

PREFACE

This document is the Division of Allergy, Immunology, and Transplantation (DAIT) protocol template, which is required for developing DAIT-sponsored interventional (clinical trials) protocols. 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.

This template attempts to provide a general format applicable to all clinical trials evaluating an investigational product. Where specific examples are provided, they are often from DAIT areas of investigation.

Throughout this protocol template, there may be subject headings that do not apply to your particular study. In such instances, please write “not applicable.”

In places where the information is duplicative, it is acceptable to reference another section rather than repeating the information.

Refer questions regarding use of this protocol template to the appropriate DAIT Program Officer or Medical Officer.

Version 1.0

April 2013

CONSORTIUM NAME

PROTOCOL NUMBER

LONG TITLE

SHORT TITLE (if applicable)

VERSION NUMBER / VERSION DATE

IND#

Study Sponsor(s): The National Institute of Allergy and Infectious Diseases (NIAID)
(Insert Institute, if co-funding)

NIAID Funding Mechanism: *(e.g., grant, cooperative agreement or contract #)*

IND Sponsor/Number *(when applicable)*

Study Drug Manufacturer/Provider: *(Insert If Applicable)*

PROTOCOL CHAIR- [NAME]	MEDICAL MONITOR-[NAME]	BIostatistician- [NAME]
[Title]	[Title]	[Title]
INSTITUTION	INSTITUTION	INSTITUTION
ADDRESS	ADDRESS	ADDRESS
CITY/STATE/ZIPCODE	CITY/STATE/ZIPCODE	CITY/STATE/ZIPCODE
Phone:	Phone:	Phone:
Fax:	Fax:	Fax:
E-mail:	E-mail:	E-mail:
	PROJECT MANAGER-[NAME]	REGULATORY OFFICER-[NAME]
	Division of Allergy, Immunology, and Transplantation	Office of Regulatory Affairs
	National Institute of Allergy and Infectious Diseases	Division of Allergy, Immunology, and Transplantation
	5601 Fishers Lane	National Institute of Allergy and Infectious Diseases
	Bethesda, MD 20892-9828, USA	5601 Fishers Lane
	Phone:	Bethesda, MD 20892-9828, USA
	Fax:	Phone:
	E-mail:	Fax:
		E-mail:

Confidentiality Statement

The information contained within this document is not to be disclosed in any way without the prior permission of the Protocol Chair, or the Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases of the National Institutes of Health.



INVESTIGATOR SIGNATURE PAGE	
Protocol:	Version/Date:
Site Principal Investigator: <i>[Insert name]</i>	
Title:	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
<p><i>INSTRUCTIONS:</i> <i>The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:</i></p> <p style="text-align: center; color: blue;"><i>[Insert Name/Title and Address]</i></p>	
<p>I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document <i>Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance</i> dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.</p> <p>As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.</p>	
<p>_____</p> <p>Site Principal Investigator (Print)</p>	
<p>_____</p> <p>Site Principal Investigator (Signature)</p>	<p>_____</p> <p>Date</p>

Protocol Synopsis

Title	
Short Title	
Clinical Phase	
Number of Sites	<i>[Specify the number of sites/centers and location (N="x" United States versus Rest of the World) where study participants will be enrolled/evaluated]</i>
IND Sponsor/Number	<i>[Specify the IND Sponsor and IND number when applicable]</i>
Study Objectives	
Study Design	<i>[Describe whether open-label, blinded/masked, randomized, controlled, single- or multiple-center, study arms, study phases, etc.]</i>
Primary Endpoint(s)	
Secondary Endpoint(s)	
Accrual Objective	<i>[Sample size]</i>
Study Duration	<i>[Specify total duration (accrual + follow-up period)]</i>
Treatment Description	
Inclusion Criteria	
Exclusion Criteria	
Study Stopping Rules	<i>[Specify the definition of proposed stopping guidelines for the study]</i>

Study Contacts: Participating Centers *[Options: Document
in the Study Protocol or Manual of Procedures (MOP)]*

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

SITE PRINCIPAL INVESTIGATOR

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

Study Contacts: Core Laboratories *[Options: Document in the Study Protocol or MOP]*

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[ROLE]

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

Table of Contents

- 1. Background and Rationale..... 13
 - 1.1. Background and Scientific Rationale 13
 - 1.2. Rationale for Selection of Investigational Product or Intervention 13
 - 1.3. Preclinical Experience 13
 - 1.4. Clinical Studies 13
- 2. Study Hypotheses/Objectives..... 13
 - 2.1. Hypotheses 13
 - 2.2. Primary Objective(s) 14
 - 2.3. Secondary Objective(s) 14
- 3. Study Design 14
 - 3.1. Description of Study Design..... 14
 - 3.2. Primary Endpoint(s)/Outcome(s) 15
 - 3.3. Secondary Endpoint(s)/Outcome(s) 15
 - 3.4. Exploratory Endpoint(s)/Outcome(s) 15
 - 3.5. Stratification, Randomization, and Blinding/Masking..... 16
 - 3.5.1. Procedure for Unblinding/Unmasking..... 16
- 4. Selection of Participants and Clinical Sites/Laboratories 16
 - 4.1. Rationale for Study Population..... 16
 - 4.2. Inclusion Criteria 16
 - 4.3. Exclusion Criteria 17
 - 4.4. Selection of Clinical Sites/Labs 17
- 5. Known and Potential Risks and Benefits to Participants..... 17
 - 5.1. Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert 17
 - 5.2. Risks of Investigational Product or Intervention cited in Medical Literature..... 18
 - 5.3. Risks of Other Protocol Specified Medications 18
 - 5.4. Risks of Study Procedures..... 18
 - 5.5. Potential Benefits 18
- 6. Investigational Agent /Device/Intervention 18
 - 6.1. Investigational Agents/Devices/Interventions 18
 - 6.1.1. Investigational Agent #1..... 18
 - 6.1.1.1. Formulation, Packaging, and Labeling..... 18

