**PREFACE**

The Clinical Intervention Study Protocol Template is a suggested format for clinical trials conducted at the University of Michigan. Investigators are encouraged to use this format, as appropriate, when developing protocols for their studies. It is not intended to supersede the scientific development of the protocol. All sections should be modified to meet the scientific aims of the study – if a section is not applicable – indicate N/A in the respective section. Large multi-site observational studies will also benefit from this protocol template.

An intervention is a drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study, e.g., health-related quality of life, efficacy, safety, pharmacoeconomics. Synonyms: therapeutic intervention, medical product; see also test articles; devices; drug product; medicinal product; combination product (from the Clinical Data Interchange Standards Consortium [CDISC] glossary).

Or

An intervention, as it pertains to [research](http://grants.nih.gov/grants/policy/hs/glossary.htm#research) involving [human subjects](http://grants.nih.gov/grants/policy/hs/glossary.htm#hs) defined in 45 CFR Part 46 ([46.102](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102)) within the Human Subject definition, includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

Note that instructions and explanatory text are indicated by italics and should be replaced in your protocol document with appropriate protocol-specific text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template. Text should be formatted using Body Text style. Bulleted lists should be formatted using Bullet (listing) style. An accompanying Protocol Working Shell that contains headers and blank space for text is available to help with writing the protocol document.

This template may be used for clinical research studies (non-interventional studies). Some sections (e.g., Study Intervention and Study Product Description) will not apply to a non-interventional study and may be removed.

In places where the information is redundant, it is acceptable to reference another section, or if more appropriate, to delete the section rather than repeat the information.

*Version Control:*

*Protocol should* include version number and date on every page - 0.x (for draft) or x.0 (for final). Write out the month and use international date format, e.g., 01 January 2010. When making changes/amendments to an approved and “final” protocol, a summary of the changes with the date should be provided at the front of the protocol or in the appendices.

*.*

**FULL PROTOCOL TITLE**

(If not obvious from the protocol title, consider adding a subtitle that briefly summarizes the trial, such as: A Phase <insert phase> randomized, placebo-controlled, double-blinded, 300-subject clinical trial of <insert intervention> in the treatment of <insert indications>.)

Principal Investigator:

(List Principal Investigator’s name, degree, position an affiliation)

**Supported by:** (e.g., application, grant or cooperative agreement #)

**Study Intervention Provided by:** (Name of pharmaceutical or device manufacturer, if any providing support)

**Other Identifying Numbers:** (e.g., Institution-assigned number, HUM #)

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

**Protocol Amendments:**

(Any modifications 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, and the date it became effective.)

**Draft or Version Number: 0.x (for draft) or x.0 (for final)**

**Day Month Year:** (Write out the month and use international date format, e.g., 23 January 2008)

## STATEMENT OF COMPLIANCE

Refer to:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46>
*http://www.fda.gov/*
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html>

Provide a statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

Example text:

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following (use applicable regulations depending on study location and sponsor requirements; samples follow):

* United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
* NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

**SIGNATURE PAGE**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

|  |
| --- |
| Site Investigator:\* |
| Signed: |  | Date: |  |
|  | NameTitle |  |  |

\* The protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site; i.e., if Investigational New Drug (IND) study, the individual who signs the Form FDA 1572.

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**Abbreviations**

<Insert Protocol Specific Abbreviations>

## PROTOCOL SUMMARY

## **Limit to 1-2 pagesPut key words in boldface in Protocol Summary.**

|  |  |
| --- | --- |
| **Title:** | Include type of trial (e.g., dose-ranging, observational, double‑blind) |
| **Précis:** | In 400 words or fewer, provide an overview of the study design, including study arms, sample size and schedule of interventions, if applicable. A detailed schematic describing all visits and assessments (schedule of events) will be included in Appendix A. |
| **Objectives:** | Copy objectives and clinical/laboratory outcome measures from the appropriate sections of the protocol. Include primary/secondary outcome measures and method by which outcome will be determined.Primary:Secondary: |
| **Population:** | Include sample size, gender, age, general health status, geographic location |
| **Phase:** | I, II, III, IV |
| **Number of Sites:** | 3 or fewer, list here; otherwise, list only in Section 1. |
| **Study Duration:** | Provide time from when the study opens until the monitor completes the close out visit. |
| **Subject Participation Duration:** | Provide time it will take to conduct the study for each individual subject. |
| **Description of Agent or Intervention:** | Include dose and route of administration. |
| **Estimated Time to Complete Enrollment:** | Provide estimated time from enrollment into study of the first subject to enrollment into study of the last subject. |

**\*Schematic of Study Design:**

 Example #1: Table format (e.g., dose escalation)

|  |  |  |  |
| --- | --- | --- | --- |
| Cohort A | ARM 1 | Sample Size | Intervention 1 |
| ARM 2 | Sample Size | Intervention 2 |

 Instructions for progressing to next phase (if applicable):

|  |  |  |  |
| --- | --- | --- | --- |
| Cohort B | ARM 1 | Sample Size | Intervention 1 |
| ARM 2 | Sample Size | Intervention 2 |

 Example #2: Flow diagram



\*This schematic study design may be modified to include 3 arms or your protocol-specific design.

