Icahn School of Medicine at Mount Sinai

Conduits
The Institutes for Translational Sciences

PROTOCOL TEMPLATE

Instructions to User:

1. **Sections and text that are in regular font and that have not been highlighted in grey** represent standard language. In general, these sections should be present in your final protocol and the language should not be changed. However, every protocol is unique and changes to standard sections and language may be necessary to meet the needs of your protocol. Please review the language carefully to make sure that it is accurate for your study.
2. **Sections that are highlighted in grey, but that have regular font**, represent sections or information that needs to be customized as applicable to your study, but the language that is present is generally considered to be standard if that section (or procedure) applies to your protocol.
3. **Sections that are highlighted in grey, and where the text is italicized**, represent instructions with some example text. All require complete customization for your study.
4. As you customize each section of the protocol, **remove the highlighting and restore the font to regular (from italics)** to denote that section as having been completed.
5. When your protocol is complete, **review** it to ensure that all highlighting and italics have been removed.

SPONSOR NAME

Clinical Research Protocol

PROTOCOL NAME

Protocol Number:	
Version Date:	
Investigational Product:	
IND Number:	
Development Phase:	
Sponsor:	Name *(please note – for academic studies, the sponsor is the Investigator, not the funding agency.)* Address City, State
Funding Organization:	
Principal Investigator:	Name: Telephone: Fax: E-mail:
Medical Monitor:	Name: Telephone: Fax: E-mail:
Coordinating Center:	If applicable

Approval:

PI or Sponsor Signature (Name and Title) *Date*

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing [Sponsor Name] with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: Number

Protocol Title: Title

Protocol Date: TBD

_____ _____

Investigator Signature *Date*

_____

Print Name and Title

Site # _____

Site Name _____

Address _____

_____

_____

_____

Phone Number _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Add all other abbreviations referenced in the protocol and delete any not referenced in the protocol.

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	case report form
CRP	C-reactive protein
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
$FEF_{25\%-75\%}$	forced expiratory flow
FEV_1	forced expiratory volume over one second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-8	Interleukin-8
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
mEq	milliequivalent
PI	Principal Investigator
PK	pharmacokinetic
SAE	serious adverse experience
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase

PROTOCOL SYNOPSIS

TITLE	
SPONSOR	
FUNDING ORGANIZATION	
NUMBER OF SITES	
RATIONALE	*This should be very brief – 2 paragraphs or so, just highlighting why it makes sense to study product X in these patients and that there is a medical need.*
STUDY DESIGN	*This is a randomized, double-blind, placebo-controlled phase 2 study.*
PRIMARY OBJECTIVE	
SECONDARY OBJECTIVES	
NUMBER OF SUBJECTS	
SUBJECT SELECTION CRITERIA	Inclusion Criteria: Exclusion Criteria:
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	*Product XX at XX dose* *Product will be administered every XX hours (or days) for X length of time. Describe administration (orally, IV, or by inhalation). If inhalation describe delivery system.*
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	*Product XX (indicate if comparator or placebo) at XX dose* *Product will be administered every XX hours (or days) for X length of time. Describe administration (orally, IV, or by inhalation) If inhalation describe delivery system.*
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	*Subjects will be on study for up to 28 days* ***Screening:*** *up to 7 days* ***Treatment:*** *5 days (subjects to be admitted to the hospital)* ***Follow-up:*** *16 days* *The total duration of the study is expected to be XXX. XXX months for subject recruitment and XXX for final subject follow-up.*

CONCOMMITANT MEDICATIONS	Allowed: Prohibited:
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	•
SECONDARY ENDPOINTS	•
OTHER EVALUATIONS	*PK, research lab evaluations, etc., would go here*
SAFETY EVALUATIONS	*Change in clinical safety labs from baseline to XXX* *Incidence of adverse events*
PLANNED INTERIM ANALYSES	*Fill in details of DMC. Please note: if this is a NIH-funded study, all references should be "DSMB"; for non-NIH funded studies, refer to the" DMC." Sample text:* When approximately 50% of patients have completed the study through Visit X, an interim analysis for safety will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	*Describe plan for analyzing the primary endpoint.*
Rationale for Number of Subjects	

1 BACKGROUND

Identify the product to be studied, and describe it briefly.