- 6.1.1.2. Dosage, Preparation, and Administration 18
- 6.1.2. Investigational Agent #2 18
 - 6.1.2.1. Formulation, Packaging, and Labeling..... 18
 - 6.1.2.2. Dosage, Preparation, and Administration 18
- 6.2. Drug Accountability 19
- 6.3. Assessment of Participant Compliance with Investigational Agent 19
- 6.4. Toxicity Prevention and Management 19
- 6.5. Premature Discontinuation of Investigational Agent..... 19
- 7. Other Medications..... 19
 - 7.1. Concomitant Medications 19
 - 7.2. Prophylactic Medications 20
 - 7.3. Prohibited Medications 20
 - 7.4. Rescue Medications..... 20
- 8. Study Procedures..... 20
 - 8.1. Enrollment 20
 - 8.2. Screening/Baseline Visit 20
 - 8.3. Study Visits or Study Assessments 21
 - 8.4. Unscheduled Visits 21
 - 8.5. Visit Windows 21
- 9. Mechanistic Assays..... 21
- 10. Biospecimen Storage..... 21
- 11. Criteria for Participant Completion and Premature Study Termination 21
 - 11.1. Participant Completion 21
 - 11.2. Participant Withdrawal Criteria 22
 - 11.3. Participant Replacement..... 22
 - 11.4. Follow-up after Early Study Withdrawal 22
- 12. Safety Monitoring and Reporting..... 22
 - 12.1 Overview 22
 - 12.2 Definitions..... 22
 - 12.2.1 Adverse Event (AE)..... 22
 - 12.2.2 Unexpected Adverse Event..... 23
 - 12.2.3 Serious Adverse Event (SAE) 23
 - 12.3 Grading and Attribution of Adverse Events 24

12.3.1 Grading Criteria..... 24

12.3.2 Attribution Definitions 24

12.4 Collection and Recording of Adverse Events 25

12.4.1 Collection Period..... 25

12.4.2 Collecting Adverse Events..... 25

12.4.3 Recording Adverse Events..... 25

12.5 Reporting of Serious Adverse Events and Adverse Events 26

12.5.1 Reporting of Serious Adverse Events to Sponsor..... 26

12.5.2 Reporting to Health Authority 26

12.5.3 Reporting of Adverse Events to IRBs/IECs 27

12.6 Pregnancy Reporting 27

12.7 Reporting of Other Safety Information..... 28

12.8 Review of Safety Information 28

12.8.1 Medical Monitor Review..... 28

12.8.2 DSMB Review 28

13. Statistical Considerations and Analytical Plan..... 29

13.1. Overview..... 29

13.2. Endpoints/Outcomes..... 30

13.3. Measures to Minimize Bias 30

13.4. Analysis Plan 30

13.4.1. Analysis Populations..... 30

13.4.2. Primary Analysis of Primary Endpoint(s)/Outcome(s) 30

13.4.3. Supportive Analyses of the Primary Endpoint(s)/Outcome(s) 30

13.4.4. Analyses of Secondary and Other Endpoint(s)/Outcome(s) 30

13.4.5. Analyses of Exploratory Endpoint(s)/Outcome(s)..... 30

13.4.6. Descriptive Analyses..... 30

13.5. Interim Analyses 30

13.5.1. Interim Analysis of Efficacy Data 31

13.5.2. Interim Analysis of Safety Data 31

13.5.3. Futility Analysis..... 31

13.6. Statistical Hypotheses 31

13.7. Sample Size Considerations..... 31

14. Identification and Access to Source Data..... 31

- 14.1. Source Data 31
- 14.2. Access to Source Data 31
- 15. Protocol Deviations 32
 - 15.1. Protocol Deviation Definitions 32
 - 15.2. Reporting and Managing Protocol Deviations 32
- 16. Ethical Considerations and Compliance with Good Clinical Practice 32
 - 16.1. Statement of Compliance..... 32
 - 16.2. Informed Consent Process 33
 - 16.3. Privacy and Confidentiality..... 33
- 17. Publication Policy 33
- 18. References 33

Glossary of Abbreviations

CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
PI	[Site] Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction

Study Definitions Page [Optional]

Lost to Follow-up	
Medical Monitor	
NIAID Project Manager	
Principal Investigator	
Program Officer	
Protocol Mandated Procedures	
Randomized	
Regulatory Affairs Officer	
Site Principal Investigator	
Site Study Coordinator	
Study Termination	
Study Therapy	
Withdrawal from Therapy	

1. Background and Rationale

1.1. Background and Scientific Rationale

[This section should not be longer than one page]

[A] {one short paragraph} What is the impact of the disease(s) this study focuses on (e.g., prevalence, morbidity/mortality, personal suffering, societal and economic impact)? B) What is the scientific basis leading to the proposed study (e.g., in vitro, ex vivo or animal mechanistic data)? C) What new does this study bring to the field? D) How will knowledge generated from this study help towards the alleviation of the problems described in (A)?]

1.2. Rationale for Selection of Investigational Product or Intervention

[This section should not be longer than two pages]

[A] What is the nature of the product(s) or intervention(s) to be tested in this study? B) What is the current development stage of this product(s) or intervention(s) (e.g., first in man stage, Phase II etc. – clinical experience will be described in section 1.4)? C) What is the mechanism of action of this product(s) or intervention(s) {if unknown, state}? D) Why is this product(s) or intervention(s) the most suitable to address the overall objective of this study described in section 2? E) How does this product(s) or intervention(s) compare to other products/interventions currently available {advantages should be listed}?

