studies to be built in minutes. Built-in training resources allow new users to learn as they go. NC TraCS Institute offers weekly tutorial training sessions in Brinkhous-Bullitt. Web-based data entry can take place almost anywhere.
* Data Quality. REDCap supports critically important data quality features such as: Structured data dictionary, Skip logic, Mandatory fields, Range checking, Form locking/unlocking. The data quality module provides customized data quality checks. Data resolution workflow allows for data queries to be raised and resolved. For data monitoring limited reports/graphs can be generated by REDCap.
* Features. REDCap supports a broad range of project types from simple surveys through complex longitudinal clinical trials. Additionally, REDCap also includes support for: randomization and concealment, survey scheduling, data quality workflows, data coding (via Bioportal), text and voice messaging.
* Data export. REDCap exports CSV files along with Stata/SAS/R/SPSS code easily used to create formatted datasets.
* For further information see the following:

<https://tracs.unc.edu/index.php/services/informatics-and-data-science/redcap>

<https://ictr.johnshopkins.edu/wp-content/uploads/import/1426-recap.pdf>

**NOTE: UNC’s REDCap is not 21 CFR 11 compliant. If your study is FDA regulated, you will need to use a Part 11 compliant system. If you have questions about Part 11 compliance, contact the UNC OCT.**

**Final checks prior to submission to the IRB1 or SRC2 or PRC3 should assure:**

* All of the specific aims are explicitly stated (no unstated aims)
* The aims, measures, and analysis plans are well aligned.
* Each aim is fully detailed in terms of the variables involved and the population parameters of interest
* For each specific aim there is an appropriate well-written statistical analysis plan in Section 8
* The outcome variables and all other measures of interest are well-defined
* For all variables used in the study, the units of measure (or set of valid values) are specified
* Internal consistency: the various sections are in agreement (i.e., sections do not contradict one another)
* Boilerplate language has been replaced with study-specific details
* The version number and date of this draft of the protocol are current
* The table of abbreviations is complete and specific to the study; no missing or extraneous abbreviations
* Update the table of contents (so that it shows the correct page numbers of all sections)
* Delete pages i, ii, iii

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1 IRB – Internal Review Board -- research.unc.edu/human-research-ethics

2 SRC – Scientific Review Committee -- research.unc.edu/clinical-trials/src

3 PRC – Oncology Protocol Review Committee -- UNClineberger.org/protocolreview

<< End of the PREFACE section. Please delete the PREFACE section from your protocol document. >>

**Master Protocol Document**

|  |  |
| --- | --- |
| **Title** | < insert text > [should match IRB title] |
| **Sub‑Title** | < insert text > [sub-title or brief statement of purpose] |
| **Principal Investigator** | < name, department/division/unit >  < phone number > |
| **Co‑Investigators** | < name, department/division/unit >  < name, department/division/unit >  < name, department/division/unit > |
| **Statistical  Co‑Investigators** | < name, department/division/unit > [Names of the statisticians that are  < name, department/division/unit > involved in study planning and will  be involved as co-investigators in all  stages of the study.] |
| **Research Sites** | < insert text >  < insert text >  < insert text >  < insert text > |
| **Version Number**0.0 | DD MONTH YYYY |

**I have read, understood, and approved this version of the protocol.** [electronic signatures accepted]

Principal Investigator: Date:

Statistical Co-investigator: \_\_\_\_\_\_\_\_ Date:

|  |
| --- |
| **Statement of Confidentiality and Nondisclosure** This document is a confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior written approval of the Principal Investigator or other participating study leadership, except that this document may be disclosed in any medium to appropriate investigators, Institutional Review Boards, Scientific Review Committees, and others who are directly involved in the study specified herein under the condition that they keep the information confidential. |

# **Table of Version Changes**

|  |  |  |  |
| --- | --- | --- | --- |
| Previous  Version No. | Affected  Sections | Summary of the Changes  to the Protocol | Reason for Changes |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

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# **Statement of Compliance**

This study will be conducted as specified in the protocol and in accordance with the *International Conference on Harmonisation Guidelines for Good Clinical Practice* (ICH E6) and the *Code of Federal Regulations on the Protection of Human Subjects* (45 CFR Part 46).

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

If required by the IRB, the master protocol document, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *Scientific Review Committee* (SRC) prior to IRB review (research.unc.edu/clinical-trials/src).

The statistical analysis plans will be consistent with guidance in CONSORT Statement [1] or STROBE Statement [2], ICMJE recommendations [3], the 2016 and 2019 statements of the American Statistical Association [4,5], and recommendations in Nature [6,7].[[1]](#footnote-1)

All personnel involved in the conduct of this study have completed human subjects protection training.

# **Table of Abbreviations**

|  |  |
| --- | --- |
| AE / SAE | adverse event / serious adverse event |
| CFR | U.S. Code of Federal Regulations (www.eCFR.gov) |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences (cioms.ch) |
| CoC | certificate of confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials (www.consort-statement.org) |
| CRF | case report form |
| CRO | contract research organization |
| CSCC | UNC Collaborative Studies Coordinating Center (sites.cscc.unc.edu/cscc) |
| CT.gov | ClinicalTrials.gov website |
| DCC | data coordinating center |
| DSMB | data and safety monitoring board |
| eCRF | electronic case report form |
| eCTD | electronic common technical document |
| DOH! | I need to delete this example term (and others not used in this protocol) from this table |
| FDA | U.S. Food and Drug Administration (www.fda.gov) |
| GCP | good clinical practice |
| HIPAA | U.S. Health Insurance Portability and Accountability Act (www.hhs.gov/hipaa) |
| ICF | informed consent form |
| ICH | International Council for Harmonization (www.ich.org) |
| ICMJE | International Committee of Medical Journal Editors (www.icmje.org) |
| IDE | investigational device exemption |
| IDS | UNC Investigational Drug Services (uncids.web.unc.edu) |
| IND | investigational new drug application |
| IRB | institutional review board |
| MAR | missing at random criterion |
| MCAR | missing completely at random criterion |
| MNAR | missing not at random criterion |
| MICE | multiple imputation by chained equations |
| MOP | manual of procedures |
| MPD | master protocol document |
| N | number of enrolled participants |
| NDA | new drug application |
| OCT | UNC Office of Clinical Trials (research.unc.edu/clinical-trials) |
| OHRP | Office for Human Research Protections |
| PHI | protected health information |
| PI | principal investigator |
| PRC | UNC Oncology Protocol Review Committee (UNClineberger.org/protocolreview) |
| QA | quality assurance |
| RCT | randomized controlled trial |
| REDCap | Research Electronic Data Capture system |
| SD | standard deviation |
| SE | standard error |
| SOP | standard operating procedures |
| SRC | UNC Scientific Review Committee (research.unc.edu/clinical-trials/src) |
| STROBE | Strengthening Reporting of Observational Studies in Epidemiology (www.strobe-statement.org) |
| TraCS | N.C. Translational and Clinical Sciences Institute (tracs.unc.edu) |
| UNC | The University of North Carolina |
| UNCH | UNC Hospitals |

[Edit this table to include all of your study’s acronyms, abbreviations, or non-standard terminology.

Delete this guidance text and all entries in the table that are not used in the text of this protocol. ]

# **Protocol Synopsis**

[Brief 2-3 page overview of key elements more broadly described in the protocol.

When text in the body of the protocol is revised, please also update this Synopsis to match. ]

|  |  |
| --- | --- |
| Title | <insert text> [ If grant-funded, the text of the title should match the title of the grant or the title of a project within the grant.] |
| Study Description | <insert text> [ Brief description of the research questions to be addressed, interventions or observational exposures/conditions to be investigated, and general features of the study.] |
| Specific Aims  **(objectives)** | **Aim 1.** <insert text>  **Aim 2.** <insert text>  **Aim 3.** <insert text>  **Aim 4.** <insert text>  **Aim 5.** <insert text>  …  [Guidance: List here all of the study aims (objectives). Clear and complete specification of the aims is critically important.  Aims are usually numbered in order of importance beginning with Aim 1. It may be that some of the aims naturally have sub‑aims; e.g., Aim 1a, Aim1b, etc. It is most important to list all of the aims.  Each aim is often phrased as, for example, "Estimate the efficacy of…", "Evaluate the feasibility of…”, "Investigate the effects of…”, “Investigate association of …”, or "Explore relationships among …", etc. Avoid using the word “determine” which is a catch-all word. There is usually a more meaningful word to use instead.  The aims of this study should not be confused with the aims of the entire line of research. For example, if this is a feasibility study designed to assess patient-reported tolerability of using a health-tracking device that you plan to use in a future study of Drug X, then the objective of this study is *not* “to establish efficacy of X.”  There may be only one aim, or there may be many. For example, some of the aims might be to “Obtain preliminary data to support a research proposal” or “Obtain information needed to support the planning of a full-scale study and its sample size”.  Most studies have a mix of aims; e.g., While some aims may be to assess efficacy and safety, other aims may be exploratory for purposes of generating new hypotheses, and some aims might seek to pilot-test new assays, procedures or facilities.  Section 3 will provide comprehensive details of the aims.] |
| Target Population | **Inclusion Criteria** <insert text>  **Exclusion Criteria** <insert text>  [Guidance: The target population/s of interest are defined by the inclusion / exclusion criteria stated in terms of defining characteristics such as health status (known conditions, healthy control), exposures (smokers), age, sex, and location.] |
| Numbers of Enrollees | **A total of N = 00000 eligible individuals will be enrolled.**  [N is the ‘target sample size for enrollment’. The rationale for this choice of N should take into account a generous guess about the expected number of patients who will drop out, be withdrawn, or have incomplete data. N should be large enough to ensure that an adequate number of participants will have sufficiently complete data to support the planned statistical analyses.]  **We anticipate that at leastn = 0000 of the enrollees will complete all aspects of the protocol and have complete data.**  **Up to 000000 individuals will be recruited and screened.**  [Those who are found to be ineligible at screening are, by definition, not members of the target population/s.] |
| Interventions or  Exposures/Conditions | <insert text>  [Interventional Studies: If your study will administer one or more interventions to some/all of the enrolled participants after enrollment, please describe the interventions here and you may change the text “Interventions or Exposures/Conditions” to read “Interventions”. *Examples* of interventions include (but are not limited to) medical treatment regimens, therapeutic behavioral regimens, therapeutic device regimens, surgical procedures, diagnostic procedures, and imaging procedures. The experimental design will be randomized or non-randomized. The study will be controlled or uncontrolled (e.g., as in a single-arm trial). The study data will be cross-sectional or longitudinal.]  [Observational Studies: The enrolled participants will be observed and evaluated, but the investigators do not influence what treatments/exposures/conditions the participants experience. If your study will not be administering any interventions to any of the participants after enrollment, describe here the exposures or conditions investigated in your study and you may change the text “Interventions or Exposures/Conditions” to read “Exposures” or to read “Conditions” as appropriate. Some examples of exposures and conditions are as follows: previous exposure to tobacco, current lung cancer status (case or control), exposure to a medical procedure that was or will be performed as part of routine health care, vaccination status, CFTR genotype (FF, Ff, ff), etc. The study may involve a single cohort of participants or multiple cohorts. It may be prospective, retrospective, or some of both. The data may be cross-sectional or longitudinal. The study may (or may not) be a descriptive study such as a survey of a cohort, or a study of developmental trajectories in a cohort of infants.] |
| Outcome Measures | [Outcome measures that will used to address each specific aim]  **For Aim 1.** <insert text>  **For Aim 2.** <insert text>  **For Aim 3.** <insert text>  **For Aim 4.** <insert text>  **For Aim 5.** <insert text>  … |
| Statistical Analysis Plans  for Each Aim | [Very *brief* overview for each aim.]  **Aim 1 Plans.** <insert text>  **Aim 2 Plans.** <insert text>  **Aim 3 Plans.** <insert text>  **Aim 4 Plans.** <insert text>  **Aim 5 Plans.** <insert text>  … |
| Study Duration | <insert text>  [Estimated time from study activation to analysis of the data.] |
| Participation Duration | <insert text>  [Estimated time from the individual’s enrollment to their completion of all study procedures and activities.] |
| Enrollment Duration | <insert text>  [Time from enrollment of first participant to enrollment of the last] |