1.1 Overview of Non-Clinical Studies

Provide a brief summary of the non-clinical data that has clinical significance.

1.2 Overview of Clinical Studies

Provide a brief summary of the clinical data that are relevant to the study. For more detail refer to the Investigator's Brochure. *(or, package insert).*

2 STUDY RATIONALE

Describe why it makes sense to study this product in this patient population or in the event of an observational study, why the information is needed.

2.1 Risk / Benefit Assessment

If applicable, describe how the specific risks of the product will be mitigated in the study and why the potential benefits outweigh the risks.

3 STUDY OBJECTIVES

3.1 Primary Objective

State the primary OBJECTIVE (do not put endpoints here). For example: "The primary objective is to assess the clinical efficacy as measured by the change in pulmonary function over the six month treatment period." Other examples of objectives are maximum tolerated dose, proof of dose selection, or to assess the safety and pharmacokinetics.

3.2 Secondary Objectives

State the secondary OBJECTIVE. The secondary is usually one of the other items listed above or may be research related, etc.

4 STUDY DESIGN

4.1 Study Overview

Insert a very short description of the study. For example:

This is a single center, double-blind, placebo-controlled, randomized, incomplete block, 3 period crossover trial. XX (number) of subjects are planned. Each subject will be administered a single dose of study drug three times, one week apart, consisting each time of various doses of active or placebo. Each subject will receive three of the four experimental treatments. Subjects will be assigned to the treatments in random order. Evaluations will be taken at baseline and 4 hours at each of the 3 study visits.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

- Experimental treatment XXX at the following doses 0.2%, 0.4% or 0.8%
- Placebo or Comparator – XXXX

Total duration of subject participation will be three weeks. Total duration of the study is expected to be 10 weeks.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Enter primary endpoint - generally whatever the study was powered on. (May also want to include a brief statement about why the endpoint is appropriate.). Include the time course for which the endpoint will be assessed (i.e. from baseline to end of treatment)

5.2 Secondary Efficacy Endpoints

- *Enter all secondary efficacy endpoints (ditto on why endpoints are appropriate)*

5.3 Safety Evaluations

- *Change in clinical laboratory findings (if there are specific labs, then why they are appropriate to measure, e.g., BUN or Creatinine for an aminoglycoside)*
- *Incidence of adverse events*

5.4 Other Evaluations (include only if applicable)

- *Research endpoints, PK analyses, etc.*

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of *XX* who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.
2. *Add others as appropriate.*

6.3 Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3. *Add others as appropriate.*

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for *XX* is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- TBD

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Describe the randomization scheme and any randomization procedures.

Example text: Up to 90 eligible patients will be randomly assigned to XXX or placebo treatment groups in a 1:1 ratio using a SAS-based computer-generated randomization scheme developed by the study data management provider. The investigator or designee will complete a randomization worksheet (at Visit 1), as detailed in the Study Manual, and fax it to XXXX or if IVRS describe.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments. *Describe as appropriate. The text below is example.*

- Access to the randomization code will be strictly controlled.
- A taste-matching agent.
- Packaging and labeling of test and control treatments will be identical to maintain the blind.

- If active drug concentrations are going to be measured describe how those results will be maintained in confidence to avoid breaking the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked. *Describe if and when investigators will be made aware of their subjects treatment assignments.*

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the *Medical Monitor* prior to unblinding. *Describe the procedures for unblinding.*

8.3 Formulation of Test and Control Products

Identify the study drug product (active and placebo or comparator), manufacturer, specify the formulation of the test article and placebo or comparator, etc. If drug must be reconstituted or otherwise prepared indicate in this section. See sample text below:

8.3.1 Formulation of Test Product

Identify the active study drug product, manufacturer; specify the formulation of the test article. If drug must be reconstituted or otherwise prepared indicate in this section. See sample text below:

XXX is a new formulation of ABC, developed by Manufacturer, for aerosol administration in the management of XX patients. XXX is a yellow-colored solution that requires no reconstitution. See Table X for the formulation of XXX.