1.3. Preclinical Experience

[This section should not be longer than two pages]

[If the product(s) or intervention(s) is approved and already used in clinical practice, this section should describe preclinical experience only in the context of the disease/mechanism that it will be used for in this clinical study; in contrast, if this is a product(s) or intervention(s) under clinical development, preclinical studies (in vitro, in vivo) that have been part of the development should be summarized, with emphasis on A) those related to mechanisms of action and B) short-term and long-term toxicology.]

1.4. Clinical Studies

[This section should not be longer than two pages]

[If the product(s) or intervention(s) is approved and already used in clinical practice, this section should describe clinical experience only in the context of the disease/mechanism that it will be used for in this clinical study; in contrast, if this is a product(s) or intervention(s) under clinical development, all clinical studies should be summarized with emphasis on A) safety, B) pharmacokinetics and dose-ranging studies to justify proposed dosing in the current study and C) efficacy for any indication that the product(s) or intervention(s) is being developed.]

2. Study Hypotheses/Objectives

[This section should not be longer than one page]

2.1. Hypotheses

[The scientific hypotheses or research questions should be stated explicitly. A hypothesis is a statement to be supported or rejected; a research question should be stated as a question. Hypotheses or research questions should be included to justify both the clinical design and any proposed mechanistic studies.]

2.2. Primary Objective(s)

[Specify the primary objective(s); an objective is descriptive and should always address one or more of the above hypotheses or research questions. Objectives (either primary or secondary) should be included to support any proposed mechanistic studies and should contain a description how clinical and mechanistic studies are related.]

2.3. Secondary Objective(s)

[Specify the secondary objective(s), if any; these may or may not be hypothesis-driven, but should relate to secondary or exploratory outcomes; you may separate into efficacy, safety, mechanistic, or exploratory objectives.]

3. Study Design

3.1. Description of Study Design

[Describe the clinical trial phase as applicable, whether the study will be controlled or uncontrolled, type/design to be used (e.g., double-blind, placebo-controlled, single/multi-site, phase), the sample size, the study arms, the randomization process and allocation ratio, and the level of blinding/masking; briefly describe the study population(s); state the expected duration of subject participation and describe the sequence and duration of all study periods/phases, including follow-up, if any. Summarize the study agent(s)/interventions(s), changes in scheduling, such as dose escalations, and protocol-specified concurrent therapy. Specify any centralized evaluations (if applicable). Specify the approximate time to complete subject enrollment.]

[Insert a schematic diagram of the trial here (include study cohorts and sample size, treatment allocation, time points of study intervention and subject follow-ups)]

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:

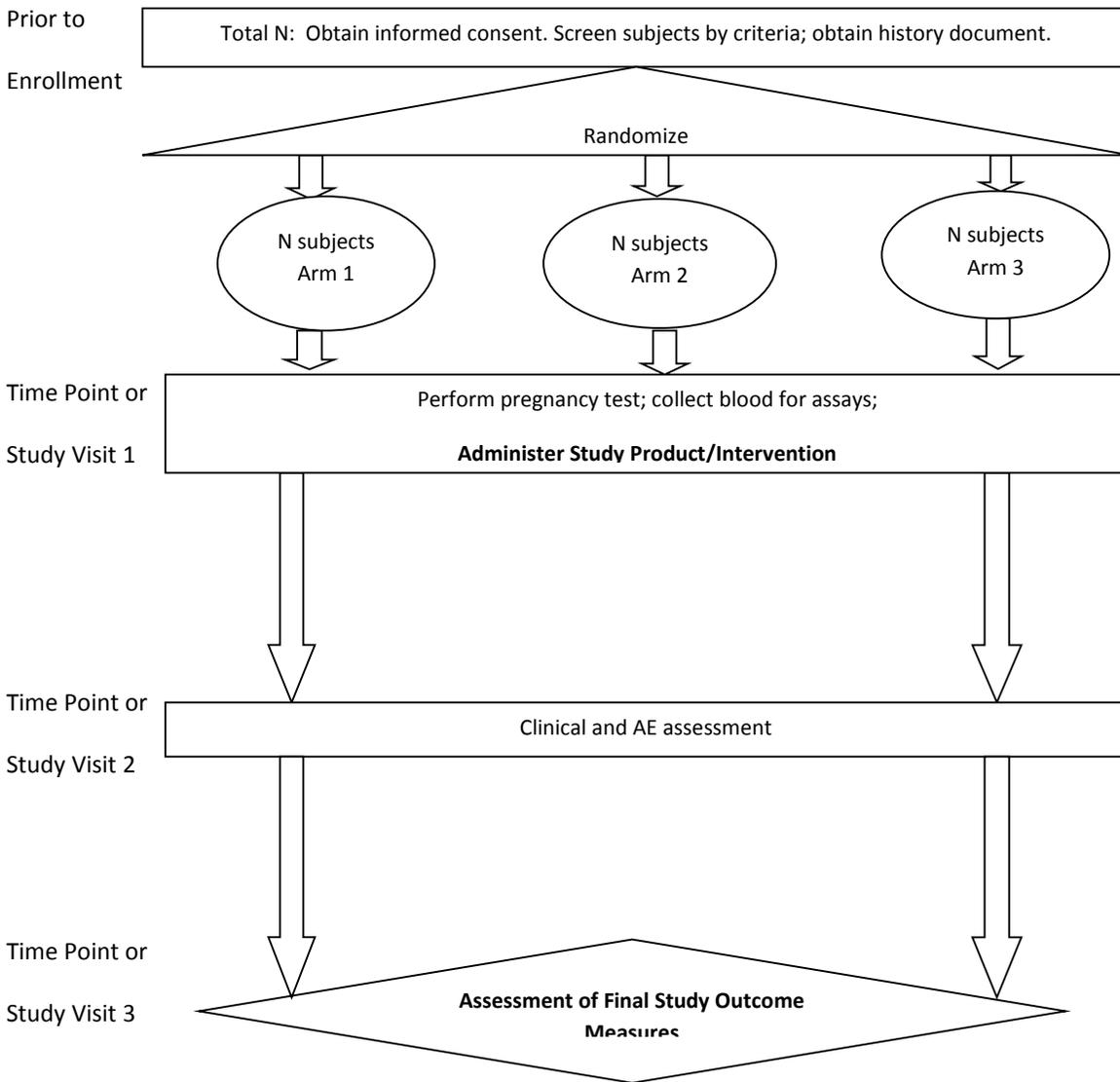


Figure X. (Caption for study design figure)

3.2. Primary Endpoint(s)/Outcome(s)

[Measurable outcome(s) of the study that will be used to test whether the primary objective(s) has(ve) been met; include the nature of the outcome, timing, as well as the method of assessment. The endpoint should contain a word that defines the measurement for example “incidence”, “rate”, “number”, “prevalence”, “time-to-event”, etc. Endpoints may be further broken down into safety, efficacy and/or mechanistic.]

3.3. Secondary Endpoint(s)/Outcome(s)

[Measurable outcome(s) of the study that will be used to test whether secondary objective(s) has(ve) been met; include the same information as in primary endpoints.]

3.4. Exploratory Endpoint(s)/Outcome(s)

[Measurable outcome(s) of the study that will be used to test whether tertiary/exploratory objective(s) has(ve) been met; include the same information as in primary endpoints]

3.5. Stratification, Randomization, and Blinding/Masking

[Describe essential components of the randomization and masking methodology. Include any stratification, blocking procedures, or other methods used to avoid or minimize bias. State the procedure for randomization and the entity maintaining the treatment assignments for the study.]

3.5.1. Procedure for Unblinding/Unmasking

Unblinding must be approved by the study Medical Monitor unless an immediate life threatening condition has developed and the Medical Monitor is not accessible. *[Include other individuals who should be contacted and any specific instructions for this particular study]* The site investigator will notify the protocol chair(s) and the study Statistical and Clinical Coordinating Center team *[delete if not applicable]* of the unblinding event on the next business day. The emergency unblinding will also be reported to the Data and Safety Monitoring Board (DSMB) *[replace with the name of other review bodies, (e.g. Safety Monitoring Committee) if applicable]*.

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the Medical Monitor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

Unblinding the study due to an approved interim analysis, final analysis, or study termination will require written approval from NIAID.

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

[A) Why is the population(s) proposed the most suitable for this study? B) If a different population is used as a "control", provide justification for its necessity. C) If specific age groups, sex or racial groups are not included, provide a rationale for their exclusion.]

4.2. Inclusion Criteria

[The same criterion should not be repeated in both the inclusion and exclusion sections]

Individuals who meet all of the following criteria are eligible for enrollment as study participants: *[Suggested line items are included in italics; modify, add or remove as needed; line item #1 should be included without modification]*

1. Subject and/or parent guardian must be able to understand and provide informed consent
2. *[Demographic characteristics]*
3. *[Specify the disease or disorder under study and how it is to be documented (i.e., diagnostic methods, criteria for classification)]*
4. *[Specify prior or current therapy requirements and allowable duration of prior therapy for each specific population to be studied]*
5. *[Female subjects of childbearing potential must have a negative pregnancy test upon study entry]*
6. *[Female (and male) subjects with reproductive potential, must agree to use FDA approved methods of birth control for the duration of the study-specific methods may be listed, if applicable]*
7. *[Prior vaccinations requirements, if any]*
8. *[Other]*

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants: *[Suggested line items are included in italics; modify, add or remove as needed; line items #1, 10 and 11 should be included without modification]*

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. *[List specific clinical contraindications. Specify disease severity, if applicable, or grades of signs/symptom]*
3. *[Outline specific contraindications to any study drugs and/or regimens included in the protocol]*
4. *[Clinic or laboratory indicators of current status, obtained within X number of days before study entry; list the specific tests to be performed and the narrowest acceptable range of laboratory values for exclusion]*
5. *[Specify any exclusion related to pregnancy, breast-feeding, or plans to become pregnant]*
6. *[Use of excluded drugs, devices, etc. within x number of days before study entry]*
7. *[Specify any clinical, e.g., life expectancy, coexisting disease; demographic; or other characteristic that precludes appropriate diagnosis, treatment, or follow-up in the trial]*
8. *[Current, diagnosed, mental illness or current, diagnosed or self-reported drug or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements]*
9. *[Recent recipient of any licensed or investigational live attenuated vaccine(s) within x (time period) of (specify enrollment or randomization)].*
10. *Use of investigational drugs within X weeks of participation*
11. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

4.4. Selection of Clinical Sites/Labs

[optional section]

[Brief description of centers and/or laboratories being selected in order to meet recruitment goals i.e. previously qualified centers for specific consortia or new sites being selected due to the study population. Include information regarding whether or not the centers are domestic US or international.]