### 1 Key Roles

For questions regarding this protocol, contact <<insert name of appropriate staff>> at (insert contact information)>>.

|  |  |
| --- | --- |
| **Individuals:** | **Principal Investigator:** Site investigator responsible for conducting the study |
|  | **Medical Monitor or Behavioral Scientist:** (if applicable) |
|  |  |
| **Institutions:** | Study sites, clinical laboratory(ies), and other medical or technical departments and/or institutions, as applicable.Provide the following information for each organization or institution:Institution NameAddressContact Person/Local InvestigatorPhone NumberFax NumberE-mail |
| **Optional:** | Consider listing, for example:* Collaborating National Institutes of Health Institutes or Centers
* Major international collaborators, if not included as site investigators
* Industry representative(s)
* Other individuals should be listed in a separate document (e.g., the Manual of Procedures [MOP]) as appropriate
* Institutional Review Board (IRB) contact information
 |

### 2 Introduction: Background Information and Scientific Rationale

#### 2.1 Background Information

Include:

* The name and description of the study intervention/investigational products(s)
* A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance
* A summary from relevant clinical trials
* Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations are listed in Section 17)
* Applicable clinical, epidemiological, or public health background or context of the study
* Importance of the study and any relevant treatment issues or controversies

#### 2.2 Rationale

Include a description of, and justification for, the route of administration, dosage, dosing regimen, intervention periods, or behavioral intervention methods and selection of study population. Include a statement of the hypothesis.

#### 2.3 Potential Risks and Benefits

Refer to 45 CFR Part 46.116 (a) (2) and (3)
(<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116>).

Include a discussion of known risks and benefits, if any, to human subjects.

##### 2.3.1 Potential Risks

Include a review of relevant literature, which should be referenced. Add relevant websites, etc., from which the information could be drawn.

If a package insert from a licensed product is available, it should be used as the primary source of risk information. If the product is investigational, the Clinical Investigator’s Brochure (IB) should be the primary source of the risk information. If an IB is not available, documentation describing risks to human subjects and/or pre-clinical data reports must be provided to the IRB. In addition, literature searches can also provide relevant risk information. If the risk profile cannot be described from any of the above sources, the risk information discussion will result from the literature search and review.

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

* Immediate risks
* Long-range risks
* Rationale for the necessity of such risks
* Alternative data gathering procedures that have been considered or will be considered
* Why alternative procedures may not be feasible
* Why the value of the information to be gained outweighs the risks involved.

##### 2.3.2 Known Potential Benefits

If the research is beneficial, describe in detail any physical, psychological, social, legal, economic, or any other benefits to subjects that the PI foresees.

Note: Payment to subjects, whether as an inducement to participate or as compensation for pain and inconvenience, is not considered a “benefit.”

**3 Objectives**

#### 3.1 Study Objectives

A detailed description of the primary and secondary objectives of the study is included in this section. An objective is the reason for performing the study in terms of the scientific question to be answered by the analysis of data collected during the study. These typically include:

* Statement of purpose, e.g., to assess, to determine, to compare, to evaluate
* General purpose, e.g., efficacy, safety, immunogenicity, pharmacokinetics
* Specific purpose, e.g., dose-response, superiority to placebo
* Name(s) of intervention (e.g., procedure, drug, biologic, vaccine, behavioral intervention) being evaluated, specification of doses or dose ranges to be studied, dose regimens

#### 3.2 Study Outcome Measures

This section should include the methods for assessing how the objectives are met, i.e., the study outcome measures.

An outcome measure is “an observation variable recorded for [subjects] in the trial at 1 or more time points after enrollment for the purpose of assessing the effects of the study treatments” (Meinert CL. Clinical trials: design, conduct, and analysis. Oxford: Oxford University;1986). Give succinct but precise definitions of the outcome measures used to measure the primary and key secondary outcomes stated in the study objectives, including the study visits at which the samples will be obtained and the specific laboratory tests to be used.

##### 3.2.1 Primary Outcome Measures

Outcome measures should be prioritized. Generally, there should be just one primary variable, with evidence that it will provide a clinically relevant, valid, and reliable measure of the primary objective (e.g., laboratory procedures, safety assays).

##### 3.2.2 Secondary Outcome Measures

Secondary outcome measures should be included, whether or not they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.

**4 Study Design**

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

* A description of the type/design of trial to be conducted (e.g., placebo-controlled, double-blinded, parallel design, open-label, dose-escalation, dose-ranging)
* A description of the study population and location (e.g., healthy/sick, inpatient/outpatient, community)
* A discussion of the rationale for design features
* Phase of trial
* Single or multicenter
* The number of study groups/arms
* Description of study groups/arms including sample size (including a table, if appropriate)
* Approximate time to complete study enrollment
* The expected duration of subject participation
* Identification of the test agent and specifics of administration of other agents (e.g., placebo)
* A description of the sequence and duration of all trial periods, including follow-up (specify individual subjects vs. entire trial)
* Changes in scheduling, such as dose escalation
* Any stratifications
* A specific statement of the primary and secondary outcomes to be measured during the trial (must be consistent with Study Objectives, as stated in Section 3)
* Methods for collecting data for assessment of study objectives
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)
* Interim analysis plans
* Identification of the structure for safety oversight (e.g., Data and Safety Monitoring Board (DSMB), Safety Monitoring Committee (SMC) and/or Independent Safety Monitor (ISM).

#### 4.1 Substudies (if applicable)

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

Note that substudies do not have full protocols but rather are incorporated into the main protocol.

List with brief description:

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

If a substudy is added to an ongoing study, a protocol amendment is required.

### 5 Study Enrollment and Withdrawal

The study population and inclusion/exclusion criteria should be clearly defined in this section of the protocol. 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.

The study population should be commensurate with the stage of the study and the development stage for the study product. This section should include a discussion of recruitment strategies, specifically for achieving NIH gender/minority guidelines.

If the study intends to enroll children, pregnant women, prisoners, or other vulnerable populations, refer to applicable section of 45 CFR Part 46 Subpart B – Additional Protections Pertaining to Research, Development and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization (45 CFR Part 46.201-46.211); Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (45 CFR Part 46.301-46.306); Subpart D – Additional Protections for Children Involved as Subjects in Research (45 CFR Part 46.401-409). Please refer to these regulations and Office for Human Research Protections (OHRP) guidelines when choosing the study population.

