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### **DAIDS Guidance for Protocol Documents**

At this time, DAIDS does not require the use of a standard protocol format, but does require the inclusion of specific, detailed information in a written protocol for a DAIDS funded and/or sponsored clinical trial. This document identifies required content areas and provides guidance as to the level of detail required. Though not a protocol template, this document uses topic headings and presents this information in an order that is similar to many DAIDS-sponsored protocols and acceptable to DAIDS. Sections and subsections also reference regulations, guidance documents, and DAIDS policies and standard procedures that should be consulted during the development of the protocol. All DAIDS policies, standard procedures, guidance documents, and manuals referenced in this document can be accessed at the NIAID website *DAIDS Clinical Research Policies and Standard Procedures Documents*.

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## TITLE PAGE

The title page of a protocol submitted to the DAIDS for review should contain, at a minimum, the following:

- 1. The full title of the protocol**
- 2. Local Protocol Number:** This is the protocol number the applicant (i.e., applicant institution) has given the protocol. (Note: Protocols approved for DAIDS also receive a protocol number assigned at DAIDS).
- 3. NIAID Funding Mechanism:** (e.g., grant number)
- 4. Pharmaceutical Support Provided by:** List the names of any company(ies) providing Pharmaceutical Support. Pharmaceutical contact person(s) should be indicated in the study roster.
- 5. IND Sponsor (if applicable):** The entity responsible for filing the Investigational New Drug Application (IND) with the FDA. More specifically, the individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial as indicated in Box #1 of the Form FDA 1571 to be submitted to the FDA.
- 6. Principal Investigator:** Protocol Chair or other individual who is responsible for conducting the trial if different than the Principal Investigator for the grant application.
- 7. Draft or Version Number: include “DRAFT Version 0.X” or “FINAL Version 1.0” on the first page and in the header or footer of the rest of the document.**
- 8. Day Month Year:** use a date format that utilizes alphabet characters for the month and numeric characters for the date and year. (e.g. 12 February 2006 or 12 FEB 06).

## SIGNATURE PAGE (Optional)

See: ICH E6 8.2  
DAIDS Policy for Protocol Registration  
DAIDS Protocol Registration Policy and Procedures Manual

DAIDS does not require the use of Signature Pages, but does require a signed statement from the Principal Investigator or Investigator of Record for all protocols and amendments at the time of protocol registration. A signature page, such as the example listed below, may be included with the Essential Documents at the performance site.

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

Principal Investigator: \_\_\_\_\_

Print/Type

Signed: \_\_\_\_\_ Date: \_\_\_\_\_  
Name/Title

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## TABLE OF CONTENTS

A detailed table of contents, clearly identifying the location of major sections and subsections is required in every protocol. The Table of Contents of this document is an example that generally follows the format of this guidance document.

## LIST OF ACRONYMS

Provide a glossary of acronyms and protocol-specific terms or spell out the acronym/term the first time mentioned in the protocol (with the acronym immediately following in parentheses).

## PROTOCOL SUMMARY

A Protocol Summary should be included that is limited to 1-2 pages and briefly includes the following information. Schematic representations of study design can be extremely useful and should also be considered.

<b>Full Title</b>	Include type of trial (e.g., dose-ranging, safety, efficacy, pharmacokinetic)
<b>Short Title</b>	An abbreviated title (either a few descriptive words or an acronym of the full title)
<b>Clinical Phase</b>	I, II, III, IV, IIB, I/II, etc.
<b>IND Sponsor (if applicable)</b>	Name of IND Sponsor. (if applicable)
<b>Principal Investigator</b>	Name of Principal Investigator (Protocol Chair)
<b>Sample Size</b>	Include the total number of participants as well as the number to be enrolled per arm.
<b>Study Population</b>	Include a brief description such as health status (healthy volunteers or HIV-positive), antiretroviral-naïve or treatment-experienced, adults or children, etc.
<b>Participating Sites</b>	If there are a large number of sites, list them on a separate page at the end of the protocol summary.
<b>Study Design</b>	Provide an overview of the study design, including description of type (e.g., double-blinded, placebo-controlled, open label, dose-finding, parallel or crossover design, randomized), study arms, stratification, sample size, and intervention. A schematic in table or diagram format may be provided at the end of the protocol summary to further illustrate the study design.
<b>Study Duration</b>	State duration per participant and total planned study duration. Provide the total length of time participants will be on study (intervention + follow-up)
<b>Study Regimen/Intervention</b>	Provide a brief description of treatment regimen (study product names and dosages), including treatment duration. Difference in treatment by arms, steps, or group should be delineated.
<b>Primary Objective</b>	
<b>Primary Endpoint</b>	

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## 1. KEY ROLES

See ICH E6 GCP, Section 6.1.

## 2. INTRODUCTION

### Background Information

See ICH E6 GCP, Section 6.2.

