Clinical Interventional Study

Protocol Template

# PREFACE

*The Clinical Intervention Study Protocol Template is a suggested format for clinical trials sponsored by the National Institute on Aging (NIA). Investigators are encouraged to use this format, as appropriate, when developing protocols for their studies. Large multi-site observational studies will also benefit from this protocol template.*

*Note that instructions and explanatory text are indicated by italics and should be replaced in your protocol with appropriate text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template.*

*The goal of this template is to provide a general format applicable to all single- and multicenter clinical intervention trials (e.g., drug, surgery, behavioral, nutritional, device, etc).*

*As you can see the version number and date are on the bottom of each page. When making changes to an approved and “final” protocol, please provide a summary of the changes, with the date, at the front of the protocol.*

# FULL PROTOCOL TITLE

*(If not obvious from the protocol title, consider adding a subtitle that briefly summarizes the trial, such as: A randomized, placebo-controlled, double-masked, 2100-subject clinical trial of X in the treatment of Z.)*

**Study Chairman or Principal Investigator:**

*(List Study Chairman’s or Principal Investigator’s name, degree, position and affiliation)*

**Supported by:**

**The National Institute on Aging**

*(Include application or grant number(s) when available)*

**Study Intervention Provided by:**

*(Name of pharmaceutical company or device manufacturer, if any, providing support)*

**Sponsor of IND/IDE:**

*(Official sponsor, i.e., IND or IDE holder, if any. Include IND/IDE # when available)*

*(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)*

**Version 1** *(Please change version number with each amendment)*

**Month Day, Year**

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**I. Procedures Schedule**

**II. Informed Consent Form Template**

**III. Other** *(add as many appendices as necessary)*

# PRÉCIS

*This section should provide a brief protocol summary of approximately 1-2 pages.*

## Study Title

*Specify the full title (and subtitle, if applicable) of the study.*

## Objectives

*Specify the primary and secondary objectives*.

## Design and Outcomes

*Provide a very brief description of the study design (e.g., double-blind, placebo controlled clinical trial to test the efficacy and safety of intervention X on outcome(s) Y in individuals 65 years of age and older).*

*The schedule and type of evaluations to be performed during the study may also be included.*

*Use overview diagram here, if applicable. Complex diagrams may be included in Section 3, Study Design, instead.*

## Interventions and Duration

*Specify the interventions to be compared. Indicate the total length of time each participant will be on study (intervention period and additional follow-up off intervention, as applicable).*

## Sample Size and Population

*Specify the target population including number and type of participants in the study and the number in each group.*

*If the randomization will be stratified, list the stratification factors. If there will be separate objectives and outcome variables for the strata, list these in the appropriate sections (above).*

# STUDY TEAM ROSTER

*List individuals who play key roles in the development and execution of the study, especially those who may need to be contacted by the sites during the course of the study. Include address, telephone, fax and e-mail address of each individual listed and include a brief summary of each individual’s main responsibilities.*

*Examples of possible roster format:*

## Principal Investigator: Name

*Address*

*Address*

*Telephone*

*Fax*

*Email address*

*Main responsibilities/Key roles:*

## Co-Investigators: Name

*Address*

*Address*

*Telephone*

*Fax*

*Email address*

*Main responsibilities/Key roles:*

# PARTICIPATING STUDY SITES

*List the name and address of each study site investigator, including telephone numbers and e-mail address. Use the same format as used for the Study Team roster.*

# Study objectives

## Primary Objective

*The primary objective should always address a specific hypothesis. State the hypothesis in quantifiable terms; e.g., “the experimental treatment will result in 12 months of additional survival compared to the control treatment.” The primary objective must match the one used in section 9, Statistical Design.*

## Secondary Objectives

*Secondary objectives may or may not be hypothesis-driven, may include secondary outcomes, and may include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data).*

# BACKGROUND AND RATIONALE

## Background on Condition, Disease, or Other Primary Study Focus

*Describe the need, relevance and priority for the study. For example, osteoarthritis in post-menopausal women affects N women over the age of 50. Patient symptoms are characterized by….*

## Study Rationale

*Describe the scientific and medical data (e.g., results of observational studies and early clinical trials) that justifies the study, its design, and the intervention groups. Include any data from animal and human studies relevant to mechanism of action, effect size, and possible effects of the intervention on selected outcomes.*

*Name and describe the intervention regimen(s) and justify why the intervention(s) have been chosen. Describe and justify the route of administration, dosage regimen, intervention period, frequency and intensity, etc. Summarize the known and potential risks of the interventions.*