Note that these regulations apply if any subjects are members of the designated population even if it is not the target population (for example, if a subject becomes a prisoner during the study). Refer to: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46> and <http://www.hhs.gov/ohrp/irb/irb_guidebook.htm>.

Provide the target sample size, including actual numbers to be enrolled.

Include numbers of women, minorities, and children expected to be recruited. If women, minorities, or children will not be recruited, explain why not. Provide justification for Exclusion in Ethics/Protection of Human Subjects, Section 14.4.
Refer to: <http://grants2.nih.gov/grants/funding/women_min/women_min.htm>.

* Indicate from where the study population will be drawn (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public). Where appropriate (single‑center studies), include names of hospitals, clinics, etc.
* Identify strategies for subject recruitment and retention.
* If subjects require screening, distinguish between screening subjects (e.g., discussing the study with them) vs enrolling subjects (e.g., obtaining informed consent and obtaining samples).

Note: if screening procedures are required for eligibility (e.g., review of medical records or laboratory tests), they must be performed under a separate screening consent form in addition to the consent form for study participation.

Eligibility Criteria:

* The eligibility criteria should provide a definition of subject characteristics required for study entry.
* The risks of the test agent/product should structure the development of the inclusion/exclusion criteria.
* The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >32 years old as an inclusion criterion and also age ≤32 years old as an exclusion criterion).
* Select screening laboratory tests carefully, if they will be used (laboratory parameters selected should be related to evaluation of safety, with ranges based on toxicity criteria).
* If males and females of reproductive potential will be enrolled, provide specific contraception requirements (e.g., licensed hormonal methods).

#### 5.1 Subject Inclusion Criteria

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

Example format:

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

* Provide signed and dated informed consent form
* Male or female, aged XX to XX
* Willing to comply with all study procedures and be available for the duration of the study
* In good general health as evidenced by medical history *or* Diagnosed with specific condition/disease *or* Exhibits specific clinical signs or symptoms or physical/oral examination findings
* Laboratory results within or outside of a specific range
* Women of reproductive potential must use highly effective contraception (specify methods of contraception acceptable for the study, e.g., licensed hormonal methods)
* Men of reproductive potential must use condoms *(if appropriate for study).*

#### 5.2 Subject Exclusion Criteria

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

Example format:

A potential subject who meets any of the following criteria will be excluded from participation in this study:

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

#### 5.3 Strategies for Recruitment and Retention

Identify strategies for participant recruitment and retention. Consider including recruitment and enrollment goals, where subjects will be recruited.

#### 5.4 Treatment Assignment Procedures

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

##### 5.4.1 Randomization Procedures

State if the trial will be randomized or not. Include plans for the maintenance of trial randomization codes. The timing and procedures for planned and unplanned breaking of randomization codes should be included.

##### 5.4.2 Blinding Procedures

State whether the treatment arms will be blinded if the study includes more than one treatment. Plans for maintaining appropriate blinding for the study should be discussed.

##### 5.4.3 Reasons for Withdrawal

Provide a list of reasons subjects may be discontinued from the study. It may be appropriate to provide distinct discontinuation criteria for subjects and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also note that subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason.

Example text:

“A study subject will be discontinued from participation in the study if:

* Any clinical adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
* The subject meets any exclusion criteria (either newly developed or not previously recognized).

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

##### 5.4.4 Handling of Withdrawals

Describe the efforts to follow subjects who withdraw from the study. It is vital to collect safety data on any subject discontinued because of 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. Describe efforts that will be made to continue follow-up, especially for safety and efficacy (if applicable) outcome measures.

This section should include a discussion of replacement of subjects who discontinue early, if replacement is allowed.

##### 5.4.5 Termination of Study

List possible reasons for discontinuation of the study in this section, e.g., development of laboratory toxicities, study closure due to DSMB review, discretion of IND sponsor.

Example text:

“This study may be prematurely terminated if, in the opinion of the investigator or the sponsor, there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator or sponsor by the terminating party.

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

* Determination of unexpected, significant, or unacceptable risk to subjects.
* Insufficient adherence to protocol requirements.
* Data that are not sufficiently complete and/or evaluable.
* Plans to modify, suspend or discontinue the development of the study drug.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).”

**6 Study Intervention/Investigational Product**

Note: If multiple products, product vehicle or adjuvant, or other interventions are to be evaluated in the study, the following sections should be repeated for each product and the sections should be renumbered accordingly. Describe placebo or control product.

#### 6.1 Study Product Description

Information in this section can usually be obtained from the IB or the package insert. Make IB or package insert available to all investigators as part of the study’s MOP or distributed separately, as appropriate.

##### 6.1.1 Acquisition

##### 6.1.2 Formulation, Packaging, and Labeling

##### 6.1.3 Product Storage and Stability

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

Provide additional information regarding stability and expiration time for studies in which multidose vials are entered (i.e., the seal is broken).

If a behavioral intervention, describe methods, how intervention will be administered, by whom, setting, duration, frequency, etc. Details of intervention, scripts, rater assessment or scoring can be described in a Manual of Procedures.

#### 6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

In this section, list investigational agents, route, doses, and frequency of administration. Include thawing, diluting, mixing, and reconstitution/preparation instructions, as appropriate. Include any specific instructions or safety precautions for administration of study products or blinding of the product or the study staff administering it. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc.