Include:

- The name and description of the study product/intervention(s)
- A summary of findings from non-clinical studies that have potential clinical significance
- A summary from relevant clinical trials, if available
- Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations are listed in Section 14)
- Applicable clinical, epidemiological, or public health background or context of the study

### Study Hypothesis and Rationale

Include a statement of the hypothesis. Describe the importance of the study and any relevant treatment issues or controversies. The rationale should justify the study and its design and support the primary objective. Justify any aspects of the study that are investigational or not approved by the FDA or regional health authorities (e.g., different dosing schedule, new combination of study agents, new study agent formulation, new study agent, new study population).

### Potential Risks and Benefits

Include a discussion of known and potential risks and benefits to participants, if any. This section should be based on the risk profile of the study product/intervention(s) or the trial strategy. Include a review of relevant literature, which should be referenced. Add relevant websites, etc. from which the information could be drawn.

If a package insert or Investigator's Brochure (IB) is available, it should be used as the primary source of risk information. If a package insert or IB isn't available, the risk information discussion will result from the literature search.

Describe other intervention options, including both clinical and economic advantages and disadvantages of each.

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### 3. OBJECTIVES

See ICH E6 GCP, Section 6.3.

Study objectives are specific, succinctly worded statements that identify each of the major and minor scientific questions addressed in the study. There should be endpoints and analyses in the statistical section to support each objective.

Each objective should include:

- Statement of purpose: e.g., to assess, to determine, to compare, to evaluate
- General purpose, e.g., efficacy, safety, immunogenicity, pharmacokinetics
- Specific purpose, e.g., dose-response, superiority to placebo, non-inferiority of intervention
- Name(s) of intervention (e.g., vaccine, drug, biologic) being evaluated, name of comparator if applicable, and specification of doses or dose ranges to be studied, or dose regimens
- Outcome measure or specified effect: i.e., the specific clinical, microbiologic, virologic immunologic, etc. markers or tests that provide quantitative information or results
- Specific study population

#### Primary Objectives

There should be only one primary objective. It should be directly related to the primary endpoint of the study, sample size, and analytic plan.

#### Secondary Objectives

There may be several secondary objectives.

### 4. STUDY DESIGN

See ICH E6 GCP, Section 6.4.

A description should include:

- Identification of major design elements (e.g., phase of trial, randomized, placebo-controlled, open-label, double-blind, parallel design, dose escalation, dose-ranging)
- Name of study product/intervention(s)
- A statement of the major endpoints to be measured (must be consistent with Study Objectives, as stated in Section 3, and Study Endpoints in Section 10)
- Description of study population, including major inclusion and exclusion criteria
- Approximate time to complete study enrollment
- Description and number of study groups or arms, including elements such as dose escalations or stratifications
- Size of each study group or arm and overall study sample size

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- A description of the sequence and duration of all trial periods, including follow-up (specify individual participants vs. entire trial)
- The expected duration of participant participation
- Single-, few-, or multi-center

## 5. STUDY POPULATION

See ICH E6 GCP, Section 6.5.1 and 6.5.2

See Applicable section of 45 CFR 46 if the study intends to enroll children, pregnant women, prisoners, or other vulnerable populations:

- Subpart B – Additional DHHS Protections Pertaining to Research, Development and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization (45 CFR 46.201-46.211);
- Subpart C – Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (45 CFR 46.301-46.306);
- Subpart D – Additional DHHS Protections in Children Involved as Subjects in Research (45 CFR 46.401-409).

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

### Selection of the Study Population

Describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such participants. The study population should reflect the community and be appropriate for the intended use of the study intervention and to meet the scientific objectives of the study. If women, minorities and children will not be recruited, explain why not. Refer to: [http://grants2.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants2.nih.gov/grants/funding/women_min/women_min.htm)

Describe the process for participant recruitment and retention, including a description of the community from which the study population will be drawn as well as the recruitment locations (e.g., in-patient hospital setting, out-patient clinics, student health service). Where appropriate (e.g., limited or single-site studies), include names of hospitals, clinics, etc.

### Co-enrollment Criteria

If pertinent to the study, describe co-enrollment criteria including studies or the types of studies for which participants might also be enrolled as well as those for which participants may not be enrolled.

### Inclusion/Exclusion Criteria

Define participant characteristics required for study entry in the inclusion criteria and exclusion criteria sections. The risks of the study product/intervention(s) or strategy should structure the development of the inclusion/exclusion criteria.



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The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >32 years old as an inclusion criterion and also age ≤32 years old as an exclusion criterion).

Select screening laboratory tests appropriately and judiciously (laboratory parameters selected should be related to evaluation of safety, with ranges based on toxicity criteria).

#### Participant Inclusion Criteria

Provide a statement that participant must meet all of the inclusion criteria to participate in this study and then list each criterion. Provide timeframes where applicable (e.g., within 14 days prior to study entry).

Examples include the following: informed consent obtained and signed, age, presence or absence of a medical condition/disease, required laboratory result, required concomitant medication(s), understanding of study procedures, ability to comply with study procedures for the entire length of the study, requirements for agreement to avoid conception, etc. If men and women of reproductive potential will be enrolled, include details of allowable or required contraception methods for trial participants (e.g., use of both a barrier method and licensed hormonal methods).