8.3.2 Formulation of Control Product

Identify the placebo or comparator, manufacturer; specify the formulation of the placebo or comparator. If drug must be reconstituted or otherwise prepared indicate in this section. See sample text below:

A placebo solution (0.9% saline) will be provided by the Sponsor in an aluminum foil pouch containing four (4) clear single use ampules ready for administration.

8.3.3 Packaging and Labeling

This section should describe how the drug will be packaged and labeled and by whom. This section should also describe how labeling will maintain blinding for blinded studies. Can insert a label mock-up here.

Packaging example: Study drug is supplied in cartons containing 32 single use ampules. The ampules will be packaged in sets of 4 enclosed within a laminated foil pouch. Eight pouches will be contained in each carton (1 extra pouch containing 4 ampoules in the event of breakage).

Labeling example: Each carton (kit) of study drug will be labeled with the required FDA warning statement, the protocol number, a treatment number, the name of the

sponsors, and directions for patient use and storage. Each ampoule will be labeled with XXX and XXX:

8.4 Supply of Study Drug at the Site

Describe when and how medication will be supplied to the site, if the study drug supply should go to the site pharmacy at start-up or after subjects are randomized. Also if subjects are randomized but withdraw from the study prior to treatment will be replaced, describe how replacement kits will be provided. See example text below:

The Sponsor (or designee) will ship Study Drug to the investigational sites. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

8.4.1 Dosage/Dosage Regimen

This section should contain information of the doses to be tested, dosing schedule, the route of administration, optimal timing between doses, adjustments for weight, age, meals, and other pertinent information, and the treatment period(s).

8.4.2 Dispensing

This section should describe who has authority to dispense the drug (investigator, pharmacist, etc.) and any other significant dispensing requirements.

8.4.3 Administration Instructions

Include step-by-step instructions including order of other medications, chest physiotherapy, etc. Include how the subject should administer the study drug and/or how the study site should administer the study drug.

8.5 Supply of Study Drug at the Site

Describe when and how study drug will be supplied to the site. Also if subjects who are randomized but withdraw from the study prior to treatment will be replaced describe how replacement kits will be provided.

8.5.1 Storage

Describe study drug storage conditions: temperature, light, moisture, etc. Note that drug is to be stored in a secure location [such as the drug will be stored in the site pharmacy (or state other locations)]. See sample text below:

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Sponsor or designee and captured as a deviation. Subjects will be instructed to store the medication in original packaging (foil pouch and protected from light) at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Indicate how treatment compliance will be monitored. Example:

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject *or subject's legal representative*. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study Days or Visits 3, XX XXX, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Visit #. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam

findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes on Study Days XXX (or at Visits XX).

9.1.6 Other Clinical Procedures

A separate section should be created for each clinical assessment to be performed. A brief description of the method of the assessment and timing (similar to above) should be included.

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements (*include sections as appropriate*)

9.2.1 Hematology

Blood will be obtained and sent to each site's clinical hematology lab for (*list as applicable*) a complete blood count, *etc*.

9.2.2 Blood Chemistry Profile

Blood will be obtained and sent to each site's clinical chemistry lab for determination of (list as applicable) serum sodium, *etc.*

9.2.3 Pregnancy Test

A urine or serum pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

9.2.4 Urinalysis

Urine will be obtained and sent to each site's clinical laboratory for determination of (*list as applicable*) color, *etc*.

9.3 Pharmacokinetic Measurements

Example text: Blood for determination of serum concentrations of XXX will be collected pre-dose as well as at 30 minutes, 1, 2, 4, 8, and 12 hours after the start of dosing on Study Days XX and XX. XX concentrations will be determined at XX laboratory using XX method.

9.4 Research Laboratory Measurements (*include sections as appropriate*)

9.4.1 Cell Count and Differential

10 EVALUATIONS BY VISIT

(The text below is sample text. Select and add to list as appropriate. Order the procedures as appropriate and Review against schedule of events to confirm consistency.)