#### 6.3 Modification of Study Intervention/Investigational Product for a Subject

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

#### 6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

Provide plans for how the study intervention/investigational product(s) will be distributed including participation of a drug repository, frequency of product distribution, amount of product shipped, and plans for return of unused product.

#### 6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

Include this section, if applicable.

Include plans for compliance assessment (e.g., questionnaires, direct observation, pill counts) in this section.

#### 6.6 Concomitant Medications/Treatments

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

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

**7 Study Schedule**

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

Allowable windows should be stated for all visits. The schedule must include clinic visits and all contacts, e.g., telephone contacts. To determine the appropriate windows, consider feasibility and relevance of the time point to study outcome measures (e.g., pharmacokinetic (PK) studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).

#### 7.1 Screening

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

This section should include instructions for obtaining signed informed consent. State if a separate screening consent will be used. If a separate screening consent form will not be used, the study consent form must be signed prior to screening.

If an individual’s medical chart or results of diagnostic tests performed as part of an individual’s medical care are going to be used for screening, written informed consent must be obtained prior to review of that information.

The evaluations to be done may be listed individually in this section, or alternatively, refer to the Schedule of Events (Appendix A).

Example format:

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

* Obtain signature of potential subject on written informed consent for screening form.
* Review medical/dental history to determine eligibility based on inclusion/exclusion criteria.
* Review medications history to determine eligibility based on inclusion/exclusion criteria.
* Perform medical/dental examinations needed to determine eligibility.
* Collect blood/urine (if required for screening laboratory tests; specify tests to be done).
* Schedule study visits for subjects who are eligible and available for the duration of the study. Provide subjects with instructions needed to prepare for first study visit (specify instructions to be provided).

#### 7.2 Enrollment/Baseline

Discuss evaluations/procedures necessary to assess or confirm whether a subject still meets the eligibility criteria and may be enrolled, and discuss those assessments that are required at baseline for later outcome measure comparison after study intervention (e.g., baseline signs and symptoms prior to treatment). Discuss the sequence of events that should occur during enrollment and/or initial administration of study product. List any special conditions (e.g., results of the pregnancy test must be negative and available prior to administration of study product). List the procedures for administering the study product or intervention and follow-up procedures after administration (e.g., assessment of vital signs, mucosal reactions).

The evaluations to be done may be listed individually in this section or, alternatively, refer to the Schedule of Events (Appendix A).

Example format:

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

* Obtain signature of subject on study informed consent form.
* Verify inclusion/exclusion criteria. Obtain urine pregnancy test (if required by protocol).
* Obtain demographic information, medical/dental history, medication history, alcohol and tobacco use history (as required for the study).
* Record vital signs, results of examinations, other assessments (as required for the study; specify the information to be recorded).
* Collect blood/urine (for baseline laboratory tests as required for the study).
* Administer the treatment, medication, etc. (specify procedures, instructions provided to subjects, observations after the intervention, etc.).

#### 7.3 Follow-up

Include discussion of evaluations/procedures required to assess or confirm study outcome measures and study evaluations. Discuss the sequence of events that should occur during the visit, if applicable. Include, as applicable, counseling, review of mucosal reactions, medications, assessment of AEs, etc.

The evaluations to be done may be listed individually in this section or, alternatively, refer to the Schedule of Events (Appendix A).

Example format:

**Follow-up Visit (Visit 2, Day X±Y)** (repeat for each visit, providing a study-appropriate window for the visit)

* Record adverse events as reported by subject or observed by investigator.
* Record vital signs, results of examinations, other assessments (as required for the study; specify the information to be recorded).
* Collect blood/urine (for follow-up laboratory tests as required for the study).
* Administer the treatment, medication, etc., or, for self-administered medication, provide additional medication to subject (specify procedures, instructions provided to subjects, observations after the intervention, etc.).
* Record subject’s compliance with treatment regimen.

#### 7.4 Final Study Visit

Define when the final study visit should occur and any special procedures/evaluations or instructions to the subject. Describe provisions for follow-up of ongoing AEs/serious adverse events (SAEs). Consider discussing if or when subjects will be informed of study results.

The evaluations to be done may be listed individually in this section or, alternatively, refer to the Schedule of Events (Appendix A).

Example format:

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

* Record adverse events as reported by subject or observed by investigator.
* Record vital signs, results of examinations, other assessments (as required for the study; specify the information to be recorded).
* Collect blood/urine (for final laboratory tests as required for the study).
* Record subject’s compliance with treatment regimen.
* Provide final instructions to subject (e.g., follow-up of ongoing adverse events, oral hygiene instructions, etc., as required for the study).

#### 7.5 Early Termination Visit

Specify which of the evaluations required for the final study visit should be done at a termination visit if early termination occurs and if the subject is willing. Clearly differentiate between what evaluations are to be done in each of these circumstances.

#### 7.6 Unscheduled Visit

Specify how unscheduled visits(s) will be handled and documented.

### 8 Study Procedures/Evaluations

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

#### 8.1 Clinical Evaluations

List all clinical evaluations to be done during the protocol, and provide details of what are included and special instructions, if any.

Examples:

* Medical history (describe what is included for history, e.g., time-frame considerations, whether history will be obtained by interview or from medical records).
* Medications history (e.g., describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter). Assessment of eligibility should include a review of permitted and prohibited medications.
* Physical examination (list the vital signs [including height and weight] and organ systems to be assessed); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur. If an adverse event occurs, describe if a full physical examination should be done.
* Oral exams
* Counseling procedures.
* Criteria for dose adjustment.
* Rescue therapy.

#### 8.2 Laboratory Evaluations

##### 8.2.1 Clinical Laboratory Evaluations

List all laboratory evaluations. Differentiate screening laboratories from those taken after treatment, as appropriate. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods (e.g., use consistent laboratory method throughout study) to provide for appropriate longitudinal and cross-comparison. If more than one laboratory will be used, specify which evaluations will be done by each laboratory.