# **Introduction**

## Background Information

<insert text>

[Do not copy the background section from a grant application. This protocol should reflect only information relevant to the current study, which may be smaller in scope than a grant award.

This Background Information section should include a brief discussion of elements such as the following:

-- the target population of interest;

-- the health problem or question that the study will address (knowledge gaps);

-- the importance of the study;

-- previously published studies, unpublished data, and experiences that provide context and scientific justification for conducting the study. (Include references in support of claims. In-text citations should be numeric in ascending order to match the reference list.) ]

[Provide essential details of any as-of-yet unpublished data (if any) used to justify the proposed study, including any adverse event data.]

## Scientific Rationale

<insert text>

[Example: “The uncontrolled single-arm open-label single-center interventional clinical trial will be used to prepare for a full-scale RCT by investigating feasibility issues and by exploring changes in psychometric measures before, during, and after 3 days of treatment with drug XYZ base on a convenience sample of N=10 adult patients with condition ZZYYXX.”]

[Please provide a rationale for the following: the inclusion/exclusion criteria that define the target population of interest, the choice of specific aims, the study design.]

[If your study is interventional, provide a rationale for the interventions (including details such as dosage, timing, schedule, method of administration, validity of scales, … etc., as applicable).]

# **Specific Aims**

## Aim 1

<insert text>

## Aim 2

<insert text>

## Aim 3

<insert text>

## Aim 4

<insert text>

## Aim 5

<insert text>

…

[The specific aims are some of the most important part of the protocol. If they are not well-defined and clearly stated in adequate detail, then the other study design features, data analysis plans, and sample size rationale cannot be well-defined. Verify that the MPD specifies a statistical analysis plan for each aim; if there are statistical analyses or uses of the data that do not address any of the stated specific aims, then that is an indication that there exist some unstated aims. Be sure to explicitly state all of the aims. The most important aims should be the primary drivers of decisions about study design and choice of sample size. Further guidance is mentioned in the “Specific Aims” row of the Synopsis. Five examples of specific aims are as follows:

Aim 1. Characterize and compare regimens *A*, *B*, and *C* in terms of the regimen-specific proportions of patients who experience sustained viral response. The estimands of interest are the proportions and differences of proportions in the target population.

Aim 2. Investigate the safety of regimen *A* in terms of occurrences of AEs during treatment and follow-up. The estimand of interest is the proportion of patients in the target population who would experience one or more AEs when treated with regimen *A*.

Aim 3. Estimate the magnitude of association between exposure to pesticide *XYZ* and subsequent case-control disease status. The estimands of interest are the odds and the ratio of odds in the target population.

Aim 4. Pilot-test the performance of a monitoring device in terms of a patient-reported tolerability/discomfort score. The estimand of interest is the proportion of patients in the target population who would experience an acceptably low level of discomfort.

Aim 5. Explore relationships among the system of variables in order to generate new hypotheses.]

[ The specific aims, study design, variables of interest, and aim-specific statistical analysis plans should be well-aligned; for example, if investigating feasibility issues is a specific aim, then the protocol should specify outcome measures addressing feasibility and plans for statistical analysis of feasibility data. ]

|  |  |  |  |
| --- | --- | --- | --- |
| **Examples of Alignment of the Specific Aims with Measures and Aim-Specific Statistical Analysis Plans** | | | |
| **Specific**  **Aim** | **Outcomes**  **Measures** | **Population Parameters to be Estimated (“Estimands”)** | **Statistical**  **Estimators** |
| Investigate feasibility  of using a wearable monitoring device | questionnaire score  for tolerability (ordinal) | proportion of the patients in the target population expected to have adequately‑high tolerability. | observed proportion and 95% C.I. |
| duration of wearing device (days:hours) | proportion of the patients in the target population expected to wear the device per protocol. | observed proportion and 95% C.I. |
| binary indicator of drop‑out (Y,N) | proportion of the patients expected to drop out in samples from the target population. | observed proportion and 95% C.I. |
| Obtain information  needed to plan a  future full-scale study | periodic measures  of salivary cortisol (mg/dL) | (1) mean concentrations in the target population,  (2) standard deviations in the target population,  (3) intra-class correlation in the target population,  (4) proportion of values expected to be missing in samples from the target population. | (1,2,3) model-based estimates.  (4) observed proportion of enrollees with complete data,  all with 95% C.I. estimates. |
| Evaluate the relative efficacy of a treatment regimens A and B | post-treatment viral burden (log10 copies/mL) | (1) expected mean levels for regimens A and B,  (2) proportions of patients with undetectable levels for regimens A and B, and  (3) differences thereof in the target population. | model-based estimates of the means and the proportions of values observed to be undetectable, all with 95% C.I. estimates. |
| Investigate the accuracy  of established predictive models for FEV1. | FEV1 and predicted FEV1 | mean differences between FEV1 and  predicted values expressed as a function of  height and age in the target population. | model-based point- and interval-estimates of mean differences, regression coefficients, and components of variance. |

# **Study Design**

<insert text> [Briefly summarize the study design and rationales for its features.]

[The following aspects of your study design should be addressed and justified:

* Interventional vs. observational study design.
* Controlled vs. uncontrolled study design.
* Randomized vs. non-randomized allocation of enrollees to interventions (if any).
* Longitudinal vs. cross-sectional evaluations.
* Prospective vs. retrospective (e.g., use of medical records) vs. both (enrollees and historical controls).
* Single-site vs. multi-center; and the number of sites.
* Use of multiple stages (e.g., a preparatory study followed by a randomized trial).
* Use and impact of sub-studies (e.g., some of the enrollees are studied further).
* Use of sub-group analyses.
* Choice of dosage/route/regimen of study drugs (if any).
* For clinical trials: Phase I vs. Phase II vs. Phase III.
* Use and purpose of stratification during recruitment and enrollment.
* Use and purpose of stratification in randomization and/or in data analyses.
* Use and purpose of matching during enrollment (1:1, 1:2, 1:many, etc.)
* End-of-study criteria and discontinuation criteria for the participant.
* End-of-study criteria or stopping-rules for the entire study.

Note: the schedule of study procedures should be provided in section 7.

Briefly summarize the schedule of activities and procedures

* pre-screening, screening, enrollment, baseline, procedures/intervention, follow-up, unscheduled visits
* use of centralized services (e.g., lab assays, radiographic readings, genomics, metabolomics)
* brief summary of data collection]

[Consider including a Study Schema in the MPD to facilitate explanation of the proposed design. For example:

Figure 1. An Example Figure: This Example is for a Randomized Clinical Trial.

Obtain informed consent.

Obtain screening data and baseline data.

Apply inclusion and exclusion criteria.

*Recruitment*

*and Screening*

*Verification of Eligibility*

*and Enrollment*

Allocations by 1:1:1 Randomization

Perform additional baseline assessments.

*Visit 1*

Begin treatment regimens A, B, C

*Visit 2*

Follow-up assessments of outcome measures and safety

*Visit 3*

Final follow-up assessments of outcome measures and safety.

Participation completed.

*Visit 4*

## Treatment Design

<insert text> [Briefly describing the interventions or exposures or conditions of interest.]

[For both kinds of studies (interventional, observational), we generically refer to the specifications of the treatments/exposures/conditions of interest as the “Treatment Design”. Admittedly this use of “treatment” is short-hand jargon that refers to the given condition regardless of whether the given condition is a drug therapy assigned by randomization, a historical exposure to tobacco, a previous exposure to vaccine, or having the “case” condition in a retrospective case-control study.

In observational studies, we observe the effects of treatments/exposures/conditions without intervening to influence the treatments/exposures/conditions of the participants. For example, an observational cohort-comparison study might enroll a cohort of individuals who received vaccination, along with a cohort of individuals who chose not to be vaccinated.

In interventional studies, we observe the effects of treatments/exposures/conditions after assigning and administering interventions to the enrollees; e.g., a vaccine trial might randomize enrollees to vaccine or placebo.]

[If your study is an Interventional Study: If your study will administer one or more interventions to some/all of the participants after enrollment, please specify the details of the interventions and provide a rationale for the interventions chosen.

Examples of interventions are: medical treatment regimens, therapeutic behavioral regimens, therapeutic device regimens, surgical procedures, diagnostic procedures, and imaging procedures. The study might be controlled or uncontrolled. The data may be cross-sectional or longitudinal. The experimental design (i.e., how enrollees are allocated to treatment regimens) may be randomized or non-randomized.]

[If your study is n Observational Study: If your study will NOT administer any interventions to any of the participants after enrollment, you should specify the exposures or conditions that will be investigated and provide a rationale for choosing to study those exposures or conditions.

Examples of exposures and conditions are: previous exposure to tobacco, current lung cancer status (case or control), exposure to a medical procedure that was or will be performed as part of routine health care (e.g., a vaccination), CFTR genotype (FF, Ff, ff). The study may involve a single cohort of participants or multiple cohorts. Data might be collected prospectively, retrospectively, or some of both. The data might be cross-sectional or longitudinal. The study might be (for example) a descriptive study such as a survey of a sample from the target population, or a longitudinal study of height and weight trajectories in a sample cohort of infants.]