#### Participant Exclusion Criteria

Provide a statement that all participants meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. Provide timeframes where applicable (e.g., within 14 days prior to study entry).

Examples of reasons to exclude participants include the following: recent (with time frame) acute illness that precludes or delays participation, pregnancy or breastfeeding, characteristics of household or close contacts (e.g., household contacts who are immunocompromised), known allergic reactions to components of the study product(s), use of [excluded drugs, biologics, or vaccines] within [a specific time frame] prior to study entry [e.g., systemic cancer chemotherapy, systemic investigational agents]; laboratory finding that precludes participation, history of drug/alcohol abuse, which in the opinion of the investigator, would interfere with adherence to study requirements, receipt of prohibited concomitant medications, etc.

## **6. STUDY PRODUCT/INTERVENTION(S)**

See ICH E6 GCP, Sections 6.4.4 and 6.6.

For studies utilizing Recombinant DNA molecules, see NIH Guidelines For Research Involving Recombinant DNA Molecules (NIH Guidelines) [http://www4.od.nih.gov/oba/rac/guidelines\\_02/NIH\\_Guidelines\\_Apr\\_02.htm](http://www4.od.nih.gov/oba/rac/guidelines_02/NIH_Guidelines_Apr_02.htm) and DAIDS Protocol Registration Policy and Procedure Manual (<http://rcc.tech-res.com/forms.htm>)

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### **Regimen (dose, schedule, route)**

See ICH E6 GCP, Section 6.6.1.

Use the generic names for study product(s), and the convention *Placebo for Generic Name* for naming placebos.

### **Study Product Formulation and Preparation**

See ICH E6 GCP, Section 6.4.4.

Also include the formulation, manufacturer, strength, and/or concentration. Include excipient information if not in the Investigator's Brochure or the Product Package Insert. Exclude information about study formulation that could inadvertently unblind the study.

Include appropriate preparation information such as thawing, diluting, mixing, reconstitution, and preparation procedures, equipment and supplies needed for preparation. Include requirements for aseptic technique, or biosafety level containment requirements. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted. Include acceptable storage temperatures, storage conditions [humidity, protection from light, protection from carbon dioxide], security, storage times, for all study products and study supplies and storage temperature/conditions during transport to the clinic or in the participants' home if different from in the pharmacy.

### **Study Product Supply and Accountability**

See ICH E6 GCP, Section 6.4.7.

Provide plans for how the study products/interventions will be distributed including information about the company or entity providing or supplying the study products, participation of a clinical research product distribution center, and details about how the pharmacist is to acquire the study products.

Include instructions for the receipt, handling, storage, dispensing, accountability, retrieval of unused study products from subjects, and provide directions regarding participant returns and the return or destruction of unused study products both during and after the study is completed.

### **Assessment of Participant Adherence with Study Product/Intervention(s)**

See ICH E6 GCP, Section 6.6.3.

Determine if and how adherence with study product/intervention of participants enrolled in the protocol will be assessed (e.g., pill counts, electronic monitoring devices, adherence questionnaires, direct observation). If so, provide details on procedures for monitoring participant adherence. In the Analysis Plan in section 10 describe how this information will be incorporated into the analysis of the study results. If no such assessment is planned, state why it is not needed or cannot be incorporated into this protocol.

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## Concomitant Medications and Procedures

See ICH E6 GCP, Section 6.6.2.

Consider providing specific directions regarding the use of concomitant medications or procedures. For example,

- *“Medications/procedures not listed under precautionary and prohibited medications and procedures are permitted.*
- *“Below is a list/are lists of selected concomitant medications. This (These) list(s) is/are only current as of the date of this protocol. Therefore, whenever a concomitant medication or study agent is initiated or the dose changed, investigators must review the concomitant medications’ and study agents’ most recent package inserts, investigator’s brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.”*

## Permitted Medications and Procedures

List types of medications procedures (e.g. specific or classes of investigational agents, immunomodulators, prophylaxis or treatment for concurrent morbidities) that are permitted on study.

## Prohibited Medications and Procedures

List all medications/procedures that are NOT permitted while receiving study product or while on study. Include drugs from the exclusion criteria if they are also prohibited while the participant is on study.

## Precautionary Medications and Procedures

List all medications/procedures for which there are precautions for concomitant use with the study products/interventions. Include instructions for dose modification, if appropriate.

## Required Medications and Procedures

List all medications and/or procedures that will be required on study. This may include prophylaxis. Indicate whether or not the medications and/or procedures will be provided through the study.

## Rescue Medications and Procedures

If applicable, list all medications and/or procedures that may be provided or required on study for “rescue therapy.”

## 7. STUDY PROCEDURES/EVALUATIONS

Use of a Schedule of Procedures/Evaluations is strongly recommended. See Appendix A for an example. Information outlined in the Procedures/Evaluations/Timing sections should refer to and

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be consistent with the information in the Schedule of Procedures/Evaluations in Appendix A. The description of the procedures/evaluations and the sequence of procedures/evaluations can either be written as separate sections or combined into one section, as appropriate or as preferred. Investigators must decide on the best presentation of study evaluations. Either way, all information that is required to be within the protocol is described in Section 7 and should be included under appropriate title headings.