Examples:

* Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.
* Biochemistry: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).
* Urinalysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.
* Pregnancy test, usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.

##### 8.2.2 Special Assays or Procedures

List special assays or procedures required to assess the study product (e.g., immunology assays, PK studies, photographs). For laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. For procedures, provide special instructions or precautions. If more than one laboratory will be used, specify which assays will be done by each laboratory.

##### 8.2.3 Specimen Preparation, Handling, and Shipping

###### 8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

Special instructions for the preparation, handling, and storage of specimens should be explained clearly in this section), including required temperatures, aliquots of specimens, if samples are frozen, where they will be stored, and how they will be labeled. Include a discussion of long-term access and consent for future use of specimens (Section 14.7).

###### 8.2.3.2 Specimen Shipment

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

### 9 Assessment of Safety

#### 9.1 Specification of Safety Parameters

Reference safety parameters that are outcome measures (Section3.2). Include other parameters if not primary study outcome measures.

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

##### 9.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

* Describe which AEs will be collected as solicited events. Plan the reporting and data collection system to avoid double capture.
* Describe how decisions will be made regarding determining relatedness and grading severity.
* Describe how unsolicited events will be captured.
* Include time period of collection (e.g., Days 0 -28) and note how long SAEs are collected – usually collected through entire study.

Example text:

“**Adverse Event:** AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, DDS, DMD, PA, Nurse Practitioner or DO), 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 subject is screened will be considered as baseline and not reported as an AE. If a pre-existing condition or illness, which is not expected to exacerbate or worsen, deteriorates at any time during the study it should be reported as an AE.

All AEs must be graded for severity and relationship to study product.

**Severity of Event:** All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, the following guidelines will be used to quantify intensity.

* **Mild:** Noticeable to the subject, but does not interfere with subject’s expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study .
* **Moderate:** Interferes with the subject’s expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.
* **Severe:** Extremely limits the subject’s daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolved. Severe events are usually incapacitating.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

**Relationship to Study Products:** The clinician’s assessment of an AE's relationship to test article (study drug) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: associated or not associated. To help assess, the following guidelines are used.

* **Associated** – The event is temporally related to the administration of the study product and no other etiology explains the event.
* **Not Associated** – The event is temporally independent of study product and/or the event appears to be explained by another etiology.”

##### 9.2.2 Expected Adverse Reactions

Expected adverse reactions are AEs that are common and known to occur for the intervention/investigational product being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Provide a definition of expected vs. unexpected AEs and local vs. systemic events, based on the risk profile of the intervention/investigational product. Expected reactions/events will be identified in this section and will differ depending on the study product used. This information is found on the IB or package insert (current edition) or in the informed consent document.

##### 9.2.3 Serious Adverse Events

An SAE is any adverse event/experience occurring at any study drug dose that results in any of the following outcomes:

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

Example text:

**“Serious Adverse Event (SAE):** An SAE is defined as an AE that meets one of the following conditions:

* Death during the period of protocol-defined surveillance
* Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
* An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
* Results in congenital anomaly or birth defect
* Results in a persistent or significant disability/incapacity
* Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse/overdose or cancer.

All SAEs will be:

* recorded on the appropriate SAE Report Form and CRF
* followed through resolution by a study clinician
* reviewed and evaluated by a study clinician.”

##### 9.2.4 Unanticipated Problems

Refer to the following guidance documents:
<http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm>
<http://www.fda.gov/>

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

* unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
* related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
* suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others.

Some incidents, experiences, and outcomes that occur during the conduct of human subjects research represent unanticipated problems but are not considered adverse events. These may involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs. Unanticipated problems must be reported, even if they do not involve adverse events. However, adverse events that do not meet the criteria to be considered unanticipated problems are not subject to these reporting requirements.

Example text:

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

* unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
* related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
* suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

* changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects
* modification of inclusion or exclusion criteria to mitigate the newly identified risks
* implementation of additional procedures for monitoring subjects
* suspension of enrollment of new subjects
* suspension of research procedures in currently enrolled subjects
* modification of informed consent documents to include a description of newly recognized risks
* provision of additional information about newly recognized risks to previously enrolled subjects.

Unanticipated problems will be recorded and reported throughout the study.”

##### 9.2.5 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Collection of laboratory data should be limited to those laboratory parameters that are relevant to safety, study outcome measures, and/or clinical outcome.

The toxicity tables will define what values or findings are considered abnormal. Reporting will be dependent on the abnormality, the study intervention, and the study population and should be stated specifically. Consider the context of the trial and adjust reporting procedures appropriately for the study population and agent being studied.

Define the circumstances in which abnormal laboratory values will be reported as AEs/SAEs. In sick populations, define in terms of a change from baseline and disease progression. For example:

 “Symptoms of the original or targeted disease are not to be considered adverse events in this study”

 “Abnormal laboratory values or test results constitute adverse events if they include clinical signs or symptoms or require therapy.

#### 9.3 Reporting Procedures

All clinical trials must have a safety reporting system in place. or address why AEs won’t be systematically collected.

Include details of the protocol-specific reporting procedures and time lines, including the individual responsible for each step (e.g., the investigator, the Medical Monitor), how decisions will be made regarding determining relatedness and severity, which forms should be completed, how reports will be distributed, and what follow-up is required.