## Experimental Design

<insert text>

[Interventional Studies. If your study will administer one or more interventions to some/all of the participants after enrollment, please specify the complete details of the experimental design; i.e., how the interventions will be allocated to the enrollees (e.g., by randomization, systematic assignment, or self-selection.) Randomization could be simple, stratified, cluster-randomized, adaptive, use permuted blocks, etc.]

[Observational Studies. If your study will NOT administer any interventions to any of the participants after enrollment, enter the text “Not applicable. This is not an interventional study.”]

## Measurement Design

[Specify the occasions of evaluation, the measures evaluated on each occasion, their units of measure, and the roles they will play in the aim-specific data analyses. If your study is interventional then a table format such as **Table 1** is recommended. If your study is observational, then a table such as **Table 2** is recommended.]

[For interventional studies, Table 1 illustrated a recommended table format.]

**Table 1. Variables of interest: their occasions of evaluation, their uses for the aims, their roles in the study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables within Domains** | **Scale1** | **Occasions2** | **Aims3** | **Main Roles** |
| **Identifiers** |  |  |  |  |
| Participant’s unique ID | nominal | all | all | identifier |
| Treatment Regimen (A or B) | binary | E | all | identifier |
| **Clinical Health Profile** |  |  |  |  |
| systolic blood pressure (SBP) | mmHg | 0, 2, 6, 12 | Aim 1 | primary outcome |
| diastolic blood pressure (DBP) | mmHg | 0, 2, 6, 12 | Aim 1 | primary outcome |
| pulse wave velocity (PWV) | m /sec | 0, 2, 6, 12 | Aim 1 | secondary outcome |
| weight | kg | 0, 2, 6, 12 | Aims 1, 2 | covariate uses |
| height | cm | 0 | Aims 1, 2 | covariate uses |
| body mass index (BMI) | kg/m2 | 0 | Aims 1, 2 | covariate uses |
| age | decimal yrs | 0 | -- | screening |
| sex | categorical | 0 | -- | screening |
| smoker (current, former, never) | categorical | E | all | stratification |
| self-reported exercise per day | minutes | 0, 2, 6, 12 | Aims 1, 2 | covariate uses |
| **Medical Records** |  |  |  |  |
| concomitant medications list | nominal | 0, 2, 6, 12 | Aim 1 | exploratory uses |
| previous procedures list | nominal |  | -- | screening |
| co-morbidities list | nominal |  | -- | screening |
| **Research Lab Assays** |  |  |  |  |
| PK profiles (blood, urine) | multi-dim | 2, 6, 12 | Aim 1 | mediation4 |
| **Clinical Lab Assays** |  |  |  |  |
| hemoglobin A1c | % | 0, 2, 6, 12 | Aim 2 | primary outcome |
| pregnancy test | binary | S, 0, 2, 6 | -- | safety monitoring |
| complete metabolic profile | multi-dim. | S, 0, 2, 6, 12 | -- | safety monitoring |
| **Patient-Reported Outcomes** |  |  |  |  |
| self-reported hypoglycemia | binary | 0, 6, 12 | Aim 3 | exploratory uses |
| diabetes distress (self-reported) | ordinal 0-10 | 0, 6, 12 | Aim 3 | exploratory uses |
| daily glucometer readings | mg/dL | 0, 6, 12 | Aims 3, 4 | exploratory uses |
| use of wearable monitoring device | hours | 0, 6, 12 | Aim 4 | exploratory uses |
| device tolerability score | ordinal 0-10 | 0, 6, 12 | Aim 4 | exploratory uses |
| **Safety Monitoring** |  |  |  |  |
| AEs and SAEs documentation | events | 0, 6, 12 | Aim 5 | safety monitoring |

1 Units of measurement or the scale.

2 Occasions of evaluation or retrieval: **S** = screening, **E** = enrollment, **0** = baseline visit,

**2** = 2 weeks, **6** = 6 weeks, **12** = 12 weeks.

3 The specific aims in which the variable will play a role in data analyses.

4 Uses: assess medication adherence, mediation analyses, and exploratory analyses

In Table 1, the treatment regimens are:

A = ‘drug A’ + standard of care,

B = placebo + standard of care.

Recruitment and randomization will be stratified by smoking status.

[For observational studies, Table 2 illustrated a recommended table format.]

**Table 2. Variables of interest: their occasions of evaluation, their uses for the aims, their roles in the study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables within Domains** | **Scale1** | **Occasions2** | **Aims3** | **Main Roles** |
| **Identifiers** |  |  |  |  |
| Participant ID | nominal | all | all | identifier |
| Cohort (A or B) | binary | E | all | identifier |
| **Clinical Health Profile** |  |  |  |  |
| systolic blood pressure (SBP) | mmHg | 0, 12, 24, 40 | Aim 1 | primary outcome |
| diastolic blood pressure (DBP) | mmHg | 0, 12, 24, 40 | Aim 1 | primary outcome |
| pulse wave velocity (PWV) | m /sec | 0, 12, 24, 40 | Aim 1 | secondary outcome |
| weight | kg | 0, 12, 24, 40 | Aims 1, 2 | covariate uses |
| height | cm | 0 | Aims 1, 2 | covariate uses |
| body mass index (BMI) | kg/m2 | 0 | Aims 1, 2 | covariate uses**4** |
| age | decimal yrs | 0 | -- | covariate uses**4** |
| smoker (current, former, never) | categorical | E | all | stratification |
| self-reported exercise per day | minutes | 0, 12, 24, 40 | Aims 1, 2 | exposure |
| **Medical Records** |  |  |  |  |
| pregnancy status | binary | S | -- | screening |
| concomitant medications list | nominal | 0, 12, 24, 40 | Aim 1 | exploratory uses |
| previous procedures list | nominal |  | -- | screening |
| co-morbidities list | nominal |  | -- | screening |
| **Research Lab Assays** |  |  |  |  |
| metabolomic and proteomic profile | multi-dim | 0, 12, 24, 40 | Aim 5 | exploratory uses |
| **Clinical Lab Assays** |  |  |  |  |
| hemoglobin A1c | % | 0, 12, 24, 40 | Aim 2 | primary outcome |
| complete metabolic profile | multi-dim. | 0, 12, 24, 40 | -- | safety monitoring |
| **Patient-Reported Outcomes** |  |  |  |  |
| self-reported hypoglycemia | binary | 0, 12, 24, 40 | Aim 3 | exploratory uses |
| diabetes distress (self-reported) | ordinal 0-10 | 0, 12, 24, 40 | Aim 3 | exploratory uses |
| daily glucometer readings | mg/dL | 0, 12, 24, 40 | Aims 3, 4 | exploratory uses |
| use of wearable monitoring device | hours | 0, 12, 24, 40 | Aim 4 | exploratory uses |
| device tolerability score | ordinal 0-10 | 0, 12, 24, 40 | Aim 4 | exploratory uses |
| **Safety Monitoring** |  |  |  |  |
| AEs and SAEs documentation | events | 0, 12, 24, 40 | Aim 6 | safety monitoring |

**1** Units of measurement or the scale.

**2** Occasions of evaluation or retrieval: **S** = screening, **E** = enrollment, **0** = baseline visit,

**12** = 12 weeks, **24** = 24 weeks, **40** = 40 weeks.

**3**The specific aims in which the variable will play a role in data analyses.

**4**These variables are assumed to be confounding factors:

they influence both the exposure to exercise and the cardiovascular outcomes

Cohort membership is based on the pregnant enrollee’s self-report of first trimester exercise:

Cohort A = exercised ≥ 30 minutes per day during first trimester,

Cohort B = exercised < 30 minutes per day during first trimester.

[Table 1 and Table 2 are examples illustrating the recommended format and information.]

<insert text>

[Section 4.3 should define ALL variables (measures) involved in the study:

(1) ‘baseline’ variables that represent status prior to an intervention or exposure (e.g., genotype),

(2) variables representing the observational treatment/exposure/condition experienced

-or- variables indicating the treatment regimens assigned and administered to enrollees,

(3) outcome variables representing responses of interest,

(4) other variables ‘in the causal pathway’ (e.g., blood concentration of an interventional drug),

(5) all other variables used in the study.

For each variable, specify the units of measurement (or the range of valid values for categorical variables)

and the occasions of evaluation --as in Table 1 or Table 2.]

[Each outcome variable described in Section 4.3 should play a role in the statistical analysis plans (Section 8).]

[In Section 4.3, provide narrative text to explain further details; for example: if information about concomitant medications will be collected, identify which medications are relevant; specify the range of valid values for questionnaire sub-scales (which is required information for CT.gov); if there are multiple validated instruments or approaches for measuring an outcome indicate why you selected the one you chosen.]

[If the study is interventional. The outcome variables might be measured before, during, and after treatment.

Examples of outcome variables: viral burden values (log10 copies/mL), laboratory assay values, spirometric measures, genotypes, time-to-event values, radiographic image measures, questionnaire scores.

[If the study is observational. The outcome variables might be measured before, during and after an exposure, or could be measured longitudinally or cross-sectionally in cohorts with conditions of interest.

Examples of outcome variables: a binary indicator of new diagnosis of a disease in members of exposed and unexposed cohorts, longitudinal measures of height and weight in one or more cohorts of infants, viral burden values (log10 copies/mL), laboratory assay values, spirometric measures, genotypes, time-to-event values, radiographic image measures, questionnaire total scores and sub-scale scores.

[In both interventional and observational studies.

As an advantageous best practice, the specific aims should be prioritized in order of importance, and within each aim the outcome variables should be prioritized in order of their importance within the aim. Some/all of the outcome variables for an aim may be equally important. Often it is clear that one/some of the aim’s outcome variables are most important (‘primary’) and the aim’s other outcome variables have less important roles that logically deserve other labels (e.g., ‘secondary’, etc.) However, in some studies an aim’s outcome variables are all equally important; i.e., all are ‘primary’ for the aim and there is no logical reason to force some of them to be labeled otherwise. There should be logical compelling reasons for applying categorical labels such as ‘primary’, ‘secondary’, ‘tertiary’, ’other pre‑specified’, etc. to an aim’s outcome variables.

‘Exploratory’ is an appropriate label for statistical analyses that seek to generate new hypotheses; however, ‘exploratory’ is not a valid label for outcome variables. Example: the objective of Aim 1 is to use a particular ‘primary’ outcome variable in exploratory analyses.

Similar statements apply to the ‘post-hoc’ label; it is a valid label for analyses but is not a valid label for outcome variables.

If the study uses a multi-dimensional outcome (e.g., a vector of 10 symptom scores), the statistical analysis plans (Section 8) should explain how the scores will be used; e.g., as a multi-dimensional outcome, used in a composite score. For example, if you are using a questionnaire with sub-scales, indicate if the statistical analyses will use the set of sub-scales, the total score, or both; and why.]

[If your study is a clinical trial, then it is useful to anticipate requirements of ClinicalTrials.gov when developing

the MPD. For example, results for questionnaire sub-scales are required for ClinicalTrial.gov reporting.