## Clinical Evaluations and Procedures

List all clinical evaluations and procedures to be conducted during the protocol, and provide details/timelines related to each action (and special instructions, if any) at each study visit.

### *Examples:*

- *Medical History (describe what is included for history, e.g., timeframe considerations, whether history will be obtained by interview or from medical records).*
- *Medications History (e.g., describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter). Assessment of eligibility should include a review of permitted and prohibited medications.*
- *Physical Exam (list the vital signs and organ systems to be assessed); if appropriate, discuss what constitutes a targeted physical exam and at what visits it may occur.*
- *Reactogenicity assessments (e.g., pain, tenderness; describe rating scale).*
- *Review of diary cards (e.g., food diary, adherence assessment for taking medications, signs/symptoms diary).*
- *Counseling procedures.*
- *Radiologic procedures (e.g., chest x-rays, dual-energy x-ray absorptiometry (DEXA) scans, computed tomography (CT) scans).*
- *Questionnaires (e.g., adherence, quality of life, behavior).*

## Laboratory Evaluations

- List all laboratory evaluations to be conducted during the study, and provide details/timelines at each visit of what is included and special instructions, if any.
- Include specific test components (see table below) and specify laboratory methods (e.g., plasma HIV-1 viral load by RNA PCR); use consistent laboratory method throughout the study to provide for appropriate longitudinal and cross-comparison.
- If evaluations are used for diagnosis of infection (e.g., HIV, hepatitis B or C virus, tuberculosis), provide the diagnostic algorithm in the entry criteria, endpoints, or clinical management section of the protocol, as appropriate.
- Relevant information on the assays' validation, sensitivity, and specificity should be included in the Manual of Operational Procedures (MOP) or accompanying documents. Refer to *Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials*.

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## Laboratory Evaluations and Specimen Collection

The protocol must specify all laboratory tests/assays to be used. The choice of assays pertains to:

- The purpose of the study and the associated outcomes being assessed;
- The study product(s) being evaluated and the expected safety and pharmacologic/immunogenicity profile;
- The clinical and epidemiologic attributes of the population from which the participants are selected and for which they are considered representative.

### *Examples:*

- *Clinical hematology: hemoglobin, hematocrit, WBC with differential, platelet count, white cell subsets*
- *Clinical chemistry: creatinine, total bilirubin, ALT, AST, glucose (fasting/ non-fasting), lipid profile*
- *Urinalysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic is required.*
- *Pregnancy test usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.*
- *Biopsy (tissue) or other specimens (swabs, lavages, sputum, cerebrospinal fluid, blood) for microbiology culture, viral load determination, or other testing (resistance mutations).*
- *Immunology: CD4+ / CD8+ cell counts, lymphoproliferative assays, intracellular cytokine assays, immunohistochemistry assays, advanced flow cytometry.*
- *Pharmacokinetic studies.*

## Specimen Preparation, Handling and Shipping

Details on specimen preparation, handling, and shipping should not be included in the protocol document and must be included in a Manual of Operational Procedures, an Appendix to the protocol, or other accompanying documents. Refer to *Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials* and *Requirements for Manual of Operational Procedures*.

## Biohazard Containment

Describe the procedures for biohazard containment that will be used in the study. The Principal Investigator is responsible for ensuring that procedures for biohazard containment are in accordance with local, national, and international regulations, as applicable.

An example of protocol language for U.S. sites is as follows: “*As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.*”

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Any protocol requiring the transfer of specimens or infectious substances must include the following language: “*All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.*” This applies to both U.S. and international sites.

### Sequence of Procedures/Evaluations: Timing and Definitions

A table can be used to define the Schedule of Procedures/Evaluations at each study visit and should include all study procedures/evaluations. Define the procedures/evaluations in this section.

Throughout the protocol, refer to the Schedule of Procedures/Evaluations (e.g., as protocol Appendix A).

The schedule must include not only clinic visits but all contacts with the participants, e.g., telephone contacts.

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

Examples of typical visits that are required in protocols are included in the table that follows. A protocol might not require the use of each visit example.

Sample Visit Name	Guidance
Screening	Include only those evaluations necessary to assess whether a participant meets enrollment criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the timeframe prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment).
Enrollment/Baseline	Discuss evaluations/procedures necessary to assess or confirm whether a participant still meets the eligibility criteria and may be enrolled, and those assessments that are required at baseline for later outcome measure comparison after study intervention (e.g., baseline signs and symptoms prior to vaccination). Discuss the sequence of events that should occur during enrollment and/or initial administration of study product. List any special conditions that must be met (e.g., results of the pregnancy test must be negative and available prior to administration of study product). List the procedures for administering the study product or intervention, and follow-up procedures after administration (e.g., assessment of vital signs, reactogenicity).