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

[Using the Investigator Brochure or package insert, briefly describe the most commonly reported side effects and their frequency, as well as other risks and contraindications associated with the investigational product /intervention being used in this trial]

5.2. Risks of Investigational Product or Intervention cited in Medical Literature

[List any additional, significant risks or side effects that may have been reported in peer-reviewed literature and are not part of the Investigator Brochure or the package insert; in case the study involves a product for which no Investigator Brochure or package insert is available, this section should list all the known risks of the investigational product or intervention; cite references]

5.3. Risks of Other Protocol Specified Medications

[List the risks of any other concurrent therapy such as concomitant medications, prophylactic medications and/or rescue medications that are specified in the protocol]

5.4. Risks of Study Procedures

[List the risks of all the procedures that will be performed in this trial]

5.5. Potential Benefits

[List the potential benefits that the investigational product/intervention, may offer to the individual study participant and/or to society. Describe the benefits in terms of acquired knowledge that may facilitate clinical testing, treatment or future mechanistic studies. This section could include any benefits that would be associated with the study procedures]

6. Investigational Agent /Device/Intervention**6.1. Investigational Agents/Devices/Interventions**

[The term “Investigational Agent” refers to any drug that is being tested in this trial – this can be an unapproved drug or an approved drug that is used within or outside its current approval indications; same for “Investigational Device”; the term “Investigational Intervention” refers to procedure (e.g. lung reduction surgery, islet cell transplantation) that is being tested in this trial. In the case of Investigational Devices or Interventions, sections 6.1.1.1 and 6.1.1.2 will need to be modified, replaced or expanded]

6.1.1. Investigational Agent #1

[List name of Investigational agent as well as manufacturer – replace with “Device” or “Intervention” as applicable]

6.1.1.1. Formulation, Packaging, and Labeling

[Provide the following information, or summarize from the package insert or investigator’s brochure if it is available: Dosage form, components, and packaging method e.g., multiple-dose vial, single-use ampoule. Identify distributor and provide business location (city/state).]

6.1.1.2. Dosage, Preparation, and Administration

[Describe dosage and preparation procedure for investigational agent e.g., reconstituting, filtering, or diluting. Describe frequency, duration, and route of administration. Specify storage conditions. For licensed products use information from package inserts.]

6.1.2. Investigational Agent #2

[If applicable- may also add more; follow same instructions as above]

6.1.2.1. Formulation, Packaging, and Labeling**6.1.2.2. Dosage, Preparation, and Administration**

6.2. Drug Accountability

[In addition to the existing text, which should be modified in case the trial takes place outside the US where additional regulations may apply, indicate any specific steps or procedures that will be used to implement the requirements below]

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

[Indicate the disposition of unused product(s): where and to whom product(s) will be sent and whether it will be destroyed or retained and for what duration]

6.3. Assessment of Participant Compliance with Investigational Agent

[List methods of assessment e.g., pill count, vial weight, etc.]

6.4. Toxicity Prevention and Management

[List the situations in which the investigational product or intervention may be modified based on specific toxicities and provide a description of permitted modifications, if applicable. This should include the procedure for evaluating the signs and symptoms that indicate a need for dose modification, interruption or institution of additional therapies.]

6.5. Premature Discontinuation of Investigational Agent

[The intent of this section is to outline the situation(s) where a subject will discontinue the investigational agent but will remain in the study for follow-up. Please also describe the plan for follow-up e.g., remainder of scheduled study visits and/or abbreviated schedule. It is recommended that study participants who discontinue investigational agent remain in the study and undergo evaluation per protocol]

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

[List all reasons]

Study therapy may also be prematurely discontinued for any participant if the investigator believes that the study treatment is no longer in the best interest of the participant.

7. Other Medications

7.1. Concomitant Medications

7.1.1. Protocol-mandated

[If applicable, list and describe the protocol-mandated concomitant medication(s) to be administered, including the name(s) of all product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period for subjects for each investigational agent treatment/trial]

treatment group/arm of the trial. Note that this section should be consistent with the study's inclusion/exclusion criteria.]

7.1.2. Other permitted concomitant medications

[If applicable, list and describe other permitted concomitant medication(s); if needed, including the name(s) of all product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s). Note that this section should be consistent with the study's inclusion/exclusion criteria.]

7.2. Prophylactic Medications

[If applicable, list and describe the protocol-mandated prophylactic medication(s) to be administered, including the name(s) of all product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period for subjects for each investigational agent treatment/trial treatment group/arm of the trial.]

7.3. Prohibited Medications

[If applicable, list and describe any drug(s) or other treatments that are NOT permitted during the study; include drug(s) or other treatments from the exclusion criteria if they are prohibited while the participant is on study.]

7.4. Rescue Medications

[If applicable, list and describe the protocol-mandated rescue medication(s) to be administered, including the name(s) of all product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s). Note that this section should be consistent with the study's inclusion/exclusion criteria.]

8. Study Procedures

[Describe each procedure conducted throughout the study by study visit (e.g., skin testing, biopsies, questionnaires, physical examination, laboratory blood draws, etc.). It is preferable to avoid details for each procedure in the protocol and to instead incorporate those details in the standard operation procedures, which will become part of the study's manual of operations.]

8.1. Enrollment

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. *[Define enrollment and when a participant will be assigned a unique number. e.g., "once the informed consent has been signed, the participant is considered enrolled in the study and will be assigned a unique participant number".]*

8.2. Screening/Baseline Visit

The purpose of the screening period is to confirm eligibility to continue in the study. *[The screen and baseline may be separate visits and should be described in separate subsections if this is the case. Also, clarify if screen and/or baseline are divided over several visits.]*

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility (bullet or number format):

- 1.
- 2.

[For screening, if applicable, indicate under what conditions re-screening may occur and the time period within which re-screening can occur.]

If laboratory data are required for study participation, specify the timeframe from blood draw to study entry for eligible subjects.