Also, ClinicalTrials.gov recognizes four kinds of outcome variables: ‘primary’, ‘secondary’, ‘other pre‑specified’, ‘post hoc’. If an outcome variable is not given one of those labels, then ClinicalTrials.gov assumes that the variable is a ‘secondary’ outcome; reporting is required for all ‘primary’ and ‘secondary’ outcome variables.]

[Describe the procedures for collection of the study data from sources such as: medical records, clinical evaluations, laboratory assays, bio-specimens, images, questionnaires, physical tests, etc. Discuss how and by whom (clinician, investigator, research assistant, technician) measurements will be taken/data will be obtained.

The procedures explained here in Section 4.3 should be specific to the study and not part of standard clinical care (the latter should be summarized in a separate section). For procedures that require lengthy specifications, it may be best to locate the information in an appendix to the MPD. For example, a manual of operations (MOP) or standard operating procedure (SOP) may be a separate supporting document.]

Examples of variables by domains:

Baseline characteristics of participants

▪ Age, genotype, initial pain score, exposure status, …

Membership identifiers

▪ Condition status (case, control), Smoker (yes, no), Regimen assigned (A, B, C, D), Regimen received, …

Derived measures

▪ BMI (kg/m2) = weight(kg) / [height(m)]2, Survey total score = sum of sub-scores, …

Outcome Measures for Evaluation of Safety

▪ [e.g., rate of hospitalization, rate of safety events, rate of drop-outs due to adverse events]

Measures for investigations of feasibility of a protocol

▪ Binary indicator of refusal to consent, indicator of drop-out, regimen tolerability score, …

Laboratory assay measures (Please specify the lower and upper limits of detection given the methodology used)

▪ Viral load (log10 copies/mL)

Demographic variables

▪ Age, sex, education, employment, income, ….

Medical history variables

▪ Diagnoses, vaccinations, hospitalizations, …

Medication history variables

▪ Specific medications (dose, dates), current prescription, over-the-counter, …

Physical exam findings and vital signs

▪ Heart rate (bpm), Systolic and diastolic blood pressures (mmHg), …

Laboratory assays for statistical analyses (screening, baseline, pre-treatment, post-treatment, …)

▪ Comprehensive metabolic panel (glucose, BUN, creatinine, …), lipids (HDL, LDL, etc.), …

Laboratory assays for continuous monitoring of safety

▪ ALT, AST, occurrence of an AE or SAE, …

Imaging measures and assessments (describe equipment, duration, frequency, dose, etc.)

▪ Diagnostic results, lean mass, fat mass, bone density, …

Questionnaires/survey instruments (describe scales, sub-scales, version, psychometric properties, etc.)

▪ Tolerability score for a wearable device, PROMIS T-score for fatigue, depression score, …

Measures of videotaped behavior (describe protocol, rating systems, inter-rater reliability, etc.)

▪ Frequencies, durations, and scores for affect, intensity, etc.

Special assays (pharmacokinetic, immunologic, microarray, etc.)

▪ Cmax, Tmax, Cmin, CL, AUC0-24, …

[Note: The term "endpoint" applies only to time-to-event analyses. Examples of “end points” are death; hospitalization; hospital discharge; and disease remission, progression, relapse, and cure. The following

are not “endpoints”: outcome variables, estimators, estimands, hypotheses, tests, the date the study ends.

NIH and FDA guidance blurs the use the word ‘endpoint’ to refer to a special class of outcome measures such as an indicator of the occurrence of mortality or irreversible morbidity or other event. As a best practice the word ‘endpoint’ should be reserved to refer to endpoint events.]

# **Study Participants**

## Numbers of Participants

5.1.1. Number to be screened: ≤ 00000

<insert text> [some will not be eligible for enrollment]

5.1.2. Number to be enrolled: N = 00000

<insert text> [this is the “target sample size” for enrollment]

[Discuss the number to be enrolled, which should take into account a generous guess about the expected number of patients who will drop out, be withdrawn, or have incomplete data. The target sample size for enrollment should be large enough to ensure that an adequate number of participants will have sufficiently complete data for the statistical analyses. Clearly state that participants who drop-out or have missing data will *not* be “replaced”; replacing participants who drop out is an unnecessary complication (adaptive enrollment) that has the potential to induce selection biases and thus may be a threat to the validity of the study.]

[Specify the sources of recruitment; e.g., clinics, out-patients, in-patient, student health, general population.]

[Interventional Studies. If your study will administer one or more interventions to some/all of the participants after enrollment, discuss the numbers of enrollees you expect to receive each of the treatment regimen.

(The study is interventional even if the patient chooses the regimen they will receive.]

[Observational Studies. If your study will NOT administer any interventions to any of the participants after enrollment, discuss the expected distribution of the levels of exposures or categories of conditions.

For example: the numbers of cases and controls you expect to enroll; the expected numbers of exposed and unexposed enrollees; the distribution of levels of exposure among the exposed; the numbers of enrollees in each of the cohorts. Also describe the study cohorts; e.g., cases/controls, exposed/unexposed.]

## Eligibility Criteria

<insert text>

[The inclusion/exclusion criteria define the target population/s of interest. (Location of recruitment is an implicit eligibility criterion if it is not listed explicitly.) Usually, the enrolled participants are treated as a sample from the target population of interest and data from the sample is used to generate inferences or new hypotheses about that target population.]

[“Descriptive statistical methods” (e.g., frequencies, proportions, percentiles, sample mean, sample SD, etc.) describe the sample of participants enrolled.]

[“Inferential statistical methods” (e.g., point-estimates and interval-estimates of population parameters, hypothesis tests) are used to make inferences about the target population. ]

[Use the following guidance when developing participant eligibility criteria to be listed as inclusion and exclusion criteria below.

* For interventional studies, the risks and benefits of the interventions should be considered when choosing the inclusion/exclusion criteria.
* If reproductive status is an eligibility consideration, describe procedures for assessing eligibility, frequency of pregnancy testing, specific contraception requirements, etc.
* Identify specific lab tests or clinical characteristics to be used as eligibility criteria.
* Do not list the same eligibility consideration as both inclusive and exclusive. For example, it would be redundant to write “Inclusion: age >21 years. Exclusion: age ≤ 21 years.”
* Lifestyle Considerations - Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, timing of meals relative to dosing, intake of caffeine, alcohol, or tobacco, or limits on activity), and considerations for household contacts. Describe what action will be taken if prohibited medications, treatments or procedures are indicated for care (e.g., early withdrawal)
* Valid eligibility criteria must be evaluable during the screening process. For example, “Completing all of the study procedures and activities” is not a valid criterion. In contrast, “Completing a set of baseline questionnaires during the screening process” is a demonstration of willingness to adhere to protocol and can be used as a valid criterion during screening.]

5.2.1. Inclusion Criteria

[Specify the inclusion criteria and their source – e.g., self-report, medical chart review, etc. – and the timeframe/window, such as “lifetime history” or “within 3 months of randomization”. If there are criteria that apply to a subset of participants only, provide a separate list for that group. Include the following statementpreceding (bulleted or numbered) criteria: ]

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

* <insert text>

5.2.1. Exclusion Criteria

[Specify the exclusion criteria and their – e.g., self-report, medical chart review, screening procedures including laboratory test results – and the timeframe/window, such as “lifetime history” or “within 3 months of randomization”. If there are criteria that apply to a subset of participants only, provide a separate list for that group. Include the following statementpreceding (bulleted or numbered) criteria: ]

**Any individual who meets one or more of the following criteria will be excluded from participation:**

* <insert text>

## Enrollment/Selection Strategies

5.3.1. Prospective Recruitment -or- Retrospective Selection

<insert text>

[If your study will retrospectively retrieve data from selected individuals (e.g., a study of existing electronic medical records), describe the methods you will use to select and include (“enroll”) the individuals of interest. Even if the study is entirely retrospective, there nevertheless should be well-defined inclusion/exclusion eligibility criteria for “enrollment” of individuals into the study.]

[If your study will prospectively enroll individuals, describe the recruitment strategy and frame it in terms of prior institutional/personal experience recruiting from the target population/s. If vulnerable populations (children, pregnant women, fetuses, neonates, prisoners) will be enrolled, briefly describe additional protections that will be employed: <http://www.hhs.gov/ohrp/humansubjectsguidance/45cfr46.html>.]

[For multi-site studies, specify numbers to be screened and enrolled at each site.]

[For studies that sequentially enroll groups of participants (e.g., dose-escalation studies, group-sequential studies, studies with adaptive designs or interim-analysis designs, etc.) specify the details of those enrollment plans.]

5.3.2. Screen Failures

<insert text>

[“Screen Failures” refers to consented individuals who prove to be ineligible for the study; i.e., they do not satisfy the inclusion/exclusion eligibility criteria. Ineligible individuals are not members of the target population defined by the eligibility criteria.

Explain how screen failures will be handled, including conditions and criteria upon which re-screening is acceptable (as an individual might become eligible at a later date). Discuss the proportion of screened individuals that you expect will be ineligible.]

## Strategies for Retention

<insert text>

[If your study follows some enrollees prospectively, then describe your study’s plans for minimizing drop-out and enhancing retention (e.g., visit reminders, methods of maintaining contact, incentives for visit attendance). Consider and discuss the likelihood of withdrawals / drop-outs. The risk can be higher in studies that involve a worsening health condition, increasing participant burdens, and requirements for long-term study participation. Drop-out can occur at any time; e.g., in clinical trials drop-out can occur before, during, and after the treatment period.]

[If your study is entirely retrospective, enter the text “Not applicable” in this section.

## Matching and Stratification

<insert text>

[Enrollment of participants (prospective or retrospective) might involve stratification, matching of individuals, or frequency matching among cohorts. If applicable, specify *exactly* how any matching and/or stratification of enrollees will be accomplished. Specify the details of algorithms and procedures to be used.]

## Randomization and Concealment

<insert text>

[Interventional studies. If the enrollees will be allocated to treatment regimens by some form of randomization, then identify who will create and maintain the randomization schedule (table) or schema.]

[Provide complete details on the methods and algorithms used for computing and preparing the randomization tables. If stratified randomization will be used, provide a justification for the particular stratification chosen. If adaptive design strategies will be used, provide complete details and provide a rationale for the chosen strategy.]

[Specify the procedure(s) for randomization concealment, i.e., the technique used to prevent selection bias by concealing the allocations from those recruiting, enrolling, and assigning individuals, until the moment of assignment. Randomization without allocation concealment is *not* reliable randomization (as explained in the CONSORT Statement publications).]

[Observational studies. Enter the text “Not applicable” in this section.]

## Blinding

<insert text>

[Explain whether treatments/exposures/conditions will be masked (blinded), who will be blinded (e.g., enrollees, recruiters, coordinators, investigators, lab technicians) and when they will become unblinded.]