Include specific details of reporting procedures for:

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

The example language presented in the following sections may be used in protocols. These sections may be customized by including protocol-specific information such as:

* Time frame for collecting and reporting AEs and SAEs, specify duration follow-up.
* Identification of additional protocol-specific parameters (safety issues) that need to be reported in an expedited fashion, either to the investigator, sponsor, or regulatory body.
* Information on any Data Safety Monitoring Plan or Board that will be implemented to oversee the safety of the study. (Check with your department on whether a Data Safety Monitoring Plan is available.)

##### 9.3.1 Serious Adverse Events

The study will comply with IRB and FDA reporting requirements and guidelines.

##### 9.3.2 Regulatory Reporting for Studies Conducted Under IND

Example text:

“Following notification from the investigator, the IND sponsor, will report events that are both serious and unexpected and that are associated with study product(s) to the Food and Drug Administration (FDA) within the required timelines as specified in 21 CFR Part 312.32: fatal and life-threatening events within 7 calendar days (by phone or fax) and all other SAEs in writing within 15 calendar days. All serious events designated as “not associated” with study product(s), will be reported to the FDA at least annually in a summary format.”

##### 9.3.3 Regulatory Reporting for Studies Not Conducted Under IND

If a study is not being conducted under an IND, it may be appropriate to name alternative ways to report AEs (e.g., MEDWATCH, VAERS). .

##### 9.3.4 Other Adverse Events (if applicable)

Describe any other non-serious AEs that merit reporting to the sponsor, study leadership, IRB, and regulatory agencies.

##### 9.3.5 Other Unanticipated Problems

Institutions engaged in human subjects research conducted or supported by DHHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)). Furthermore, for research covered by an assurance approved for federalwide use by OHRP, DHHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.

Describe the reporting procedures to be followed for incidents or experiences that meet the OHRP criteria for unanticipated problems, although they may not be SAEs. Include the individuals responsible for each step in the reporting process (PI, DCC, IRB, etc.) and the required time frames for reporting.

For multicenter research protocols, if a local investigator at one institution engaged in the research independently proposes changes to the protocol or informed consent document in response to an unanticipated problem, the investigator should consult with the study sponsor or coordinating center regarding the proposed changes because changes at one site could have significant implications for the entire research study.

Example text:

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

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

##### 9.3.6 Reporting of Pregnancy

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

#### 9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Describe how AEs will be followed until resolved or considered stable. Specify procedures for reporting and follow-up of AEs that are consistent with the Schedule of Events. Include duration of follow-up after appearance of AEs (e.g., 1 week, 2 months).

#### 9.5 Halting Rules

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

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

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

#### 9.6 Safety Oversight

In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety in the study. State who is responsible for safety oversight, i.e., DSMB. Will they meet at prearranged time points (enrollment milestones, prior to next stage in protocol) in the study? Will meetings be dependent on the halting rules? State which safety outcome measures will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

Example text:

Data and Safety Monitoring Board (DSMB)

The first DSMB meeting will occur <insert time frame>. In addition to reviewing Serious Adverse Events (SAEs), the first DSMB meeting will focus on over all safety of the trial and study agent and will make a determination as to whether or not the study should proceed. The DSMB will then meet quarterly throughout the remainder of the study and at any time during the study in which an unexpected and possibly related SAE occurs.

The DSMB will be composed of the following members: (list members and roles)

**10 Clinical Monitoring**

Refer to: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46>.

This section will give a general description of how site monitoring will be conducted. A separate clinical monitoring plan can be developed and referenced in this section to describe who will conduct the monitoring, at what frequency monitoring will be done, and at what level of detail monitoring will be performed.

#### 10.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the sponsor, and, when appropriate, regulatory guidelines. This section will give a general description of how site monitoring will be conducted.

Example text:

To assure adequate protection of the rights of human subjects, per 21 CFR 312.50, 312.53, <Insert name of person(s)> to conduct monitoring of the study per Monitoring Agreement, located in <Insert Appendix number>. The established monitoring plan will ensure the quality and integrity of the data through pre-investigation visits, periodic site visits, review of adverse events/subject records, and a complete record of on-site visit, etc.

**11 Statistical Considerations**

This section should be “self-contained” for coherence and ready reference. It should show how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible.

#### 11.1 Study Hypotheses

State the formal, testable, null, and alternate hypotheses for primary and key secondary objectives, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose-response).

#### 11.2 Sample Size Considerations

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

In particular, specify all of the following:

* Outcome measure used for calculations (almost always the primary variable)
* Test statistic
* Null and alternate hypotheses
* Type I error rate
* Type II error rate
* Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible
* Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., also justified
* Approach to handling withdrawals and protocol violations, i.e., whether subjects will be included in the “intent-to-treat” population
* Statistical method used to calculate the sample size, with a reference for it and for any software utilized, and
* Method for adjusting calculations for planned interim analyses, if any (see Section11.3).

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

Discuss whether the sample size also provides sufficient power for addressing secondary objectives or for secondary analyses in key subgroup populations.

#### 11.3 Planned Interim Analyses (if applicable)

If interim analyses will be reviewed by a DSMB or similar committee, describe its composition, and how often it will meet.

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

Within the following sections, pre-specify, to the extent possible, the criteria used to determine decisions.

##### 11.3.1 Safety Review

Provide details of the proposed rules for halting study enrollment or study intervention/administration of study product for safety, including whether they pertain to the entire study, specific study arms or subject subgroups, or other components of the study.

State which safety outcome measures will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

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

##### 11.3.2 Efficacy Review

Provide the same information as in Section11.3.1, but for efficacy outcome measures. Also discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

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

#### 11.4 Final Analysis Plan

This section can be used to elaborate on primary analyses that underlie the sample size calculation in Section 11.2 and to describe secondary analyses for the primary or secondary objectives. Even more details can be provided in a separate statistical analysis plan written later but prior to performing any analyses.