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Sample Visit Name	Guidance
Follow-Up	Include discussion of evaluations/procedures required to assess or confirm study outcome measures and study evaluations. Discuss the sequence of events that should occur during the visit, if applicable. Include, as applicable, counseling, review of reactogenicity, medications, assessment of adverse events, etc.
Early Termination Visit	Specify which evaluations should be done at an early termination visit (treatment discontinuation and/or study discontinuation) if early termination occurs and if the participant is willing. Participants may withdraw voluntarily from participation in the study at any time. Participants may also withdraw voluntarily from receiving the study intervention for any reason but may be willing to remain in study follow-up. Clearly differentiate between what evaluations are to be done in each of these circumstances, if necessary.  In some circumstances, it may be reasonable to ask the participant to continue scheduled evaluations, complete an end-of-study evaluation, or be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.
Pregnancy Visit	The protocol should address the procedures to be followed if a participant becomes pregnant while on study. Indicate whether the participant will be allowed to continue to receive the study product/intervention(s). Provide any other guidance relevant to the study product/intervention and pregnancy and/or breastfeeding. (For example, the participant may be allowed to continue to receive study product during pregnancy but will not be allowed to have biopsies or certain radiologic procedures.)  See also Section 9, Pregnancy.
Other Visit	Additional visits might be needed to specify evaluations to be performed at treatment failure, at premature discontinuation of study products, or for other special circumstances or events. For example, there might be alterations in the evaluations performed or schedule of evaluations for participants after permanent discontinuation of study intervention. In complicated studies with multiple registration/randomization points, the investigator may wish to include the time of registration/randomization/product dispensed.
Final Study Visit	Define when the final study visit should occur and any special procedures/evaluations or instructions to the participant. Describe provisions for follow-up of ongoing adverse events/serious adverse events.

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## 8. ASSESSMENT OF SAFETY

- See NIAID Adverse Events Reporting Requirements SOP located on the NIAID website at <http://www.niaid.nih.gov/ncn/sop/adverseevents.htm>
- See DAIDS Expedited Adverse Event Reporting Policy
- All protocols requiring expedited reporting of adverse events to DAIDS must include the current version of the “Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-Sponsored Protocols.”

The template language for the EAE Reporting Section specifies the use of the current version of the following documents (available at the Regulatory Compliance Center website <http://rcc.tech-res.com/eae.htm>):

- Manual for Expedited Reporting of Adverse Events to DAIDS
- Division of AIDS Safety Office Expedited Adverse Event (EAE) Form
- The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

A section detailing the assessment of safety should include a precise definition of an adverse event as well as procedures for collecting, recording, evaluating severity, determining expectedness, and assessing the relationship to study product/intervention(s). It should also include specific criteria and procedures for determining the reporting of adverse events and procedures for those adverse events that require expedited reporting.

### Definition of an Adverse Event (AE)

See ICH E6 GCP, Section 1.2.

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

### Adverse Event Procedures and Reporting Requirements

**Note:** All clinical trials must have an AE reporting system in place.

#### Adverse Events

Describe the AEs that will be collected and how. Define the time period for AE collection. Describe which AEs will be collected as solicited events and the format used to capture the solicited event (e.g., in a diary card or as structured questions). Describe how unsolicited events will be captured.

Complete description of all AEs must be available in the source documents. The event description should include: time of onset, investigator assessment of severity, relationship to study product/intervention(s), and time of resolution/stabilization of the event.



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The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004, will define the severity/intensity of the abnormality. A protocol-defined grading system may be provided for parameters not specified in this table.

Define the circumstances (for instance, severity grades >2) in which clinical findings and abnormal laboratory values will be recorded as AEs on the case report forms (CRFs) and included in periodic safety reports. Define a timeframe for CRF completion and entry of the AE information into the study database.

Any medical condition that is present before administration of study product should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study it should be recorded as an AE.

### **Expedited Adverse Events**

U.S. federal regulations (21 CFR 312) require DAIDS, as a study sponsor, to submit serious adverse events to the FDA. Similar reporting to collect information on serious adverse events criteria is also described in ICH E2A. Investigators are also required by U.S. federal regulations (45 CFR 46.103) to inform DAIDS of unanticipated problems involving risks to subjects. DAIDS uses an expedited adverse event reporting system to fulfill the reporting requirements for clinical trials.

All protocols requiring expedited reporting of adverse events to DAIDS must include the “Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-Sponsored Protocols” in this section.

In the event that DAIDS is not the primary recipient for expedited adverse event reports (for example, if another entity serves as the study sponsor), this template language can be used as a guide to fully describe the components of the alternative adverse event reporting system.

### **Local Regulatory Requirements**

In addition to submitting EAE information to the DAIDS Safety Office through the Regulatory Compliance Center (RCC), DAIDS requires the site investigator to submit AE information in accordance with local regulatory agencies’ or other local authorities’ requirements. Reporting procedures per local regulatory agencies or other local authorities should be specified in this section.

## **9. CLINICAL MANAGEMENT**

### **Toxicity Management**

Toxicity management is usually described by adverse event, or clinical or laboratory finding, not by study product/intervention.