10.1 Visit 1 (Day/Week/Month #)

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, *if appropriate*.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including a history of *XX*, diagnosis date, and prior *XX* treatments.
5. Record concomitant medications.
6. Perform a complete physical examination.
7. Perform and record vital signs.
8. Collect blood for clinical laboratory tests (chemistry, hematology, prothrombin time, pregnancy test, methemoglobin, and serum nitrate).
9. Schedule subject for Visit 2 in *XX* days.
10. *List all additional procedures, such as Randomize subject, Dispense study drug, Initiate subject diary, etc*.

10.2 Visit 2 (Day/Week/Month # include visit window)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Concomitant medications review.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. *List all additional procedures*.

10.3 Visit 3 (Day/Week/Month # include visit window)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.

5. *List all additional procedures*.

10.4 Visit 4 (Day/Week/Month # include visit window)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. Collect blood sample for clinical laboratory tests: Chemistry*, etc*.
6. List all additional procedures, such as collect all unused study drug.

10.5 Visit 5 (Follow-up or Day/Week/Month # include visit window)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.
2. Record changes to concomitant medications.
3. Perform complete physical examination.
4. Perform and record vital signs.
5. Collect blood for clinical laboratory tests: Chemistry, *etc*.
6.

10.6 Early Withdrawal Visit

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.
2. Record changes to concomitant medications.
3. Perform complete physical examination.
4. Perform and record vital signs.
5. Collect blood for clinical laboratory tests: Chemistry, *etc*.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An AE is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known,

already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

AE Severity

List criteria for AEs (*such as the National Cancer Institute's Common Terminology Criteria for Adverse Events, if used*) and the version should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment

Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening experience defined as any adverse experience that places the subject, in the view of the treating physician, at immediate risk of death at the time of occurrence; ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Important medical events that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the protocol, must be reported as an SAE.

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

AE/SAE Reporting Procedures

To Mount Sinai PPHS (IRB)

AEs are reportable to the IRB within 5 business days (SAEs within 24 hours of knowledge of the event) *when they meet the following definition*:

> Any 'harm' experienced by a subject or other individual that in the opinion of the investigator is *unexpected* AND *at least probably related* to the research

All AE/SAEs with an onset date after the subject signs consent for study participation must be reported to the IRB *at the time of annual renewal*. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome.

All AE/SAEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected. AE/SAEs that completely resolve and then recur should be recorded as a new AE/SAE. AE/SAEs continuing at 30 days post-last dose should have a comment in the source documents by the PI that the event has stabilized or is not expected to improve.

To Pharmaceutical Company

[*Discuss with the pharmaceutical company what AE/SAEs should be reported to them and how*]

To FDA

A report on the MedWatch 3500A form must be sent to the FDA when

> the event is (1) serious, unexpected suspected reaction (the investigator judges there is evidence to suggest a causal relationship); (2) findings from other clinical, animal, or *in-vitro* studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction no later than 15 days after determining that the information qualifies for reporting.
>
> Unexpected fatal or life-threatening suspected SAEs should be reported no later than 7 calendar days after initial receipt of the information.

The subject should be identified using initials and the unique IND number issued for for this protocol.

Pregnancy

The subject must immediately inform her doctor if any of the following occur:

- She becomes pregnant while taking the study drug
- She misses her menstrual period, or experiences unusual menstrual bleeding
- She stops using birth control

- She thinks, FOR ANY REASON, that she may be pregnant

Pregnancies occurring while the subject is on treatment or within 30 days after the subject's last dose of study drug are considered expedited reportable events. [*Study drug]* is to be discontinued immediately and the subject instructed to return any drug to the Investigator. The pregnancy must be reported within 24 hours of the Investigator's knowledge of the pregnancy to the pharmaceutical company.

[*Describe additional steps as per the pharmaceutical company guidelines for pregnancies as appropriate*]

11.3 Protocol Defined Important Medical Findings Requiring Real Time Reporting

This is a special section that should be deleted if not needed. This section should define events that are to be reported in real time that may or may not meet the definition of serious. The SAE section should not be changed, because SAE is a regulatory term with regulatory implications. If events in addition to SAEs are being requested to be reported in real time, they should be described here.