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

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

### 12 Source Documents and Access to Source Data/Documents

 Describe who will have access to records.

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. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, recorded audio tapes of counseling sessions, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject 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.

Refer to: (<http://www.fda.gov/>)

**13 Quality Control and Quality Assurance**

This section will address the plans for local quality assurance and quality control.
(<http://www.fda.gov/>)

Quality control is the ongoing, concurrent review of data collection forms for completion and logic. Quality assurance is a comprehensive, retrospective review of all components of research records to assess adherence to protocol, standard operation procedures, and regulations, and to evaluate the accuracy of the records. Quality management is the process of assessing the quality of processes within a system and encompasses quality assurance and quality control.

Each site should have standard operating procedures (SOPs) for quality management which describe:

* How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
* The documents to be reviewed (e.g., CRFs, clinic notes, product accountability), who is responsible, and the frequency for reviews. These should be identified, either in a formal quality management plan or in site SOPs.
* Methods of training for staff, and methods of tracking such training.

See Section 10.1 for detail on Site Monitoring.

You can access the Office of Human Research Protections Quality Assurance Self Assessment tools at <http://www.hhs.gov/ohrp/humansubjects/qip/qatooli.htm>.

**14 Ethics/Protection of Human Subjects**

This section should include a description of the ethical considerations and context for the conduct of the trial.

#### 14.1 Ethical Standard

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

Example text:

“The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46; 62 Federal Regulations 25691 (1997) and the Declaration of Helsinki and Good Clinical Practice (GCP). ”

If the study is conducted at international sites, the statement could be as above and/or could reference compliance with the 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.

#### 14.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federalwide Assurance issued by OHRP may participate. Refer to: [http://www.hhs.gov/ohrp/assurances/.](http://www.hhs.gov/ohrp/assurances/)

*For IND/IDE(s)*

Prior to study commencement, an Investigator Initiated Investigational New Drug (IND)/Device (IND) will be submitted to the Food and Drug Administration (FDA), for review and approval

All protocol amendments must be FDA and IRB approved prior to implementing, except when change is for patient safety.

#### 14.3 Informed Consent Process

Refer to FDA regulations on informed consent 21 CFR Part 50 - Subpart B (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=50>).

Refer to DHHS Regulation on Informed Consent 45 CFR Part 46 - Subpart A, 46.116 [(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116)).

Describe the procedures for obtaining and documenting informed consent of study subjects. Make provisions for special populations, e.g., non-English speakers, children, illiterate or non-writing individuals, vulnerable populations.
(Refer to: <http://www.hhs.gov/ohrp/humansubjects/guidance/ic-non-e.htm>).

Informed consent is required for all subjects participating in the study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to 45 CFR Part 46 and/or ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB’s written approval for the protocol, and favorable opinion of the written informed consent form(s) and any other written information to be provided to the subjects.

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

Example text:

“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. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms (written in non-technical language) describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects 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.”The consent process will be documented in detail in the participants source documents by the individual(s) who conducted the consenting process.

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

If the study intends to exclude any special populations, justify the exclusion of women, minorities, or children in the context of the study design.

#### 14.5 Subject Confidentiality

Include procedures for maintaining subject confidentiality, any special data security requirements, and record retention per the sponsor’s requirements. Possible persons that might have access to records, in addition to the clinical monitor, would be funding institutions, IND sponsor, representative from the IRB, and representatives of the pharmaceutical company supplying product to be tested.

Example text:

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

The study protocol, documentation, data, and all other information generated will be held in strict confidence.

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be de-identified of any protected health information (PHI) and replaced with study identifier to maintain subject confidentiality. Information will not be released without written permission of the participant , except as necessary for monitoring by IRB, the FDA, OHRP and/or any other government officials, safety monitors/committees that may need the information to make sure that the study is done in a safe and proper manner, learn more about side effects, and/or analyze the results of the study; insurance companies or other organizations that may need the information in order to pay medical bills or cost of study participation.”

#### 14.6 Study Discontinuation

In the event that the study is discontinued, provide a plan for the following:

* Describe procedures for subjects to continue therapy, if appropriate.
* Describe crossover to study drug for placebo recipients at the completion of the study.

#### 14.7 Future Use of Stored Specimens

Refer to Human Research Regulation Chart 2
<http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm>.

If residual specimens will be maintained after the study is complete, include the provisions for consent and the options that are available for the subject to agree to the future use of his/her specimens. Specify the location(s), if other than the clinical site, where specimens will be maintained, if the site's IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens, e.g., specimens will be coded, bar-coded, delinked. Include a statement that genetic testing will or will not be performed, if required by the IRB. A Certificate of Confidentiality may be obtained if genomic testing is planned. See Section 14.5, Subject Confidentiality, for information.

**15 Data Handling and Record Keeping**

Refer to: <http://www.fda.gov/ora/compliance_ref/part11>/

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

Briefly describe steps to be taken to ensure that the data collected are accurate, consistent, complete, and reliable. The description should include reference to source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring. Details may be provided in an MOP, User’s Guide or other citable reference document.

Example text:

“The investigator is responsible to ensure 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. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.”

#### 15.1 Data Management Responsibilities

Describe responsibilities for data collection and management. Information should include the 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 using a Coordination Center (or Data management/Statistical Center) indicate responsibilities in data management.

#### 15.2 Data Capture Methods

Provide details regarding the type of data capture that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs. Indicate/identify any data to be recorded directly on the case report forms (CRFs) at time of study visit and is to be also considered “source”. If utilizing a manual of Procedures (MOP) for study conduct, can refer to MOP in this section for description of CRFs.