# STUDY DESIGN

*Briefly describe the study design and indicate, in general terms, how the design will answer the question posed by the study. Use diagrams to explain design complexities.*

*A description of the trial design should include:*

* *Type/design of trial (e.g., placebo-controlled, double-mask, parallel design, open-label, dose escalation, dose-ranging)*
* *Specific statement of the primary and secondary outcomes (must be consistent with Study Objectives)*
* *Study population and groups/arms including sample size (including a table, if appropriate)*
* *Study location (e.g., in-patient or out-patient, clinic, community)*
* *Approximate duration of enrollment period and follow-up (specify individual participant vs. entire trial)*
* *Description of intervention and administration*
* *Randomization, blinding and any stratification*
* *Other protocol specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)*

# SELECTION AND ENROLLMENT OF PARTICIPANTS

*Key components of the success of a clinical study are the selection and enrollment of participants who are reasonably representative of the populations or characteristics under investigation to allow for sufficient generalizability. This section should define and describe the study population.*

## Inclusion Criteria

Provide a statement that participants must meet all of the inclusion criteria to participate in this study and then list each criterion. List as many criteria as necessary to clearly define your study population.

* *Demographic characteristics (e.g. gender, age) and the health state, presence or absence of a medical condition/disease.*
* *Required laboratory results, diagnostic methods, criteria for classification of current status, as measured within XX days prior to randomization. List specific tests and documentation methods.*
* *Prior therapy, if any. Consider listing specific prior treatments. Consider listing the allowable duration of prior therapy for the specific population to be studied (e.g., treatment-naïve, treatment-experienced or prior-treatment-failed “salvage” participants).*
* *Ability to understand study procedures and to comply with them for the entire length of the study.*
* *If men and women of reproductive capability will be enrolled, indicate whether contraception is necessary and required. If yes, include details of allowable contraception methods for trial.*

## Exclusion Criteria

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

*List as many criteria as necessary to clearly define your study population. The following lists possible categories of exclusion criteria:*

* *Specify health status or any clinical conditions (e.g., life expectancy, co-existing disease) or other characteristics that precludes appropriate diagnosis, treatment or follow-up in the trial.*
* *Clinical/laboratory indicators of current status, obtained within XX days prior to randomization. List the specific tests to be performed and the narrowest acceptable range of laboratory values for exclusion, consistent with disease and/or safety. Include as many as necessary.*
* *Specify any exclusion related to pregnancy, lactation, or plans to become pregnant. Specify methods for assessing current status and willingness to use contraception, if applicable. Include as many as necessary.*
* *Use of [excluded drugs, behavioral interventions, devices, etc.] within XX days prior to study entry. Treatment with another investigational drug or intervention (with time frame).*
* *For drug studies: allergy/sensitivity to study drugs or their ingredients.*
* *Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.*
* *Inability or unwillingness of individual or legal guardian/representative to give written informed consent.*
* *Current or past participation within a specified timeframe in another clinical trial, as warranted by the administration of this intervention.*

## Study Enrollment Procedures

* *Describe the method for identifying and recruiting candidates for the trial.*
* *Describe procedures for documentation of reasons for ineligibility and for non-participation of eligible candidates (e.g. Screening Log).*
* *Describe consent procedures, including documentation of the consent process and any special requirements (e.g., consent for individuals who are unable to consent for themselves)*
* *Describe the randomization procedure for assigning a participant to an intervention group.*

# STUDY INTERVENTIONS

## Interventions, Administration, and Duration

*Describe each study intervention, including how it is administered and the dosing schedule, as well as potential adverse effects. Indicate where the intervention will be administered (e.g., outpatient, exercise laboratory, intensive care unit). State guidelines for use of appropriate supportive care, medications or treatments.*

*Describe dose escalation procedures if relevant.*

*Include instructions for modifications to the study interventions, if appropriate and clearly explain modification of dose due to toxicity or any other reason. Address dose modifications for specific abnormal laboratory values of concern or other adverse events that are known to be associated with the planned intervention regimen.*

*For drug studies, package insert information can be referred to, but does not need to be included unless there is a new, significant change. Justify any aspects of the study that are not FDA-approved (e.g., different dosing schedule, new combination of drugs, new drug formulation).*