[For example, lab assays, and scoring of behavioral videos should usually be done in the blind. Double-blinding is less common in observation studies, more common in randomized studies.]

[If blinding is used, discuss procedures for handling expected and unexpected breaking of the blind.]

# **Treatment Design: Procedures**

[If your study is interventional: Here, “Treatment Design: Procedures” refers to plans for management and administration of the treatments/exposures/conditions assigned to the study participants after enrollment. The assignments may be randomized or non-randomized; the specific way of assigning interventions to enrollees is called the “experimental design”. For example, if we say “Let’s see what happens if we give a few of our patients this vaccine treatment regimen”; the study is an uncontrolled interventional trial that is subject to temporal confounding biases and limitations as can occur in observational studies.]

[If your study is observational: Here, “Treatment Design: Procedures” refers to the definitions and details of the treatments/exposures/conditions observed in the study participants. In observational studies, the enrolled participants will be observed and evaluated, but the investigators do not influence what “treatments” (regimens/exposures/conditions) the participants will experience or have previously experienced. The cohorts (‘enrollees’) represent samples from populations or sub-populations of interest. Examples of study designs include: study of a single cohort, a survey of a cohort, comparisons of cohorts, a case-control study, or observations on cohorts receiving specific treatment regimens as part of standard care.]

[ **Please complete only the sub-sections below that are relevant to your study;**

**if the subsection is not relevant, delete the sub-section.** ]

Description <insert text> [Describe the treatment regimens / exposures / conditions.

For medical treatment regimens, sources for this information about the treatment regimen/s may include: Investigator's Brochure (for investigational drug or biologic); package insert (for FDA-approved drug or biologic); proposed labeling and material safety data sheet (Material Safety Data Sheets for investigational device); final labeling (for a market device). Provide this information for each article as applicable. Provide Labeling/Packaging/Formulation information supplied by manufacturer/sponsor.

For procedural/surgical treatment regimens, provide complete information for each procedural intervention (as applicable). Sources for this information may include: administration manuals, equipment specifications, training manuals, participant educational materials. Also provide complete information regarding the training of personnel required to perform the procedures. Describe how and by whom the individuals administering the intervention will be trained and evaluated for adherence to the protocol / Manual of Procedures (MOP); include frequency of monitoring / re-training if needed. Describe how the procedural intervention will be standardized / calibrated to insure uniformity across sites, over time, and among those administering it.]

Acquisition <insert text> [State how any experimental test article/s (drugs) or device/s --if any-- will be acquired; e.g., from manufacturer, IND/IDE Sponsor, UNC Investigational Drug Services, or internally as for a device developed by a UNC faculty member or laboratory.]

Storage <insert text> [Specify storage requirements (if any) in terms of location, temperature, humidity, security, and stability (handling, expiration time for usage).]

Preparation and Administration <insert text> [Preparation, safety precautions, route, dose, frequency of administration, holding conditions once prepared. Specify policies regarding delay or modification of administration (such as due to AE or concern).]

Accountability <insert text> [Procedures to track receipt, distribution, use, return, destruction.]

Rescue Procedures/Medications <insert text> [Describe rescue procedures or medications that are permissible or required for adverse events.]

Adherence Monitoring/Evaluations <insert text> [Discuss procedures and evaluations used to assess participant adherence to protocol. For example, pill counts, pharmacokinetic assays, etc.]

Concomitant Therapies <insert text> [Describe what is therapy/s are prohibited, what is recommended, what is allowed, and what information about this topic will be collected as part of the study.]

# **Schedule of Activities and Procedures**

## Table of Events

[Provide a table of such as the following example. Revise this table or replace it with your own table.]

**Table 3. Example schedule of activities and procedures for a randomized clinical trial**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedure | | Visit 0  screening | Visit 1  baseline | Visit 2 | Visit 3 | Visit 4 | Visit 5  by phone | Early  Stop |
| Recruit a Sample of Patients | Informed consent | X |  |  |  |  |  |  |
| Eligibility assessments | X | X |  |  |  |  |  |
| Enrollment and randomization |  | X |  |  |  |  |  |
| Treatment | Administer regimens |  |  | X | X | X |  |  |
| Physical  Exams | Comprehensive exam | X |  |  |  | X |  | X |
| Symptom-directed exam |  |  |  | X |  |  |  |
| Evaluate vital signs |  | X | X | X | X |  |  |
| Safety  Monitoring | Review concomitant meds. |  | X | X | X | X | X |  |
| Medical history |  | X | X | X | X |  | X |
| Psychological surveys**1** | X |  | X | X | X |  |  |
| Assessment of AEs |  |  | X | X | X | X | X |
| Clinical  Labs | Pregnancy test | X |  | X |  |  |  |  |
| Serum chemistry**2** |  | X | X | X | X |  | X |
| Hematology**3** |  | X | X | X | X |  | X |
| Urinalysis**4** |  | X | X | X | X |  | X |
| Research  Labs | Immunology**5** (blood) |  |  | X |  |  |  |  |
| Cortisol (mg/dL, saliva) |  |  | X |  |  |  |  |
| Genotype (blood) |  |  | X |  |  |  |  |
| Patient Reported  Outcomes | Pain scores (ordinal) |  | X | X | X | X |  | X |
| Fatigue scores (ordinal) |  | X | X | X | X |  | X |
| Strength scores (ordinal) |  | X | X | X | X |  | X |

**1, 2, 3, 4, 5** Footnotes that list and define the measures of interest are used here.

[Clearly distinguish activities and procedures that participants will complete

in the course of clinical care from those that are solely for research purposes.]

## Screening

<insert text> [The purpose of screening is to identify individuals who are members of the target population/s.]

[For prospective studies (observational or interventional), specify a window for this activity; e.g., Day -14 to Day 0 with Day 0 being the day of enrollment. [Initial pre-screening (prior to informed consent) may be done by phone (with verbal consent) to assess potential eligibility; then, confirmatory tests/evaluations are performed at screening (after informed consent). State the time frame prior to enrollment within which tests and evaluations must be done, e.g., within 2 weeks, within 28 days. List all tests/evaluations that will be done to assess eligibility. Informed consent must be obtained prior to performing screening procedures required for eligibility; this may be accomplished using a separate (shorter) screening consent form or by using the (full) study consent form. List all procedures that will be done at screening, e.g., obtain consent, review medical history, schedule study visits, provide participant instructions. After obtaining consent, successful completion of baseline questionnaires can be a valid screening procedure as it demonstrates a willingness and ability to participate.]

[For studies that are entirely retrospective (and observational), explain any screening procedures used to select and “enroll” the retrospective participants.]

## Enrollment

<insert text> [For prospective studies, enrollment occurs on Day 0. List all evaluations/procedures in the sequence they will occur and that will be done to assess or confirm that a potential participant still meets eligibility criteria and may be enrolled, e.g., verify inclusion/exclusion criteria; review tobacco use, administer the intervention, provide drug diary. Clearly identify evaluations that will be used to measure outcomes, e.g., visual analog/digital pain scale; fMRI (to characterize brain network organization). Additional baseline data may be obtained on Day 0; in some cases, baseline evaluations can be obtained in a window of time such as Day 0-7.]

[For retrospective studies, explain how eligibility will be verified to ensure that only eligible individuals are selected for “enrollment”.]

## Study Visits

<insert text> [Visits can be labeled as Visit 1, Visit 2, etc. or as Time 1, Time 2, etc. Specify a window for each visit; e.g., V1 during Day 0 to Day 3, V2 during Day 14 ± 3, etc. List all interventions/evaluations/procedures in the sequence they will occur, e.g., record results of physical exam; record adverse events as reported by participant or observed by investigator; collect blood; administer intervention; review diaries.]

## Final Visit

<insert text> [Specify a window of time for this event. List all interventions, evaluations, procedures in the sequence they will occur; e.g., record AEs as reported by the participant or observed by care providers, record self-reports of adherence to protocol, provide final instruction to participant.]

## Phone Contacts

<insert text> [Describe information/data to be collected. Specify windows of time scheduled for the calls.]

## Follow-Up Contact

<insert text> [Describe information/data to be collected, e.g., adverse events, disease progression/recurrence.]

## Early Discontinuations

Data to be Collected <insert text> [If a participant chooses to withdraws consent or chooses to discontinue the treatment/exposure/condition that was being observed, or the investigator discontinues or modifies their treatment regimen, specify the visit procedures evaluations that will be performed and data that will be collected. Indicate if you plan to collect medical records data for the duration of the study for follow-up purposes, even if the study intervention is discontinued. It is a best practice to follow participants who drop out; to the extent it is feasible and ethical, their outcomes should be recorded in the database.]

Criteria for Intervention Discontinuation <insert text> [Specify criteria for discontinuing or modifying an intervention; e.g., new or worsening symptoms that indicate continuing the treatment regimen would not be in their best interest); participant develops a condition that is a contra-indication; participant noncompliance that increases participant’s risk of harm.]

## Enrollees May Drop Out

<insert text> [The MPD should clearly state that participants may voluntarily withdraw from participation at any time, for any reason, with no penalty or loss of rights. The MPD should clearly state that the reasons for drop-out and missing data will be documented in/with the database. Describe efforts that will be made to follow up those who discontinue participation. Follow-up is especially important for the major outcomes of interest. Describe what efforts, if any, will be made to re-contact participants that are ‘lost to follow-up’.]

# **Statistical Analysis Plans**

[This section should be developed in collaboration with a professional statistician. If a professional in the statistical sciences is not available to you in your department or research unit, please contact the Biostatistics Core or the N. C. TraCS Institute (tracs.unc.edu).]

## Strategies that Apply to all the Aims

<insert text> [This section should specify best practices and statistical strategies that apply to all specific aims.