#### 15.3 Types of Data

Indicate the types of data that will be collected, such as safety, laboratory (clinical, immunology, pharmacokinetic, other study specific), and outcome measure data (e.g., expected adverse reactions). Specify if safety data are collected in a separate database.

Example text:

“Data for this study will include safety, laboratory (immunologic and virologic), and outcome measures (e.g., expected adverse reactions, immunogenicity, virology).”

#### 15.4 Timing/Reports

Indicate the schedule for data review and reports, how outcome measure data are collected and monitored, data for stopping rules, and reports for DSMB. Specify whether reviews or reports are ongoing, interim, or periodic. Identify plans for data analysis and interim and final study reports, steps for freezing the data prior to analysis, and precautions related to blinded data. Indicate whether and when coding is to occur.

#### 15.5 Study Records Retention

Specify the length of time for the investigator to maintain all records pertaining to this study (e.g., a minimum of 2 years following the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product). Indicate whether permission is required (and from whom) prior to destruction of records. If under an IND, records should not be destroyed without the IND sponsor’s agreement. Pharmaceutical companies who supply unregulated products should be consulted.

Investigational product records may be addressed here if not addressed elsewhere in the protocol.

Example text:

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

#### 15.6 Protocol Deviations

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

### 16 Publication Policy

If appropriate, the publication policy may be described in the study’s MOP.

Interventional clinical trials must be registered prior to subject enrollment with [ClinicalTrials.gov](http://clinicaltrials.gov) via a web based data entry system called the Protocol Registration System (PRS) maintained by the National Library of Medicine. For more information see <http://prsinfo.clinicaltrials.gov>.

The publication and authorship policies should be determined and clearly outlined in this section. Please refer to your specific grant and/or Clinical Trials Agreements.

The following language may be used in the protocol:

“Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committeeof Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as [ClinicalTrials.gov](http://www.clinicaltrials.gov)\*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For grants and cooperative agreements, it is the Institution’s responsibility to register the trial in an acceptable registry. In addition, [NIH Public Access Policy](http://publicaccess.nih.gov/policy.htm) requires the principal investigator to submit journal articles that arise from NIH funds to the digital archive [PubMed Central](http://www.pubmedcentral.nih.gov/).

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from registering trials in a public registry such as ClinicalTrials.gov.”

**17 Literature References**

Include a list of relevant literature references in this section. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc). The preferred format is ICMJE.

Examples:

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

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

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

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

You may also refer to:
[http://www.nlm.nih.gov/bsd/uniform\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html%20).

**SUPPLEMENTS/APPENDICES**

(Modify listing according to the needs of the protocol)

Supplements and Protocol Appendices

* Schedule of Events
* Toxicity Grading Scales
* Sample Consent Form(s)

Related Documents

* Site Roster
* Manual of Procedures
* Repository instructions
* Biosafety Precautions
* Ionizing Radiation safety
* Laboratory Handling

Other Documents

* CRF copies
* Quality Management Plan
* Data Management Plan
* Clinical Monitoring Plan

## APPENDIX A: SCHEDULE OF EVENTS

A detailed schematic describing all visits and assessments.

|  | Follow-Up Schedule |  |
| --- | --- | --- |
| Procedures | Screening (Day –X to –Y) | Baseline (Day 0) | Study Visit 1(Day X ± Y) | Study Visit 2(Day X ± Y) | Study Visit 3(Day X ± Y) | Study Visit 4(Day X ± Y) | Study Completion(Day X ± Y) | Premature Discontinuation |
| Signed Consent Form | X | X |  |  |  |  |  |  |
| Assessment of Eligibility Criteria | X | X |  |  |  |  |  |  |
| Review of Medical History | X | X |  |  |  |  |  |  |
| Review of Concomitant Medications  | X | X | X | X | X | X | X | X |
| Study Intervention |  | X |  |  |  |  |  |  |
| Physical Examination | Complete | X |  |  |  |  |  | X | X |
| Symptom-Directed |  | X | (X) | (X) | (X) | (X) |  |  |
| Vital Signs |  | (X) | (X) | (X) | (X) | (X) |  |  |
| Assessment of Adverse Events |  |  | (X) | (X) | (X) | (X) | X | X |
| Clinical Laboratory | Chemistry | X | X | (X) | (X) | (X) | (X) | X | X |
| Hematology | X | X | (X) | (X) | (X) | (X) | X | X |
| Urinalysis | X | X | (X) | (X) | (X) | (X) | X | X |
| Research Laboratory | Immunology\_\_mL whole blood |  | X |  | (X) |  | (X) | X | X |
| Other Procedures |  |  | (X) |  | (X) |  | (X) | (X) | (X) |

For the screening visit and each follow-up visit, provide a window during which the visit can occur. The window should be appropriate for the parameters to be assessed at the visit.
(X) – As indicated/appropriate.
Note: List the tests applicable to your specific protocol.

Provide a list of tests to be done, e.g.:
**Hematology** – Hemoglobin, hematocrit, WBC and differential count, platelet count.
**Biochemistry** – Sodium, potassium, chloride, urea, creatinine, glucose, uric acid, bicarbonate, amylase, lipase, albumin, total bilirubin, cholesterol, triglycerides, and creatine phosphokinase, as appropriate for the study.
**Urinalysis** – Protein and glucose, as appropriate for the study.
**Immunology** – Specimen types for nonstandard laboratory assays.
**Other** – Other procedures that are done to evaluate outcome measures (e.g., photographs, x-rays).
Study intervention – Modify as appropriate if intervention is administered more than once throughout the study.
Specify time points for follow-up in days, weeks, or months, as appropriate for protocol.
At baseline, all procedures should be done before study intervention.
Indicate volume of blood if frequent or large phlebotomies over 2 months are part of the protocol.