## Handling of Study Interventions

*For studies involving drugs and dietary or nutritional supplements, describe how these are to be acquired by the participating clinical sites (e.g., the pharmaceutical company will distribute the drug in bulk to the site pharmacist), and how they are to be stored, prepared, dispensed. If applicable, describe how unused study products are to be destroyed or returned to the company supplying them.*

*Provide instructions for completing study intervention accountability records. If appropriate, reference the study Manual of Operations for detailed instructions on these issues.*

*For lifestyle/behavioral interventions, describe the intervention and general approach for delivering the intervention (e.g., manual describing procedures).*

*Note mechanisms (if any) for masking (i.e., blinding) study interventions. For example, if a placebo is being used in a drug trial, note whether it has similar color, taste, etc., as the active drug.*

## Concomitant Interventions

*Allowed, required, and prohibited interventions (e.g., medications) will depend upon the study interventions and outcomes.*

*This section should be consistent with the medications and interventions restrictions in the inclusion/exclusion criteria.*

### Allowed Interventions

*List all drugs and/or treatments/interventions that are allowed, including rescue medications, while on study.*

### Required Interventions

*For example, if in weight loss study, vitamin pills may also be required.*

### Prohibited Interventions

*Include classes of medications, devices, etc. from the exclusion criteria (section 4.2) if they are also prohibited while the participant is on study. If necessary, provide a list of prohibited medications in appendix.*

## Adherence Assessment

*Adherence to a study regimen is generally defined as the extent to which participants take medications or comply with other study requirements as prescribed by the investigators. Define adherence (e.g., at least 80% of treatment intervention pills taken, 85% of exercise sessions attended). Provide details as to how adherence to study intervention will be assessed (e.g., pill counts, electronic monitoring devices, attendance at counseling sessions) and in the section on Data Analyses (Section 9.5), describe how this information will be incorporated into the analysis of the study results.*

# STUDY PROCEDURES

*The Schedule of Evaluations in section 6.1 should include all study evaluations. Use an ‘X’ in a cell to indicate that a particular evaluation is to be performed at a particular study visit. The evaluations listed and their order in the table are only examples. The evaluations should reflect the protocol and should be arranged for clearest presentation. Fixed windows for each visit should be included, in a consistent unit, usually days or weeks. Additional columns may be needed to specify evaluations at intervention failure, at early discontinuation of study interventions, or at other special time points that require a different set of evaluations. In complicated studies with multiple study steps or multiple randomization points, it may be useful to include in the table the time of each step/randomization and the time that study intervention is given to the participant.*

## Schedule of Evaluations

| ***Assessment*** | ***Screening: Visit (Day-14 to Day -1)*** | ***Baseline, Enrollment, Randomization: Visit 1 (Day 0)*** | ***Treatment Visit 2***  ***Day 7 (±2 Days)*** | ***Treatment Visit 3***  ***Day 14 (±2 Days)*** | ***Treatment Visit 4***  ***Day 21 (±2 Days)*** | ***Treatment Visit 5***  ***Day 28(±2 Days)*** | ***Treatment Visit 6***  ***Day 35 (±2 Days)*** | ***Follow-up: Final Visit***  ***Day 70 (± 7 Days)*** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Informed Consent Form* | ***X*** |  |  |  |  |  |  |  |
| *Demographics* | ***X*** |  |  |  |  |  |  | ***X*** |
| *DXA* | ***X*** |  |  |  |  |  |  | ***X*** |
| *Medical History* | ***X*** |  |  |  |  |  |  |  |
| *General Physical Examination* | ***X*** | ***X*** | ***X*** |  |  |  | ***X*** | ***X*** |
| *Current Medications* | ***X*** | ***X*** |  |  |  |  |  |  |
| *Blood Chemistries* | ***X*** | ***X*** | ***X*** |  |  | ***X*** |  | ***X*** |
| *Hematology* | ***X*** | ***X*** | ***X*** |  |  | ***X*** |  | ***X*** |
| *Urine Analysis* | ***X*** | ***X*** | ***X*** |  |  | ***X*** |  | ***X*** |
| *Vital Signs* | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** |
| *Inclusion/Exclusion Criteria* |  | ***X*** |  |  |  |  |  |  |
| *Enrollment/Randomization* |  | ***X*** |  |  |  |  |  |  |
| *Treatment Administration Form* |  |  | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** |  |
| *Concomitant Medications* |  | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** |
| *Adverse Events* |  | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** |

## Description of Evaluations

*Descriptions for the Schedule of Evaluations define what is to be done at each study period and include special considerations or instructions for evaluations.*