If randomization is applicable, insert the timeframe in which the participant should be randomized.]

8.3. Study Visits or Study Assessments

[select applicable header]

[Describe time points for study assessments by visit (bullet or number format) or type of assessment; if by visit, list assessments or other events to occur at each visit preferably in the order they should take place]

8.4. Unscheduled Visits

[if applicable]

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an “unscheduled” visit.

[Specify, as applicable, any required procedures/assessments and under what circumstance (i.e. disease flare, drug toxicity). Address those instances in which a “for cause/unscheduled” procedure replaces a study directed procedure. If an early withdrawal visit is applicable, please include under this section.]

8.5. Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows (i.e. +/- n days) for each scheduled visit are also indicated on the Table of Events.

[Specify in table format: include time between screening and baseline/randomization and time between randomization and first study intervention if applicable as well as windows for all other study visits.]

9. Mechanistic Assays

[Briefly summarize in vitro assays that will be used to evaluate biological responses. Describe the rationale for each assay and the tissue source to be used; list, preferably under categories, the specific outcomes that will be obtained (example categories of mechanistic assays: cellular assays, antibody assays, serum or other biologic fluid biomarker/mediator analyses, gene expression, histology/immunohistology). Detailed methodology may be provided in a separate manual and is not recommended in the protocol.]

10. Biospecimen Storage

[List any biospecimens that will either be obtained with the intention to be included in an approved long-term biorepository or that will be stored for specified time periods after having been used in the context of this protocol]

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

[Define subject completion by specifying the number of required visits or a required study milestone. Alternative or additional criteria for completion may be based on the amount of study drug administered, if applicable.]

11.2. Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed). *[use specific criteria to define “lost to follow-up”]*
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. Individual safety stopping rules *[list safety criteria on the basis of which a participant would be discontinued from further participation in the study]*

11.3. Participant Replacement

Participants who withdraw or are withdrawn *[will, will not]* be replaced *[specify any conditionalities, e.g. “will not be replaced if they have received at least one dose of the investigational agent”.]*

11.4. Follow-up after Early Study Withdrawal

[If a participant is withdrawn from the study for any reason, the participant may be asked to complete a final visit and/or final assessments. This should be outlined in this section.]

11.5. Study Stopping Rules

The study may be prematurely terminated for the following reasons:

[Define the basis by which the study would be prematurely terminated]

12. Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the sponsor *[select: **DAIT/NIAID or other Sponsor, if applicable**]*. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), *[replace with “Institutional Ethics Committees (IECs)”, if applicable]* and health authorities.

Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, *ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version *[enter 4.0 or correct version applicable to trial]* : <http://ctep.cancer.gov/reporting/ctc.html>.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" <http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2>)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen:** *[Insert applicable therapy (e.g. investigational drug(s), immunosuppression withdrawal, specific immunosuppression regimen used along with investigational drug, etc.). Describe time frames for collection of AEs occurring after study, if applicable. For example: "Immunosuppression withdrawal: Any AE occurring after randomization", "Thymoglobulin: An AE occurring within 6 months after the last study-mandated dose".]*
- **Study mandated procedures:** *[Insert applicable procedures (e.g. blood draw, intravascular ultrasound, allergen provocation etc.). Describe time frames for collection of AEs occurring after a study procedure, if applicable. For example: "Plasmapheresis: Any AE occurring within 24 hours after study- mandated plasmapheresis or intra-operative plasma exchange", "Renal Transplant Biopsy: Any AE occurring within 24 hours after study-mandated biopsy."]*

12.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the *[Investigator Brochure or package insert]* or is not listed at the specificity, severity or rate of occurrence that has been observed; or, *[if an Investigator Brochure is not required or available]*, is not consistent with the risk information described in the general investigational plan or elsewhere in the IND. *[revise language as necessary if under a different health authority than FDA]*

[include if applicable: "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a))]

[insert, if applicable, study mandated procedures (e.g. bronchoscopy, allergy skin testing) that may be relevant to this section and the reference standard(s) by which "unexpected" will be assessed.]

12.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor [add DAIT/NIAID or other Sponsor, *if applicable*], it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor [add DAIT/NIAID or other Sponsor, *if applicable*], its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) *[insert version: most recent version is 4.0 – can use another version if needed for this protocol. Also, for studies where the study team chooses not to use the NCI-CTCAE, they should select the most appropriate AE grading scale for a given clinical trial that is appropriate to the target-population and disease]* This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the *[specify: Protocol Chair(s), Principal Investigator, etc.]* and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild adverse event.
- Grade 2 = moderate adverse event.
- Grade 3 = severe and undesirable adverse event.
- Grade 4 = life-threatening or disabling adverse event.
- Grade 5 = death.

Events grade *[specify Grade]* or higher will be recorded on the appropriate AE case report form *[select: eCRF or paper CRF]* for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

[It is acceptable for a protocol to use additional and/or alternative grading scale(s) for all adverse events or only for drug or procedure-specific adverse events; such scales need to be clearly described herein]

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE *[select: electronic or paper*

case report form (AE/SAE eCRF or AE/SAE paper CRF)]. Final determination of attribution for safety reporting will be determined by DAIT/NIAID, [add “Sponsor”, if applicable]. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: <http://ctep.cancer.gov/reporting/ctc.html>.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a <u>reasonable possibility</u> to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

[Alternatively, the older five category code may be used here if considered beneficial in mapping adverse event attribution to earlier or ongoing studies (Scale for Attribution of Adverse Event Table, page 3, NCI-CTCAE manual, Version 2.0, August 18, 1999, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm); however, “Related Categories” remain those characterized as “Possible” and above]

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Adverse events will be collected from the time of [select a “first” study event (enrollment, blood draw, the administration of the first dose of study drug, etc.)], until a subject completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events*.