11.4 Medical Monitoring

Insert Medical Monitor Name should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (XXX) XXX-XXXX
Pager: (XXX) XXX-XXXX

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation: *(The list should match the Study Completion/Discontinuation CRF page.)*

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to *cite section* for early termination procedures.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to *Visit X*) should have an early discontinuation visit. Refer to *cite section* for early termination procedures. Subjects who withdraw after *Visit X* but prior to *Visit X* should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment *will or will not* be replaced.

Subjects who withdraw from the study *will or will not* be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or *Sponsor* fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- *Include other specific examples as appropriate for the study (non-compliance with study drug regimen, etc.)*

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The *Sponsor* will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING (OPTIONAL SECTION – INCLUDE WHEN APPROPRIATE)

The [*Institute Name*] Data Safety Monitoring Board (DSMB) will establish a Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the [*Institute Name*] Data Safety Monitoring Board Operations Manual and a DMC Charter to be established for this protocol. There will be (number of reviews, if any) interim review(s) conducted by the DMC for the purpose of monitoring study conduct and assessing patient safety. Further details regarding the timing and content of the interim reviews is included in the statistical section below.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

Define which subjects will be included in each analysis (e.g., all randomized subjects, all dosed subjects, all eligible subjects).

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

Indicate which demographic and baseline characteristics will be summarized. For example:

The following demographic variables at screening will be summarized by dose level: race, gender, age, height and weight.

15.3 Analysis of Primary Endpoint

Describe the statistical methods to be employed for the primary endpoint.

15.4 Analysis of Secondary Endpoints

Describe the statistical methods to be employed for each secondary endpoint

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

15.5 Interim Analysis

Indicate the timing of any planned interim analysis(es).

15.6 Sample Size and Randomization

Specify the number of subjects planned to be enrolled and describe the reason for choice of sample size including reflections on (or calculations of) the power of the study and clinical justification. For example: The sample size for this protocol was determined by xxxx.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific *electronic Case Report Form (eCRF) OR paper CRF* when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a *site number, subject number and initials*.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. *For EDC studies:* Queries are entered, tracked, and resolved through the EDC system directly. *For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the *Sponsor* should be contacted prior to removing study records for any reason.

16.6 Monitoring (*if applicable*)

Monitoring visits will be conducted by representatives of the *Sponsor* according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (Health Insurance Portability and Accountability Act of 1996).

17.1 Protocol Amendments

Any amendment to the protocol will be written by *the Sponsor*. Protocol amendments can not be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB unconditional approval statement will be transmitted by the Investigator to *the Sponsor or designee* prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB -approved copy of the Informed Consent Form to *the Sponsor (or designee*) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and *subjects (or their legal representatives*) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the *subject or legal representative of the subjec*t and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. EXAMPLE OF SCHEDULE OF STUDY VISITS

	VISIT 1 (Day/Week/Month #)[a]	VISIT 2 (Day/Week/Month #)[a]	VISIT 3 (Day/Week/Month #)[a]	VISIT 4 (Day/Week/Month #)[a]	VISIT 5 (Day/Week/Month #)
Informed Consent	X				
Medical History	X				
Complete Physical Exam	X				X
Abbreviated Physical Exam		X	X	X	
Height	X	X	X	X	X
Weight	X	X	X	X	X
Vital Signs	X	X	X	X	X
Oximetry	X	X	X	X	X
Spirometry	X	X	X	X	X
Pharmacokinetics		X			
Chemistry	X			X	X
Pregnancy Test (Urine or Serum)	X			X	X
Hematology	X			X	X
ESR	X			X	X
C-Reactive Protein	X			X	X
Urinalysis	X			X	X
Randomization	X				
Dispensing or Administration of Study Drug	X	X	X	X	
Counting of Returned Study Drug		X	X	X	X
Initiate Subject Diary	X				
Subject Diary Review		X	X	X	X
Concomitant Medication Review	X	X	X	X	X
Adverse Experiences					

[a] ±2 days