*This section should include definitions of the row headings in the Schedule of Evaluations and any special instructions. All of the items listed on the Schedule of Evaluations should be described in this section.*

*For studies collecting biological samples, describe the process for obtaining, processing and storing the samples. Include details on handling, preserving and shipping the specimens (e.g., required temperatures, location of storage, labeling).*

### Screening Evaluation

*These evaluations occur to determine if the candidate is eligible for the study.*

Consenting Procedure

*Before any screening procedure is performed, informed consent must be obtained. Indicate whether there will be two consenting processes or a single informed consent form that describes both the screening and study procedures.*

*State which study staff will conduct the consent process and how it will be implemented.*

Describe individual’s education and informed consent process; the plan for reconsent if needed; and how documentation of signed consent will be maintained by the study.

Screening

*Specify allowable range of time prior to study entry during which all screening evaluations to determine eligibility must be completed. List and briefly describe all screening evaluations in bulleted format.*

Include only those evaluations that are necessary to assess whether an individual meets enrollment criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the time frame prior to enrollment within which screening tests and evaluations must be done. For example, DXA must be measured within 30 days of study enrollment.

### Enrollment, Baseline, and/or Randomization

Enrollment

*The act of enrolling a study participant should be defined. Since informed consent must be obtained if screening procedures are not a part of routine care, some studies use two informed consents: one for screening and one for enrollment. In this case the enrollment date is day the individual has met all the screening criteria and signs the second informed consent form.*

*Some studies utilize a single informed consent form that describes both screening and study procedures. In these studies enrollment is defined as the randomization date or as the date all of the screening criteria are met and the individual agrees to participate*

*In any case the enrollment date should be defined and recorded on a case report form along with the allowable window between screening and randomization.*

Baseline Assessments

*For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments are performed against which to measure the study outcome. They also ensure that the groups are balanced with respect to baseline characteristics. For example if the study hypothesis is “dietary intervention and exercise will reduce body weight by X% within one year”, body weight will be assessed and documented.*

*List and briefly describe all baseline evaluations in a bulleted format.*

Randomization

*Randomization must precede intervention administration in a randomization study.*

*Specify time window for (a) randomization relative to completion of screening and baseline and (b) initiation of study intervention relative to randomization.*

### Follow-up Visits

*Indicate treatment and follow-up visit assessments for each visit. List all measurements and procedures in bulleted format.*

*Include allowable time window in which evaluations may take place, e.g., study visits must be performed on the weeks indicated in the Schedule of Evaluations* ± *X days, as included in the Schedule of Evaluations. The evaluation time window should be as narrow as technically feasible.*

*For example:*

* *Visit 3 Day X (±X Days):*
  + *Vital Signs*
  + *Treatment Administration Form*
  + *Concomitant Medications*
  + *Adverse Events*
* *Visit 6 Day X (±X Days):*
  + *General Physical Examination*
  + *Vital Signs*
  + *Treatment Administration Form*
  + *Concomitant Medication*
  + *Adverse Events*

### Completion/Final Evaluation

*List each assessment to be performed at the participant’s final visit.*

*Specify evaluations needed for participants who discontinue study intervention early. Specify potential reasons for early termination. Specify any requirements (e.g., related to monitoring and reporting of adverse experiences) for follow-up on participants once they have stopped using the study intervention.*

# SAFETY ASSESSMENTS

*Participant safety should be monitored once an individual is enrolled in the study. A study-specific definition of “enrolled” should be provided. To assure comprehensive review of potential safety events, include a list of expected adverse experiences for each study intervention, criteria for management and modification of the study intervention regimen or participant assessments if an adverse event occurs.*

*For investigational drug studies the section should identify toxicities that have been seen in previous studies.*

## Specification of Safety Parameters

*Include examples of safety measures such as specific laboratory findings.*

## Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

*This section should be based on the risk profile of the study intervention. Include a review of relevant literature, which should be referenced.*

## Adverse Events and Serious Adverse Events

*Provide definitions for adverse events (AEs) and serious adverse events (SAEs) to be used for this trial. For example:*

***Adverse Event (AE):*** *Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants’ involvement in the research, whether or not considered related to participation in the research.*

***Serious Adverse Event (SAE):***Any adverse event that:

* Results in death
* Is life threatening, or places the participant at immediate risk of death from the event as it occurred
* Requires or prolongs hospitalization
* Causes persistent or significant disability or incapacity
* Results in congenital anomalies or birth defects
* Is another condition which investigators judge to represent significant hazards