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Include:

- Criteria for participant management and dose or schedule modification.
- If the study uses multiple study products/interventions, clearly indicate management for each product/intervention. Specify how to manage the study product(s) for various anticipated clinical or laboratory AEs. Consider providing a standardized toxicity management scheme according to commonly occurring, serious or important events associated with the use of the study product/intervention or that may occur to the participants during the course of the study due to the underlying disease process.
- Clearly explain instructions for dose modifications and changes in evaluations (e.g., additional laboratory evaluations needed, change in dose or need for additional follow up visits.) Consider the use of dose modification tables or flow charts to describe various toxicity management scenarios. This information should be described as comprehensively as necessary on the basis of the study product/intervention or population.

### Other Disease Events

Describe management of other relevant infections or clinical events and other treatment complications in this section.

Define particular events. The investigator or team may wish to standardize the definition of some clinical events, to standardize a definition between sites or for the entire duration of the study. For example, define the criteria for confirmed and probable diagnoses of a clinical event such as cryptococcal meningitis.

### Pregnancy

The protocol should describe the procedures to be followed in the event a woman becomes pregnant. Provide appropriate modifications to study procedures (e.g., discontinuation of study product/intervention(s) while continuing safety follow-up, alterations in study evaluations such as limiting radiation exposure, or following pregnant women to pregnancy outcome). If the woman remains on study, the protocol should describe what pregnancy-related information will be collected (e.g., medical complications, obstetrical complications, pregnancy outcome including births and fetal loss/abnormalities, and infant follow-up). Include appropriate mechanisms for reporting to sponsor, study leadership (as appropriate), Institutional Review Board/Ethics Committee, and regulatory agencies.

If the participant is receiving antiretrovirals, consider inclusion of a statement about the antiretroviral pregnancy registry:

*"In addition, if the subject continues her pregnancy, the site or patient are encouraged to prospectively register her pregnancy in the "Antiretroviral Pregnancy Registry" (<http://www.apregistry.com/reg.htm>) (In US, Canada: 1-800-258-4263, international: 910-256-0238))."*

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If a woman becomes pregnant while on study and is able to continue receiving the study product/intervention, indicate whether there are any modifications necessary to the study regimen/intervention during the pregnancy or after the pregnancy.

### **Breastfeeding (if applicable)**

Consider how to manage HIV-positive study participants who may want to or need to breastfeed their infants. See the joint UNICEF-WHO statement on HIV and infant feeding at:

[http://www.who.int/child-adolescent-health/publications/NUTRITION/HIV\\_IF\\_WHO\\_UNICEF.htm](http://www.who.int/child-adolescent-health/publications/NUTRITION/HIV_IF_WHO_UNICEF.htm)

The UNICEF-WHO statement is briefly quoted: “Given the need to reduce the risk of HIV transmission to infants while minimizing the risk of other causes of morbidity and mortality, UNICEF and WHO also reiterate that ‘when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life’ and should then be discontinued as soon as it is feasible.”

### **Criteria for Discontinuation**

See ICH E6, Section 6.4.6 and 6.5.3.

The reasons for permanently discontinuing study treatment for a participant and reasons for prematurely discontinuing the study for a participant may differ and will require separate clearly defined criteria.

See Section 10 for criteria for stopping rules for participant subgroups or the entire study.

### **Criteria for Permanent Treatment Discontinuation for an Individual Participant**

The protocol must provide:

- Explicit criteria for permanent discontinuation of continued administration of study product/intervention to an individual; and
- Plans for continued follow-up of the participant and, as applicable, resulting modifications to the schedule and duration of follow-up

#### *Sample language:*

*The criteria for permanent discontinuation of further study product/intervention(s) for an individual participant are:*

- \* Treatment-related toxicity (see section 9)*
- \* Requirement for prohibited concomitant medications*
- \* Pregnancy or breastfeeding (if applicable)*
- \* Reaching a defined clinical endpoint (if applicable)*
- \* Completion of treatment as defined in the protocol*
- \* Request by participant to terminate treatment*

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*\* Clinical reasons believed life-threatening by the physician, even if not addressed in the toxicity section of the protocol*

*The participant will continue to be followed with participant's permission if study product/intervention(s) is discontinued. No subsequent modifications to the visit schedule and duration of continued follow-up will be made, except no study product will be administered.*

## Criteria for Premature Study Discontinuation for an Individual Participant

Safety or other considerations may make it appropriate to have a participant prematurely discontinue the study. The reasons for premature study discontinuation are likely to vary based on the purpose or phase of the study. The protocol must provide explicit criteria for premature study discontinuation for an individual participant.