Several examples of some recommended text are provided below. ]

* To help ensure replicability of the research, the analysis plans will be reviewed and finalized prior to collection of data (*a priori*). For each specific aim, the analysis plans specify detailed steps for obtaining estimates of the population parameters of interest (e.g., treatment effects) and for making inferences.
* For each aim, sensitivity analyses will be performed to assess the robustness/fragility of the main results as indicated by their sensitivity to reasonable perturbations of the choices of the methods and assumptions used. Any question about the optimal choice of methods and assumptions are best handled by relegating competing approaches to roles in the domain of sensitivity analyses. Results of the sensitivity analyses will be used to guide our level of trust in the main results.
* Human studies are prone to drop-out, missing data, and interval-censored values. The reasons for drop‑outs, missing / censored data values, and protocol departures will be documented in the database. Best practices for dealing with incomplete data will depend on the documented causes of those occurrences. In the analysis plans established *a priori*, the strategies for coping with incomplete data will be based on anticipated causes. Alternative methods for dealing with incomplete data will play important roles in the sensitivity analyses.
* The analyses for each aim will focus on the magnitude and direction of point- and interval-estimates of the population parameters of interest. To indicate precision, all statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CI). The CI will be interpreted as the set of potential values of the population parameter that are most compatible with the observed data.
* All hypothesis tests yielding large p-values will be reported as being inconclusive. For all sample sizes, all hypothesis test procedures are (by design) incapable of establishing that the null hypothesis is true.
* If p-values are computed they should be reported to several decimal places without categorizing or dichotomizing the p-value; that is, the words “significant” and “non-significant” should be avoided. The p‑value should be reported and interpreted as a continuous measure indicating the availability of information against the (null) hypothesis being tested. The available amount of information against the null hypothesis is equal to the Shannon Information S-value, and the p-value = (½) S-value. Smaller p‑values (larger S‑values) indicate greater amounts of available information. Larger p‑values indicate a lack of information; e.g., if p = 1 then the S = 0. If p = 0.03125 then S = 5 which indicates a result that is as-surprising-as observing 5 ‘heads’ in a row when flipping a coin 5 times to test whether it is a fair coin. Due to lack of information, large p-values cannot be used to draw any conclusions as to whether the tested null hypothesis is true or false. Lack of availability of evidence of an effect is not evidence of a lack of effect.
* The proposed statistical analysis strategy acknowledges that no p-value can reveal the plausibility, presence, truth, or importance of an association or effect --which is consistent with the statements of the American Statistical Association [4,5], the recommendations in Nature [6,7], and guidance, such as the CONSORT Statement [1], STROBE Statement [2], and ICMJE guidance [3].[[2]](#footnote-2)]
* The analysis plans will include outcome-dependent exploratory analyses to generate new hypotheses.
* Graphical methods such as forest plots will be used to visualize the analysis results.

## Sample Description

<insert text>

[Provide plans for using graphical methods and other descriptive methods to characterize the cohorts and summarize their data. Recommendations: Plan to use graphical figures (e.g., forest plots with tabulations, scatter plots, histograms, box-and-whisker plots, etc.) instead of tables when feasible. Descriptive statistical methods are those used to describe the sample of individuals studied; they include graphical figures, counts, frequencies, sample means, sample standard deviations, percentiles, min, max, and standardized differences. In contrast, point- and interval- estimates of population parameters, and hypothesis tests about population parameters are not descriptive methods. They are inferential methods designed for making inferences about the target population.]

[The descriptive statistical methods may be used to characterize separately each cohort or treatment arm.

In interventional studies, comparisons of treatment arms on baseline/pre-treatment characteristics should rely on standardized differences; use of p-values is highly inappropriate and should be avoided.

In observational studies, comparisons of cohorts on initial/baseline characteristics should rely on standardized differences; use of p-values is not useful for identifying confounders and should be avoided.]

## Aim-Specific Plans

[Consider the following guidance on providing analysis plans **for each Specific Aim**:

* Specify the roles of the variables involved and define all aspects of any statistical models (including covariates included in the regression equation).
* A rationale should be provided for the categorization of any continuous measures.
* Decisions about distributional assumptions and transformations of scale should be decided a priori whenever possible based on previous studies; e.g., IL-6 generally follows a log-normal distribution in various human subpopulations, log10 RNA copies/mL is well-known, etc. Any attempts to evaluate "normality" of residual distributions or otherwise, should be relegated to a role in the set of sensitivity analyses.
* For time-to-event analyses: Explain methods and assumptions, competing risks, kind/s of censoring, etc.
* For observational studies: Discuss the strategy for dealing with confounding. Confounders are factors that have a causal influence on both the exposure and the response of interest. Confounders should be identified prior to collecting data (*a priori*) based on logical considerations and information from previous studies.
* For randomized studies: Confounding bias is not a concern in a randomized study if the missing data and drop-outs are caused by mechanisms that satisfy the MCAR criteria (or the MAR criteria in some cases).
* Describe the strategies that will be used to cope with missing data values and drop-out, and explain whether those strategies may cause selection bias.
  + If hypothesis tests will be performed during the aim-specific analyses, specify all of the tests. Include a statement that all hypothesis tests that yield large p-values will be reported as being inconclusive. This is a limitation of test procedures; in contrast, point-estimates and confidence-interval-estimates are always informative to some degree. Specify a plan for dealing with any multiplicity of hypotheses when drawing a single conclusion that relies on multiple hypothesis tests.
  + The plans should clearly state that all estimates of population parameters (treatment effects, correlations, rates, odds ratios, etc.) will be tabulated along with corresponding confidence intervals or standard errors.
  + To guide our level of trust in the main results of the study, the plans should include use of sensitivity analyses to evaluate the robustness/fragility of main results to reasonable perturbations of the statistical methods and assumptions used. Examples of sensitivity analyses include examination of the impact of the following: using alternative versions of the models fitted, including or excluding questionable data values, use of reasonable alternative methods for coping with missing data, use of various methods for minimizing biases due to confounding. Sensitivity analyses should also include assessments of assumptions, such as, use of diagnostic analysis of residuals for linear models, diagnostics concerning influential observations, and goodness-of-fit diagnostics. Sensitivity analysis results should only be used to guide our level of trust in the main results.
  + If an analysis will rely on intent-to-treat (ITT) estimation, modified-ITT estimation, as-treated estimation, or per-protocol estimation, then clearly define in exact details which participants will be included in the computations.]

Plans for Aim 1. [e.g., evaluate efficacy, characterize and compare two treatment regimens.]

<insert text>

Plans for Aim 2. [e.g., evaluate safety, characterize and compare two treatment regimens.]

<insert text>

Plans for Aim 3.[e.g., conduct pilot-testing to evaluate performance of new assays, devices, systems, etc.]

<insert text>

Plans for Aim 4.[e.g., investigate feasibility issues of protocols and methods to prepare for a future study; examples of estimands of interest: in a sample drawn from the target population the proportion of enrollees expected to dropout or have incomplete data.]

<insert text>

Plans for Aim 5. [e.g., conduct exploratory analyses to generate new hypotheses. In the plans for exploratory analyses (to search for patterns and relationships and thus generate new hypotheses), the data explored should not also be used to test the new hypotheses. Use of p-values is not a valid method for generating hypotheses and should be avoided in favor of better exploratory methods: e.g., graphical methods, simple tabulations, model-based methods, cluster-analysis methods, machine-learning methods, etc.]

<insert text>

## Planned Interim Analyses

<insert text>

[If interim analyses will not be used, clearly state in this section “**No interim analyses will be performed**.”]

[If interim analyses will be used, provide a rationale for your use of an adaptive study design that involves interim analyses. Specify the purpose, timing, the number of interim analyses, whether the interim results have the potential to change the final sample size or stop the study early, and which aims and which outcome variables will be involved.]

[If interim analyses will have the potential to stop the study early or change the final sample size, then the statistical analysis plans MUST specify methods appropriate for accommodating interim analyses, and the sample-size rationale MUST take into account the use of interim analyses.]

# **Sample Size Rationale**

<insert text>

[Guidance: In Section 9, provide a compelling rationale for the chosen target sample size (N=00000 enrollees) as well as the resulting sizes of treatment arms or cohorts (defined by condition or exposure status). The rationale should also discuss the numbers of longitudinal/repeated measures (if any) for each of the primary outcome measures as that is also an important feature of the sample size rationale. There must be some reasons why you believe the chosen sample‑size plan is appropriate. In terms of the likelihood of successfully achieving each of the study’s aims, explain in simple language why you believe the proposed sample-size plan is a good choice. The aims will be successfully achieved to the extent that their results are useful, and not inconclusive and uninformative.]

[Consider: What are the chances that the results for Aim 1 will be inconclusive, uninformative, and therefore not useful/publishable? What about the other aims? Sample size analysis is an assessment of your own personal research risk. How much risk are you willing to take? How much risk is the funding agency willing to take? Your personal research risk can be reduced: by avoiding missing data and drop-out; by ensuring data quality and best practices in data management; by increasing the sample size; by increasing the number of repeated/longitudinal measures; by use of analysis strategies and methods that are most efficient.]

[For each specific aim, a sample-size analysis is performed based on (a) the specifications of the study design and the aim, (b) the aim‑specific analysis plans, (c) existing information from previous studies about the usual distributions of the outcome variables of interest, (d) judicious conjectures and well-reasoned assumptions, and (e) choices about the level of risk the stake-holders are willing to take. That input is used to (1) obtain point- and interval-estimates of the anticipated levels of the precision of the main estimators, (2) obtain point- and interval-estimate of the anticipated power levels of the main statistical hypothesis tests (if any), and (3) assess requirements for use of desired statistical methods (e.g., logistic regression requires large sample sizes).]

[Sample size is a choice: Because decisions and conjectures must be made to perform sample-size computations, and because sample-size requirements will differ across aims, analyses, estimators, and hypothesis test procedures, judgement is involved in choosing a target sample size for the study.]

[It is important to consider the uncertainty of sample-size analysis results; the uncertainty is often large. Computations regarding precision and power should take into account uncertainty in the inputs; e.g., for a power calculation, an estimate of the population SD reported in a publication should *not* be assumed to be the true value of the population SD; rather, that SD point-estimate should be used along with its confidence-interval estimate to obtain point- and interval- estimates of the anticipated level of power. Ignoring uncertainty in the assumed input values yields highly unreliable sample size estimates that are too small or too large. A studies is more (less) likely to be conducted if a small sample size seems to be (un)satisfactory. And, as noted by Browne (1995), “If one simply uses the sample standard deviation from a small pilot sample, the chances of actually achieving the planned power may be as low as 40%.”(Browne (1995) “On the use of a pilot sample for sample size analysis”, Statistics in Medicine, 14, 1933-1940).]

[Valid considerations in choosing or justifying a sample size include the following:

* how much risk the stake-holders are willing to take,
* sample-size needs of each specific aim, with some aims being considered more important than others,
* the anticipated levels of precision of the estimators (i.e., anticipated widths of confidence intervals),
* anticipated levels of power of the hypothesis tests (if any) under reasonable realistic conjectures,
* the probability that the null hypothesis will be rejected but the sign of the treatment effect is wrong,
* the needs of any intended statistical methods that require large sample sizes for validity,
* availability of eligible participants,
* costs and time requirements,
* expert opinion (may be valid in some studies).]

[The following are not valid considerations when choosing or justifying a sample size:

* This is a pilot study.
* This particular treatment has never been studied before.]
* Another (published) study used this sample size.