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions*) on the appropriate [*select: electronic or paper case report form (AE/SAE eCRF or AE/SAE paper CRF)*] regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to Sponsor (*[DAIT/NIAID or other Sponsor, if applicable]*)

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via [*select: the SACCC eCRF, facsimile, phone hotline, safety system, etc.*] Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 12.2.3, *Serious Adverse Event*), regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE [*select: eCRF or paper CRF*] will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE [*select: eCRF or paper CRF*] will be updated and submitted.

12.5.2 Reporting to Health Authority

[This Section may be extensively modified if the study is not regulated by a Health Authority. A non-Health Authority regulated study may still require the equivalent of IND Safety Reports to IRBs/IECs for some events and the following description of reporting may be guidance for that requirement.]

After an adverse event requiring 24 hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by [*select: DAIT/NIAID or other Sponsor*], there are two options for [*select: DAIT/NIAID or other Sponsor*] to report the adverse event to the appropriate health authorities:

12.5.2.1 Annual Reporting

[*select: DAIT/NIAID or other Sponsor*] will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.1.1, *Suspected Adverse Reaction*, and Section 12.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 12.2.2, *Suspected Adverse Reaction*).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual <IND> Report <*Please insert appropriate language if under a different health authority than FDA*>.

12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: Serious and unexpected suspected adverse reaction [SUSAR] (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected.

The sponsor shall report an adverse event as a suspected adverse reaction only if there is

evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

[include if appropriate] Certain SAEs occur commonly in this study population and will not be considered as a SUSAR unless there is evidence to suggest a causal relationship to the *[study intervention]*. These events will be captured in the study database but will not be reported as expedited Safety Reports:

- *[list disease or population specific SAEs, e.g. hospitalization for myocardial infarction or stroke in an elderly population.]*

Category 2: Any findings from studies that suggests a significant human risk

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

[select: DAIT/NIAID or other Sponsor] shall notify the appropriate health authorities *[for IND studies replace with "FDA"]* and all participating investigators of *[expedited Safety Reports – replace with "safety reporting" if no IND is involved]* within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days. *[describe here any additional special reporting requirements specific to the study/IND]*

12.5.3 Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All *[Safety Reports to the FDA – replace with appropriate health authorities if no IND is involved]* shall be distributed by *[select: DAIT/NIAID or other Sponsor]* or designee to all participating institutions for site IRB/IEC submission.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject or a partner of a study subject. *[Describe pregnancies that should be reported (e.g. in a participant receiving investigational drug, in all participants in study arm, etc.)]* A pregnant subject shall be instructed to stop taking study medication. *[Describe other procedures needed once pregnancy is identified]* The investigator shall counsel the subject and discuss the

risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

The investigator shall report to the *[select: Statistical and Clinical Coordinating Center (SACCC), DAIT/NIAID]* all pregnancies within 1 business day of becoming aware of the event using the Pregnancy *[select: eCRF or paper CRF]*. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy *[select: eCRF or paper CRF]* shall be updated and submitted to the *[select: Statistical and Clinical Coordinating Center (SACCC), DAIT/NIAID]* when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study subject.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the *[select: Statistical and Clinical Coordinating Center (SACCC), DAIT/NIAID or other Sponsor, as applicable]* using the SAE reporting procedures described above. *[if applicable include additional information regarding requirements to report to health authorities]*

12.7 Reporting of Other Safety Information

An investigator shall promptly notify the site *[select: IRB, IEC]* as well as the *[select: SACCC – provide instruction here how to do that - DAIT/NIAID, other Sponsor]* when an “unanticipated problem involving risks to subjects or others” is identified, which is not otherwise reportable as an adverse event.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The *[select: DAIT/NIAID, other Sponsor]* Medical Monitor shall receive monthly reports *[amend periodicity as specified by DAIT/NIAID]* from the *[select: SACCC, protocol investigator]* compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate *[select: eCRFs, paper CRFs]*.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the *[select: SACCC, protocol investigator]* (See Sections 12.5.1, *Reporting of Serious Adverse Events to Sponsor*, and 12.6, *Pregnancy Reporting*).

12.8.2 DSMB Review *[if the study is monitored by a different body –e.g. Safety Monitoring Committee (SMC), or Independent Safety Monitor (ISM)-, provide applicable language to modify the text below]*

12.8.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner *[preferable to specify time line here]*. *[Insert criteria/rationale for DSMB review of expedited safety reports; e.g., study-specific requirements of the health authority or special risks related to this study]*

12.8.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID *[add other Sponsor if applicable]*. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

[the following are examples of suggested events that could trigger a review]

- Any death that occurs in the study, which is possibly or definitely related to study treatment regimen.
- The occurrence of a Grade 3 or higher related and unexpected SAE in *[specify number]* or more of the study participants who have received a study treatment.
- The occurrence of *[specify AE or score]* in *[specify number, greater than or equal to, of study participants]* who have received a study treatment.
- The occurrence of Grade 2 or higher *[specify condition]* in *[specify number, greater than or equal to]* of the study participants who have received study therapy.
- The occurrence of Grade 2 or higher *[specify condition]* in *[specify number, greater than or equal to]* of the study participants who have received a study treatment.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1 Temporary Suspension of <enrollment/drug dosing or both> for ad hoc DSMB Safety Review

[See Section 11.2 for Participant Stopping Rules and Withdrawal Criteria]

[Describe here the criteria for stopping enrollment/drug dosing or both for an ad hoc DSMB safety review if applicable. The bullets described in the section above may be referenced or additional language provided. The language below is suggested].