*Describe any laboratory values that will be collected to assess safety. Abnormal laboratory values should be defined (e.g. two times the normal limit or outside the reference range for a laboratory) and recorded as Adverse Events.*

*Describe AEs, if any, which may be expected based on the study intervention, and will be collected as solicited events. Describe how unsolicited events will be captured. Assure that the reporting and data collection systems avoid double capture.*

*An unsolicited AE would be collected without any prompting or in response to a general question such as “Have you noticed anything different since you started the study; began the study intervention, etc.” A solicited AE is one that is specifically solicited such as “Have you noticed any dry mouth since you started the study medication?”*

*Describe the time frames for collecting AEs and SAEs.*

*In addition, protocols may specify other events that require reporting in an expedited time frame (e.g., abnormal laboratory values). Include a description of these events in this section and reporting requirements in the following section.*

### Reporting Procedures

*All clinical trials must have a safety reporting system in place for AEs, SAEs and other reportable events. Include details of the reporting procedures and time lines, including the individual responsible for each step (e.g., the Investigator, the Medical Monitor, etc.), how decisions will be made regarding determining relatedness and severity, which forms should be completed, (specific information on where to send this form is included), how reports will be distributed and what follow-up is required.*

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

***Severity of Event***

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

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

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

*• Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.*

*• Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.*

*• Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.*

*These terms should match those collected on the Adverse Event Form.*

***Relationship To Study Intervention***

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

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

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

*• Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*

*• Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.*

*• Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by a qualified medical professional.]*

### Follow-up for Adverse Events

*Describe how AEs and SAEs will be followed until resolved or considered stable. Specify procedures for recording and follow-up of AEs and SAEs that are consistent with the information contained within Section 7.2, Methods and Timing for Assessments, including what assessment tools will be used to monitor AEs. Include duration of follow-up after appearance of events (e.g., 1 week, 2 months).*

*Include time period of collection (e.g., Days 0 -28) and note how long SAEs are collected – usually collected through entire study.*

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

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

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

*Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE.*

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

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

## Safety Monitoring

*The NIA Guidelines on Data and Safety Monitoring generally require that a NIA-appointed Data and Safety Monitoring Board or Safety Officer monitor clinical trials. Please see the* [*Data and Safety Monitoring Guidelines*](http://www.nia.nih.gov/research/grants-funding/nia-guidance-clinical-trials) *.*

# INTERVENTION DISCONTINUATION

*List criteria for discontinuing the study intervention/product (e.g., development of toxicities, study closure by institute) for a participant and methods for determining when criteria are met.*

*If relevant, include criteria for temporary discontinuation of treatment and define its length.*

Also note that subjects may withdraw voluntarily from participation in the study at any time and for any reason. Participants should continue to be followed, with their permission, even if the study intervention is discontinued. *Discuss any modifications to the schedule and duration of continued follow-up and indicate the evaluations to be completed while the participant is either temporarily or permanently discontinued from study intervention but followed for outcomes, if applicable.*

This section should also include a discussion of replacement of subjects who discontinue early, if replacement is allowed and at what stage, i.e. enrolled, randomized, received study treatment.

Note: It is vital to collect safety data on any subject discontinued due to an AE or SAE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the subject should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject’s condition becomes stable.

# STATISTICAL CONSIDERATIONS

## General Design Issues

*State the statistical hypotheses.*

*Describe the reasons for choice of study design (e.g., parallel groups, crossover, immediate versus deferred intervention, factorial, large simple trial, equivalency or non-inferiority trial); why certain design features were chosen (e.g., for a crossover trial, how the length of the washout period was chosen).*

*Describe the primary and secondary hypotheses and the primary and secondary outcome measures as well as their validity and reliability.*

## Sample Size and Randomization

*Describe sample size calculation and effect size with respect to power. Specify the test statistic; Type I and Type II error rates; assumed event rate for dichotomous outcome (mean and / or variance for continuous outcome) for each study arm; assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc.; and approach to handling withdrawals and protocol violations, in terms of an “intent to treat” approach.*

### Treatment Assignment Procedures

*Describe the treatment assignment procedures (randomization, minimization, relevant criteria, etc). If such procedures are proposed describe rationale as well as the procedure.*

Plans for the maintenance of trial randomization codes and maintaining appropriate masking for the study should be discussed, including the timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unmasking may occur and who may unmask.