(Remember that published effect sizes tend to be biased upwards because of publication selection biases. <https://statmodeling.stat.columbia.edu/2017/12/04/80-power-lie>.) ]

[Anticipated precision of key estimators should be an important consideration when justifying or choosing a target sample size. A sample size just large enough to easily reject a hypothesis such as “the treatment effect is exactly zero in the target population” is often not large enough to provide satisfactory precision for the estimator of the treatment effect. Anticipated precision a key estimator can be evaluated in terms of the anticipated half‑width of the 95% confidence interval –which is known as the “margin of error”. Calculation of an anticipated margin of error for an estimator of a population parameter (e.g., a treatment effect) is easier and requires fewer assumptions than a power calculation (a power calculation requires conjectures about magnitude of effects).]

|  |  |
| --- | --- |
| **Anticipated Precision of an Estimator** | |
|  | **Figure 2.**  **Confidence Interval Width for a**  **Proportion**  The margin of error (equal to half the width of the 95% confidence interval) is shown on the vertical axis as a function of sample size. For example, if the sample size is N=200 and the *observed estimate* of the proportion of interest is P = 0.50, then the margin of error is 0.07; in other words, the observed confidence interval is approximately [ 0.50 ± 0.07 ] = [0.43, 0.57]. |
|  | **Figure 3.**  **Confidence Interval Width for a**  **Correlation Coefficient**  The margin of error (equal to half the width of the  95% confidence interval) is shown on the vertical axis as a function of sample size. For example, if the sample size is N=200 and the *observed estimate* of  the correlation coefficient of interest is R = 0.70,  then the margin of error is approximately 0.07;  in other words, the observed confidence interval  is approximately [ 0.70 ± 0.07 ] = [ 0.63, 0.77 ]. |

[For a calculation of anticipated precision (margin of error), the following should be specified:

* the population parameter (estimand),
* the estimator: how it will be calculated, variables involved, all details of a statistical model (if model-based).
* complete details about assumptions and conjectures made, and the source references.
* sufficient details to permit a reviewer to clearly interpret and potentially reproduce the computations.]

[For a calculation of anticipated power, the following should be specified:

* the population parameter and the (null) hypothesis about that parameter that will be tested,
* complete details of the test procedure, variables involved, all details of a statistical model (if model-based).
* complete details about assumptions and conjectures made, and the source references.
* sufficient details to permit a reviewer to clearly interpret and potentially reproduce the computations.]

[The target sample size chosen for purposes of data analysis should be inflated to take into account rates of dropout and missing data. For example, "With an expected drop-out rate of 7%, we will enroll 650 participants and expect to attain complete data from 600." The rationale for a chosen number to be enrolled should explain assumptions about these rates and discuss whether data from dropouts and withdrawn participants be evaluable.]

[Avoid plans to “replace” participants who drop out or have missing data. Instead, generously anticipate the number that will be lost or have unusable/incomplete data, and use that guess or estimate to inflate the target sample size for enrollment. Replacing participants is an unnecessary complication (adaptive enrollment) that has the potential to induce selection biases and thus may be a threat to the validity of the study.]

[The various estimators, tests, and specific aims will all differ in their sample size needs. The rationale for the chosen sample size should explain how these needs were prioritized to arrive at the final chosen value of N.

Choosing a sample size is a conjectural exercise that always requires judgement.]

# **Data Capture and Database Management**

## Software for Data Capture

<insert text>

[Guidance: It is recommended that investigators use the HIPAA-compliant online REDCap software system available from NC TraCS Institute at UNC. Use of REDCap and REDCap training sessions are available at no charge to UNC investigators. Fees are charged by TraCS only for assistance provided by the Biomedical Informatics Core.

For collection and management of human research data, spreadsheet software such as MS Excel or MS Access is not recommended. ]

[ Advantages of using REDCap:

* Reliability. REDCap is in use in over 1500 institutions worldwide. Developed at Vanderbilt University, REDCap is hosted and supported locally at UNC by NC TraCS Institute. UNC REDCap is hosted on sophisticated IT infrastructure and is backed up multiple times per day.
* Security. Users access REDCap online through a secure login page. Traffic between the web browser and the database is encrypted. Data storage complies with UNC’s encryption policy. User-rights management gives you full control authorizations. Audit trails provide accountability.
* Ease of Use. The user interface is intuitive allowing simple studies to be built in minutes. Built-in training resources allow new users to learn as they go. NC TraCS Institute offers weekly tutorial training sessions in Brinkhous-Bullitt. Web-based data entry can take place almost anywhere.
* Data Quality. REDCap supports critically important data quality features such as: Structured data dictionary, Skip logic, Mandatory fields, Range checking, Form locking/unlocking. The data quality module provides customized data quality checks. Data resolution workflow allows for data queries to be raised and resolved. For data monitoring limited reports/graphs can be generated by REDCap.
* Features. REDCap supports a broad range of project types from simple surveys through complex longitudinal clinical trials. Additionally, REDCap also includes support for: randomization and concealment, survey scheduling, data quality workflows, data coding (via Bioportal), text and voice messaging.
* Export. REDCap exports CSV files along with Stata/SAS/R/SPSS code easily used to create formatted datasets.
* For further information see the following:

<https://tracs.unc.edu/index.php/services/informatics-and-data-science/redcap>

<https://ictr.johnshopkins.edu/wp-content/uploads/import/1426-recap.pdf>]

[If using REDCap, then…

“The study data will be entered into a REDCap database developed by the study personnel. REDCap is a 21 CFR Part 11-compliant data capture system provided by the NC TraCS Institute at UNC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data will be entered directly from the source documents.]

## Responsibilities for Data Capture and Database Management

<insert text>

[This section should specify the particular personnel and site that will have primary responsibility for all aspects of data management. If there is a data coordinating center for the study, provide the details.

The single site, (or each participating site if multi-center), will maintain appropriate medical and research records for this trial, in compliance/consistent with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants.

If participating in a NIH-sponsored or NIH-affiliated study, each site will permit authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity. Describe in this section who will have access to records.]

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

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

It is not acceptable for the CRF to be the only record of a participant’s inclusion in the study. Study participation should be captured in a participant’s medical record. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a research study.]

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

If data are to be generated at one site and transferred to another site, describe responsibilities of each party.]

[Provide a list of planned data standards, formats, terminologies and their versions, used for the collection, tabulation, analysis of study data. Refer to the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format — Standardized Study Data, Study Data Technical Conformance Guide and FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.]

Example text provided as a guide, customize as needed:

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

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

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

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

## Study Records Retention

<insert text>

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

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

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

Example text provided as a guide, customize as needed:

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

# **Collection and Management of Tissue Specimens**

## Use in Current and Future Studies

<insert text> [Specify plans for collection of (1) biological specimens to be used in this study and (2) biological specimens to be used in future research. (Specify purpose, volume, collection/storage methods). ]

## Sample Preparation

<insert text> [As applicable, describe measures to prevent sample loss and degradation, cooling and freezing procedures, sample labeling, etc. If there are specimens that need to be processed at an outside lab, include detailed instructions on how to prepare the shipment, where to ship, temperature considerations, how long before the specimens ‘expire’, etc. This information may, instead, go in an appendix as supporting document/SOP.]

## Record Keeping and Monitoring

<insert text> [As applicable, describe procedures for maintaining sample accountability and traceability and for ensuring regulatory compliance.]

## Storage and Security

<insert text> [As applicable, describe the location, facility, and storage method/equipment; sample chain of custody; the remote monitoring and maintenance procedures; data security system, encryption, and access restrictions for study personnel.]

# **Safety Monitoring and Management**

## Risk / Benefit Assessment

[Include known risks and benefits, if any, related to not only the study intervention but all the study procedures as a whole (i.e. infection risk from biopsy, in addition to adverse study drug reactions).]

**Potential Risks:** <insert text>

[Briefly state the anticipated risks (physical, psychological, social, legal, economic) associated with study participation and the source of risk information (FDA-approved drug package insert, prior published data). When possible, identify the anticipated risk frequency (e.g., common, uncommon, rare) and severity (e.g., mild, moderate, severe).]

**Potential Benefits:** <insert text>

[State anticipated direct benefit(s) for individual participants, if any, or to society.]

## Assessment of Safety

<insert text>

[List and describe all study procedures and evaluations to be done as part of the study to monitor safety and support the understanding of the study intervention’s safety or that are done for other purposes (e.g., screening, eligibility, enrollment). This section should discuss how safety will be assessed with the following considerations (as applicable):

* the involvement of an investigational new drug or investigational device
* risks to individuals as well as others (e.g., study interventionists, family members, general public, etc.)
* individual participant stopping rules
* the risks of the study intervention and other study procedures as well as characteristics of the study population (individuals with disease, healthy controls, and vulnerable populations).]

## Unanticipated Problems, Adverse Events, Serious Adverse Events

[Provide definitions for Adverse Events, Serious Adverse Events, Unanticipated Problems, how these events will be graded for severity and evaluated for relatedness / expectedness, follow-up procedures and reporting requirements.]

**Unanticipated Problems:** <insert text>

[Provide the definition for Unanticipated Problems that will be used for this study. For example: An unanticipated problem is any incident, experience or outcome that meets all three OHRP criteria (1) unexpected (in severity, specificity, frequency, or nature), (2) related or possibly related to the research, and (3) suggests the research places participants or others at greater risk than previously known or recognized. Only a subset of adverse events will meet criteria for unanticipated problems. See: <https://ohresop.web.unc.edu/files/2018/04/1401-Reporting-New-Safety-Information.pdf> for current UNC IRB policies regarding identification, assessment, and reporting of adverse events.]

**Adverse Event (AE) Definitions:** <insert text>

[Provide the definition of an AE that will be used for the clinical trial.]

**Serious Adverse Events (SAE) Definition:** <insert text>

[Provide the definition of an SAE that will be used for the clinical trial.]

**Grading the Severity of Adverse Events and Events of ‘Special Interest’:** <insert text>

[All AEs should be assessed by the study clinician using a protocol-defined grading system. Describe the method of grading an AE for severity and the grading system to be used. Many toxicity tables and grading scales are available including the CTCAE, DAIDS, or a mild/moderate/severe grading system (with definitions).]

**Relatedness Definition:** <insert text>

[State that an assessment of relatedness will be performed for each AE/SAE. Define relatedness criteria.]

**Expectedness Definition:** <insert text>

[State that an assessment of expectedness will be performed for each AE/SAE. Define expectedness criteria.]

**AE and SAE Assessment, Follow-up Procedures:** <insert text>

[Describe how AE’s will be assessed. Define any follow-up procedures or treatments that should occur.]

**Reporting and Documentation Procedures:** <insert text>

[Describe the AE and SAE reporting procedures, including timeframes for submitting reports to the sponsor, to the IRB, to FDA, applicable. Provide a statement on AE/SAE documentation procedures (study documentation, IRB communication, FDA communication (if required)). Consider mandatory reporting of certain events (suspected child abuse, certain communicable diseases).]