A temporary halt in *[enrollment/drug dosing or both]* will be implemented if an *ad hoc* DSMB safety review is required.

[Describe here what procedures will be implemented in the event that the study temporarily halts enrollment/drug dosing or both. For example, will new participants be consented? Will subjects already on investigational product continue on therapy? Will subjects in the screening phase of the study continue to undergo minimal risk procedures?]

13. Statistical Considerations and Analytical Plan

13.1 Overview

[Succinctly restate the scientific objective, the eligibility criteria (i.e., the study population), and the study design.]

13.2 Endpoints/Outcomes *[either term is fine, but ensure consistency with rest of protocol]*

[Give succinct but precise definition of outcome measures used to measure the primary and key secondary outcomes, including the study visits at which the sample will be obtained and specific laboratory tests to be used. Make sure that the outcomes listed in this section are identical to those presented in sections 3.2, 3.3, and 3.4. The plan should, when at all possible, include provision for collecting these outcomes even when a participant is no longer receiving treatment whether due to voluntary or involuntary treatment or study withdrawal.]

13.3 Measures to Minimize Bias

[Describe any randomization or blinding/masking procedures; however no details that might compromise these strategies, such as size of randomized blocks should be included. Other strategies to avoid bias such as use of centralized laboratories or masking of laboratory staff should be noted. Make sure that this section is consistent with section 3.5.]

13.4 Analysis Plan

[This section should describe the statistical tests and analysis plans for the protocol.]

13.4.1 Analysis Populations.

[Describe the samples to be analyzed (e.g., intent-to-treat sample)]

13.4.2 Primary Analysis of Primary Endpoint(s)/Outcome(s)

[Provide a detailed description; this includes precise specification of:

- *the statistical method*
- *the analysis sample*
- *the plan to account for various types of missing data in the primary analysis*
- *any adjustment for interim analyses or multiple comparisons*
- *any planned transformations of the data.]*

13.4.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

[Describe alternate and sensitivity analyses. These might include covariate adjustment or examination of subgroups.]

13.4.4 Analyses of Secondary and Other Endpoint(s)/Outcome(s)**13.4.5 Analyses of Exploratory Endpoint(s)/Outcome(s)****13.4.6 Descriptive Analyses**

[Provide a plan for describing other key participant variables, including:

- *baseline and demographic characteristics*
- *use of medications*
- *study completion status]*

13.5 Interim Analyses

[This section should describe the nature of these reviews. Provide relevant details below, if applicable. Whenever interim data are viewed by study arm, statistical implications should be considered. Provide

information as to who will review interim analyses (DSMB or other committees) and what is expected from such a review (e.g. recommendation for trial continuation or termination).]

13.5.1 Interim Analysis of Efficacy Data

13.5.2 Interim Analysis of Safety Data

13.5.3 Futility Analysis

13.6 Statistical Hypotheses

[State the formal, testable, null and alternate hypotheses for primary and key secondary endpoints, specifying the type of comparisons (e.g., superiority, non-inferiority, etc.). Make sure that this section is consistent with section 2.1.]

13.7 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 participants. In particular, specify all of the following as applicable:

- *Endpoint/outcome measure used for calculations (almost always the primary endpoint/outcome)*
- *Test statistic*
- *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 rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc. also justified*
- *Primary approach for handling missing data*
- *Approach to handling withdrawals and protocol violations, i.e., whether “intent to treat”*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized, and any practical limitations*
- *Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size*

Where applicable: note method for adjusting for planned interim analyses, multiple comparisons, unequal allocation to treatment groups, and randomization method. Discuss whether the sample size also provides sufficient power for addressing secondary objectives, or for secondary analyses in key subgroup populations.]

14. Identification and Access to Source Data

14.1. Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial. *[If any unique source documents will be used for this study (e.g. clinic records, surgical records, print-outs from a spirometer), identify here.]*

14.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, *[add other Sponsor and their representatives, if applicable]* as well as to relevant health authorities *[add industry partners that are not sponsors, if applicable]*. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. Protocol Deviations

15.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures. *[It is recommended that the Manual of Operations include examples of Major Protocol Deviations to facilitate their identification by staff and study monitors]*

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

15.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

[Add a detailed section describing the process of Protocol Deviation recording and reporting. For example, "Upon determination that a protocol deviation has occurred, the study staff will a) notify the site Principal Investigator, b) notify the [choose based on study organization: NIAID Project Manager, the SACC] and c) will complete a Protocol Deviation form." Specify who will make the decision as to whether the Deviation is major or not (e.g. the DAIT/NIAID Medical Monitor) and what the impact of the Deviation on the study participant or the entire study may be. Describe who will submit the Protocol Deviation reports to the appropriate review bodies (IRB, DSMB, FDA etc.) and who will review and approve the action plan that will be implemented as a result of the Protocol Deviation.]

16. Ethical Considerations and Compliance with Good Clinical Practice

16.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the *[select: IRB, Ethics*

Committee]. Any amendments to the protocol or to the consent materials will also be approved by the *[select: IRB, Ethics Committee]* before they are implemented.

16.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the *[select: Investigator of Record form, FDA 1572]* will review the consent and answer questions. *[If consent designees are to be used, list the qualifications they must have.]* The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing *[preferably identify time-points when the trial will be re-reviewed with a study participant to ensure ongoing consent and whether this will be documented in source documents]*. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

16.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

17. Publication Policy

The *[Insert Consortium Name]* policy on the publication of study results will apply to this trial.

18. References

List of Tables

List of Figures

List of Appendices