*Sample language:*

*The criteria for premature discontinuation from the study for an individual participant are:*

- \* Lost to follow up as evidenced by failure by the participant to attend [XX] consecutive clinic visits*
- \* Participant repeatedly non-compliant [define] with study treatment as prescribed*
- \* Pregnancy or breastfeeding (if applicable)*
- \* Request by participant to withdraw*
- \* Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant*
- \* Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of study results*
- \* A defined study endpoint is reached (if applicable)*
- \* At the discretion of the IRB/Ethics Committee, Food and Drug Administration, NIAID, investigator, or pharmaceutical supporter. (If a non-IND study, remove "Food and Drug Administration"; if no pharmaceutical support, remove "pharmaceutical supporter.")*

## 10. STATISTICAL CONSIDERATIONS

See ICH E9 Statistical Principles for Clinical Trials

See ICH E6 Section 6.9

See CONSORT statement (<http://www.consort-statement.org>)

NIH Policy on Data and Safety Monitoring

NIH Policy on Data Sharing

See Requirements for Data Management and Statistics for DAIDS Funded and/or Sponsored Clinical Trials

See DAIDS Study Progress and Safety Monitoring Policy

This section should show how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH

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guidance document E9 (Statistical Principles for Clinical Trials) and the CONSORT statement (<http://www.consort-statement.org>), which describes standards for improving the quality of reporting randomized controlled trials.

## Overview and General Design Issues

Succinctly restate the scientific rationale for the study and the primary and most important secondary objectives from Section 3 that motivate choice of study population, endpoints, hypotheses and design. Give a very concise restatement of the eligibility criteria, e.g., vaccinia-naïve healthy volunteers between the ages of 18 and 65. Describe any control groups (i.e., active or placebo control groups, concurrent or historical controls, etc.) and a synopsis of the rationale for choosing them (i.e., including risk/benefit or other ethical factors). State the proposed formal design (e.g., two-period crossover, two-by-three factorial parallel group, or case-control). If the design or interventions are complex, a schema may be helpful.

## Study Endpoints

### Primary Endpoint

List the primary endpoint and include its definition.

### Secondary Endpoint(s)

List the secondary endpoints and include their definitions.

## Study Hypothesis

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

## Sample Size Considerations

Provide all information needed to validate the calculations and to judge the feasibility of enrolling and following the necessary numbers of participants.

In particular, specify all of the following:

- Outcome measure used for calculations (almost always the primary variable)
- Test statistic
- Null and alternate hypotheses
- Type I error rate
- Type II error rate
- Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible
- Assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc. also justified

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- 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
- Method for adjusting calculations for planned interim analyses, if any

Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

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

### **Enrollment/Stratification/Randomization/Blinding Procedures**

Describe enrollment procedures, stratification procedures, and randomization (if applicable to the study design), including a description or a table that describes how study participants will be assigned to study groups. Do not be so specific that masking or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not). A discussion of replacement of participants who discontinue early, if allowed, should also be included.

Include any additional strategies to avoid bias or to decrease variability, such as centralized laboratory assessments or blinding of laboratory staff.

### **Maintenance of Trial Treatment Randomization Codes (if applicable)**

Plans for the maintenance of trial randomization codes and maintaining appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind.

### **Participant Enrollment Follow-Up**

Summarize the total number of enrollees and the total duration of accrual and of final follow-up, being specific about the number of clinical research sites and their enrollment and retention capabilities. Also be explicit about distinct stages in enrollment, if applicable.

### **Data and Safety Monitoring**

NIH policy on data and safety monitoring requires Institute oversight and monitoring of all intervention studies to ensure the safety of participants and the validity and integrity of the data. The policy further elaborates that monitoring should be commensurate with risks and with the size and complexity of the trials.

Refer to the DAIDS *Study Progress and Safety Monitoring* policy for a description of the type of monitoring required (e.g., Data and Safety Monitoring Board, Study Monitoring Committee, Study

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Team and Independent Safety Monitor), approval of reviewers by DAIDS, study progress and safety monitoring plan specifications, and types of study monitoring reports.

While the detailed study progress and safety monitoring plan must be provided as a separate document and approved in writing by DAIDS before study initiation, the protocol must include in the sections below a basic study monitoring plan that describes the key parameters for assessment of study progress, feasibility, safety, and efficacy, and pause rules as appropriate.

### **Planned Interim Analyses and Stopping Guidelines (if applicable)**

Describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing. The criteria used to determine decisions for a safety review and for efficacy (or immunogenicity) should be pre-specified to the extent possible.

### **Safety Review**

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

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

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

### **Efficacy (or Immunogenicity) Review**

Provide the information for efficacy or immunogenicity outcome measures. Discuss the impact of the interim monitoring plan on final efficacy analyses, particularly on Type I error.

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

### **Analysis Plan**

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

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

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## 11. DATA HANDLING AND RECORDKEEPING

See Requirements for Data Management and Statistics for DAIDS Funded and/or Sponsored Clinical Trials

See ICH E6, Section 4.9

### Data Management Responsibilities

Data collection is the responsibility of the clinical research site staff under the supervision of the site Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

If data are to be generated in one location and transferred to another group, describe the responsibilities of each party. Indicate the roles of each party with regard to interpretation of data, plans for analysis, review of tables and listings, and plans for reporting.

Briefly describe steps to be taken to ensure that the data collected are accurate, complete, reliable, legible, timely and in accordance with ICH E6 GCP, Section 4.9 guidelines. Details must be provided in a Manual of Operational Procedures (MOP) or other separate documents. Refer to Requirements for Data Management and Statistics for DAIDS Funded and/or Sponsored Clinical Trials.