**Participant Notification of New Information:** <insert text>

[State when/how participants will be made aware of new safety information for the intervention.]

## Safety Monitoring

<insert text> [Discuss how, when, and by whom participant safety will be monitored and the real-time plan for responding to adverse reactions, injury, and new safety concerns. Include criteria to be used for early study stopping. In addition to real-time evaluation, include consideration for a DSMB, Safety Monitoring Committee, or Independent Medical Monitor, as applicable, and describe in detail what their obligations will be. For a multi-site study, describe centralized safety oversight of the sites and communication of safety and quality issues.]

## Study Suspension / Early Termination of the Study

<insert text> [Describe circumstances that may warrant suspension/termination, e.g., unexpected, significant or unacceptable risk to participants; incomplete or unevaluable data; determination of futility. Provide actionable study stopping rules.]

# **Regulatory, Ethical, and Study Oversight Specifications**

## Informed Consent Process

<insert text>

[For NIH Intramural Research Program studies only: a statement referencing compliance with NIH Human Research Protections Program policies and procedures is adequate for section 13.1.

Note, the guiding ethical principles being followed by this study are included in the **Statement of Compliance** at the beginning of this protocol.

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

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

13.1.1. Consent/Assent and Documents Provided to Participants

<insert text>

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

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

Example text provided as a guide, customize as needed:

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

13.1.2. Consent Procedures and Documentation

<insert text>

[Describe where, when, and by whom potential participants will be approached, informed, and consented. Describe the consent training required for personnel. Describe steps to minimize coercion. For example: if the P.I. is the participant’s medical provider, then have someone other than the P.I. obtain consent; provide adequate opportunity for minors and vulnerable individuals to dissent; safeguard privacy.]

[Describe how informed consent will be administered. Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of language other than English. Describe procedures for obtaining surrogate consent for those unable to consent on their own behalf. ]

[This section should be consistent with sections **5.4 Strategies for Enrollment** and **5.5 Strategies for Retention** when describing consent plans and special considerations for children or other vulnerable participants. Address re-consent processes for children who become adults or emancipated during a study.]

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

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

## Study Discontinuation and Closure

<insert text>

[In this section specify criteria for termination/suspension of the study. These criteria may involve, for example, a PI decision, sponsor/funder decision, decisions by regulatory or other oversight bodies; review of serious, unexpected, and related AEs; noncompliance; futility). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, the IRB, and sponsor and provide the reason(s) for the termination or temporary suspension*.*]

[When a study is prematurely terminated, refer to section **7.8 Early Discontinuations**, for handling of enrolled study participants.]

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

[This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to < **study participants, investigator, funding agency, the IND or IDE sponsor, and regulatory authorities** >.

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Examples of circumstances that may warrant termination or suspension of the study include:

* Criteria established in the MPD for early termination of the study have been satisfied
* Detection of an unexpected unacceptable level of risk to participants
* In preparatory (pilot) studies, futility due to insufficient adherence to protocol requirements
* Unexpected inability to recruit participants

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the regulatory oversight (e.g., DSMB, sponsor, IRB, FDA.]

## Confidentiality and Privacy

<insert text>

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

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

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

**Example text provided as a guide; this text MUST be customized to address all aspects required in this section.**

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

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

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

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

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

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

13.3.1. Certificate of Confidentiality

<insert text>

**If a Certificate of Confidentiality applies to your study, insert the following text:**

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

## Future Use of Stored Specimens and Data

<insert text>

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

[See also section **10.2 Responsibilities for Data Capture and Database Management** and section **13.3 Confidentiality and Privacy**, for further information on future use of study records.]

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

[Data collected for this study will be analyzed and stored at the < **specify name of Data Coordinating Center** >.

After the study is completed, the de-identified, archived data will be transmitted to and stored at

the < **specify name of Data Repository** > for use by other researchers including those outside of the study.

Permission to transmit data to the < **specify name of Data Repository** > should be included in the informed consent.

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

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

When the study is completed, access to study data and/or samples will be provided through

the < **specify name of Data Repository** > and/or < **specify name of Repository** >. ]

## Key Roles and Study Governance

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

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

<insert text>

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

## Safety Oversight

<insert text> [Appropriate safety oversight should be used for each trial. This could include a Safety Monitoring Committee (SMC)[[3]](#footnote-3), Data Safety Monitoring Board (DSMB)[[4]](#footnote-4), Safety Assessment Committee[[5]](#footnote-5), and/or an Independent Safety Monitor (ISM)[[6]](#footnote-6). Independent oversight is an important component to ensure human participants’ protection and data integrity and should be considered for each study. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety and data integrity in the study. Describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB.]

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

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

## Clinical Monitoring Plan (CMP)

<insert text>

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

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

[A separate clinical monitoring plan (CMP) should describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. A CMP ordinarily should focus on preventing or mitigating important and likely risks, identified by a risk assessment, to critical data and processes. The types (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification)) of monitoring activities will depend on a range of factors, considered during the risk assessment, including the complexity of the study design, types of study endpoints, clinical complexity of the study population, geography, relative experience of the PI and of the sponsor with the PI, electronic data capture, relative safety of the study intervention, stage of the study, and quantity of data.

**[If using a separate CMP, the following example text is provided as a guide. Customize as needed**:

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

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

[**If *NOT* using a separate CMP, the following example text is provided as a guide. Customize as needed**:

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

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

## Quality Assurance and Quality Control

<insert text>

[This section will briefly describe the plans for quality management, the system for assessing the quality of processes within a system. Quality management encompasses quality assurance (QA)[[7]](#footnote-7) and quality control (QC)[[8]](#footnote-8).]

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

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

Regular monitoring and an independent audit, if conducted, must be performed according to ICH GCP.

See also section **13.7 Clinical Monitoring**.]

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

[Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site’s quality management.

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

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

## Protocol Deviations

<insert text>

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

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

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

These practices are consistent with ICH GCP:

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

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within < **specify number** > working days of identification of the protocol deviation, or within <**specify number**> working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to < **specify NIH Institute or Center (IC)** > Program Official and < **specify Data Coordinating Center or sponsor** >. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.]

## Publication and Data Sharing Policy

<insert text>

[The publication and authorship policies should be described in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. For other studies, the authorship plan might focus on the PI’s role (e.g., “The PI will serve as first or senior author on all publications, with co-authors included according to journal guidelines.”) Please refer to your specific contract, grant, and/or Clinical Trials Agreements. If details of the publication policy will be described in the study’s MOP, refer to it here. The study must comply with:

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

Example text provided as a guide, customize as needed:

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

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

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

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

## Conflict of Interest Policy

<insert text>

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

Example text provided as a guide, customize as needed:

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

# **Additional Considerations**

<insert text>

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

# **References**

<insert text>

[Include a list of relevant literature and citations for all publications referenced in the text of the protocol.

Choose a consistent, standard, modern format. The choice might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.).

The preferred format is International Committee of Medical Journal Editors (ICMJE).

Include citations to product information such as manufacturer’s IB, package insert, and device labeling.]

[Example formats:

* **Journal citation**  
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
* **Whole book citation**  
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
* **Chapter in a book citation**  
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
* **Web Site citation**Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
* **Electronic Mail citation**

Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]

* **References to package insert, device labeling or investigational brochure**

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

# **Appendices**

[This section should include a listing of any tables, questionnaires, investigator brochure, device manual, etcetera that should accompany the study protocol document or be appended to the end of the protocol document.]

**Appendix 1:** <insert text> [include version number and date, and a short description.]

**Appendix 2:** <insert text> [include version number and date, and a short description.]

**Appendix 3:** <insert text> [include version number and date, and a short description.]

1. [1] www.consort-statement.org

   [2] www.strobe-statement.org

   [3] www.icmje.org

   [4] Wasserstein RL, et al. (2016), The ASA's Statement on p‑Values, ***The American Statistician***, 70:2, 129-133

   [5] Wasserstein RL, et al. (2019), Moving to a World Beyond p < 0.05, ***The American Statistician***, 73:sup1, 1-19

   [6] Amrhein, et al. (2019) Scientists rise up against statistical significance, ***Nature*** 567, 305-307

   [7] Editorial (2019) It’s time to talk about ditching statistical significance: Looking beyond a much used and abused measure

   would make science harder, but better. ***Nature*** 567, 283-283. [↑](#footnote-ref-1)
2. [1] [www.consort-statement.org](http://www.consort-statement.org) , [2] [www.strobe-statement.org](http://www.strobe-statement.org), [3] [www.icmje.org](http://www.icmje.org)

   [4] Wasserstein RL, et al. (2016), The ASA's Statement on p‑Values, ***The American Statistician***, 70:2, 129-133.

   [5] Wasserstein RL, et al. (2019), Moving to a World Beyond p < 0.05, ***The American Statistician***, 73:sup1, 1-19.

   [6] Amrhein, et al. (2019), Scientists rise up against statistical significance, ***Nature*** 567, 305-307.

   [7] Editorial (2019) It’s time to talk about ditching statistical significance: … ***Nature*** 567, 283-283. [↑](#footnote-ref-2)
3. A Safety Monitoring Committee (SMC) is a small group of experts with at least two members who are independent of the protocol who review data from a particular study. Generally, independent investigators and biostatisticians should be included. The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, intervention, and target population under study. [↑](#footnote-ref-3)
4. A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises funding IC(s) and the study investigators. The members of the DSMB provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, intervention, or target population under study. [↑](#footnote-ref-4)
5. As noted on page 4 of the FDA Draft Guidance for Industry: Safety Assessment for IND Safety Reporting, “A group of individuals chosen by the sponsor to review safety information in a development program (i.e., across trials, INDs, and other sources) for IND safety reporting purposes...The safety assessment committee should oversee the evolving safety profile of the investigational drug by evaluating, at appropriate intervals, the cumulative serious adverse events from all of the trials in the development program, as well as other available important safety information (e.g., findings from epidemiological studies and from animal or in vitro testing) and performing unblended comparisons of event rates in investigational and control groups, as needed, so the sponsor may meet its obligations under § 312.32(b) and (c). The safety assessment committee’s primary role should be to review important safety information on a regular basis, with additional reviews as needed, and make a recommendation to the sponsor to help the sponsor determine whether an event or group of events meets the criteria for IND safety reporting. The safety assessment committee, possibly together with other parties (e.g., steering committees, data monitoring committees [DMCs]), can also participate in decisions about whether the conduct of the study should be revised (e.g., change ineligibility criteria, revision of informed consent). [↑](#footnote-ref-5)
6. An Independent Safety Monitor (ISM) is a physician, nurse, or other individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study. [↑](#footnote-ref-6)
7. All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with ICH GCP and the applicable regulatory requirement(s) (ICH E6 Section 1.46). [↑](#footnote-ref-7)
8. The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 Section 1.47). [↑](#footnote-ref-8)