*If the randomization will be stratified, indicate whether (and why) there is a sample size goal for each stratum. Identify what factors (if any) will be used to stratify the randomization.*

## Interim analyses and Stopping Rules

*If an interim analysis is planned, describe the rationale, effect on “spending” the Type I error, and method for adjusting calculations. As relevant, provide guidelines for stopping the study for reasons of efficacy, safety, futility, or poor study performance (e.g., slow accrual, high losses-to-follow-up, and poor quality control).*

Describe safety findings and statistical rules that would temporarily suspend enrollment and/or study intervention until a safety review is convened (either routine or ad hoc) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed.

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings are presented to the study statistician or to the Data and Safety Monitoring Board (DSMB) statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the DSMB or to the Safety Officer and/or NIA. The findings are used to determine what steps will be taken.

## Outcomes

*Discuss how the outcomes will be analyzed. Describe whether the documentation of an outcome will be reviewed and adjudicated by a committee, how quickly the committee will perform the adjudication, and whether the committee will be masked to the participant’s intervention group assignment.*

### Primary outcome

*State and define the primary outcome measure and specify at which study visit the outcome assessments will be performed.*

### Secondary outcomes

*State and define the secondary outcome measures.*

## Data Analyses

*Describe the descriptive and inferential statistical methods that will be used to analyze the outcomes and other study data. Specify any confounding variables for which it is anticipated adjustment will be made.*

*In accordance with NIH policy, unless data from prior studies strongly support no significant differences of clinical or public health importance in the intervention effect between gender and racial/ethnic subgroups, investigators should include a statement noting that a valid analysis of the intervention effect will be performed in these subgroups. If data from prior studies do not strongly support the existence of significant differences in the intervention effect between subgroups, then the analyses need not have high statistical power for detecting clinically meaningful differences.*

# DATA COLLECTION AND QUALITY ASSURANCE

## Data Collection Forms

*Indicate how information will be collected for each participant and by whom. For example if a blinded observer will perform outcome assessments, state who this person will be. Describe methods for maintaining confidentiality of participant records. Refer to Manual of Procedures (MOP) for description of study forms (also called Case Report Forms).*

## Data Management

*Briefly describe clinical site responsibilities in data collection and management.*

*Briefly describe Coordinating Center (or Data Management/Statistical Center) responsibilities in data management.*

*Briefly describe data collection forms.*

## Quality Assurance

### 10.3.1 Training

Describe types and mechanisms of training of staff for the study.

### Quality Control Committee

If there is a study quality control committee, describe membership and list the reports that they review.

### Metrics

Provide quality control metrics for outcome measures.

### Protocol Deviations

Describe how protocol deviations will be captured, documented, and reviewed.

### Monitoring

Briefly describe methods (e.g., site monitoring) for assuring protocol compliance, and data quality at the clinical sites, including review of records, consent forms, etc. The types of materials to be reviewed; who is responsible, and the schedule for reviews may be specified or referenced in the Manual of Procedures (MOP).

# PARTICIPANT RIGHTS AND CONFIDENTIALITY

*The texts in this section are examples only.*

## Institutional Review Board (IRB) Review

*This protocol and the informed consent document (Appendix XX) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.*

## Informed Consent Forms

*This section describes the procedures for obtaining and documenting informed consent of study participants. 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.*

*Example text, customize as needed:*

*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 be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice, and that the quality of their medical care will not be adversely affected if they decline to participate in this study. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will be given a copy of the ICF so that they may discuss the study with their family or surrogates or think about it prior to agreeing to participate. 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. A copy of the signed informed consent document will be given to the participants for their records.*

## Participant Confidentiality

*Include procedures for maintaining participant’s confidentiality according to the Health Insurance Portability and Accountability Act (HIPAA), any special data security requirements, and record retention per the sponsor’s requirements.*

*Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.*

## Study Discontinuation

*The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.*

# ETHICAL CONSIDERATIONS

Include in this section the guiding ethical principles being followed by the study. If the study is conducted at international sites, consider including reference to the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country’s ethical policy statement, whichever provides the most protection to human subjects.

# COMMITTEES

*Provide a list of the committees (Steering Committee or Executive Committee, Publication Committee, Adjudication Committee, etc.) and describe their roles.*

# PUBLICATION OF RESEARCH FINDINGS

*Sample text:*

*Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.*

# REFERENCES

*Provide the citations for all publications and presentations referenced in the text of the protocol.*

# SUPPLEMENTS/APPENDICES