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

Each participating clinical research site must maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Describe who will have access to records. The protocol must specify that as part of participating in a NIAID-sponsored, NIAID-affiliated or manufacturer-sponsored study, each clinical research site will permit authorized representatives of the sponsor(s), NIAID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Identify any of the data from the procedures/evaluations in Section 7 to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data.



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## Quality Control and Quality Assurance

See Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites

Each clinical research site must have standard operating procedures (SOPs) for quality management. These SOPs may be provided in a Manual of Operational Procedures (MOP) or as accompanying documents.

## 12. CLINICAL SITE MONITORING

See Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials

If DAIDS is responsible for the clinical site monitoring, include the following paragraph in the protocol:

*“Site monitors under contract to the National Institute of Allergy and Infectious Diseases (NIAID) will visit participating clinical research sites to review the individual subject records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians’ progress notes, nurses’ notes, individuals’ hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites’ regulatory files to ensure that regulatory requirements are being followed and sites’ pharmacies to review product storage and management.”*

If an entity other than DAIDS is responsible for clinical site monitoring (e.g., pharmaceutical company, other NIH institute) give a general description of how site monitoring will be conducted and specify who is responsible for this.

A separate monitoring plan document should be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and at what level of detail monitoring will be conducted.

## 13. HUMAN SUBJECTS PROTECTIONS

### Institutional Review Board/Ethics Committee

In both the United States and in other countries, only institutions holding a current U.S. Federal-Wide Assurance issued by the Office for Human Research Protections (OHRP) may participate in human subjects research funded and/or sponsored by DAIDS. Refer to:  
<http://ohrp.cit.nih.gov/efile/>.

Each participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) prior to implementation of the protocol. Any amendments to the protocol, informed consent(s), or other study-related documents must be approved by the IRB/EC and DAIDS prior to implementation.

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## Protocol Registration

See DAIDS Policy for Protocol Registration

See DAIDS Protocol Registration Policy and Procedures Manual

It is DAIDS policy that each participating institution must complete protocol registration with the DAIDS Protocol Registration Office through the RCC. Protocol registration must occur before the clinical research site can enroll any participants into the study. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>.

## Informed Consent Process

See 45 CFR 46

See 21 CFR 50

See ICH E6

See Requirements for Informed Consent Development

Informed consent is required for all participants participating in DAIDS funded and/or sponsored human subjects research. In obtaining and documenting informed consent, the investigator should comply with applicable local and/or domestic regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki (e.g., ICH E6, 45 CFR 46).

Prior to the beginning of the trial, the investigator must have the IRB/EC's written approval/favorable opinion of the protocol, informed consent form(s), and any other study-related information to be provided to the participants. Written documentation of informed consent approval must be present prior to initiation of any study-related procedures.

Investigators should be aware of and seek guidance from the local IRB/EC and local regulatory authorities regarding assent of children, waiver of consent, oral informed consent process for participants who cannot read or write, and other vulnerable populations. Describe the procedures for obtaining and documenting informed consent of study participants. Describe the procedures for special populations, e.g., non-English speakers, children, illiterate or non-writing individuals, vulnerable populations. Investigators contemplating enrollment of vulnerable populations, including prisoners and children, should consult current DAIDS policy.

Identify different consent forms that are needed for the study (e.g., screening, study participation, HIV screening, future use specimens, assent form for minors.) The consent form(s) will describe the purpose of the study, procedures to be followed, the risk and benefits of participation, and any sponsor-required language. A copy of the informed consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

The consent form must be separate from the protocol document but may be appended.

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## **Informed Consent Process or Assent Process (in Case of a Minor)**

See 45 CFR 46, Subpart D  
See ICH E6, Section 4.8.12

When a study includes participants who may be enrolled only with the consent of the participant's legally authorized representative (e.g., minors or participants with severe dementia), the participant should be informed about the trial to the extent compatible with the participant's understanding. A separate IRB/EC-approved assent form describing (in simplified terms) the details of the study product/intervention(s), study procedures, and risks may be used. Assent forms do not substitute for the consent form signed by the participant's legally authorized representative.

## **Participant Confidentiality**

See 45 CFR 46  
See ICH E6

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention and storage per the sponsor's requirements. U.S. investigators should consider obtaining an NIH Certificate of Confidentiality. Refer to the NIH website at <http://grants.nih.gov/grants/policy/coc/index.htm>.

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

Include the following protocol language: *“Documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the participant except as necessary for monitoring by the IRB/EC, FDA (if applicable), the study sponsor, OHRP, and the pharmaceutical supporter(s) (if applicable).”*

## **Study Discontinuation**

Indicate in the protocol who is allowed to discontinue the study. For example, “The study may be discontinued at any time by the IRB/EC, NIAID, the pharmaceutical supporter(s) or designee, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.” (If a non-IND study, remove “FDA”; if no pharmaceutical support, remove “pharmaceutical supporter or designee.”)

## **14. PUBLICATION POLICY (OPTIONAL)**

Plans for publication and authorship rules should be described in the protocol unless included in separate document such as a Clinical Trial Agreement, contract or study Manual of Operational Procedures (MOP).

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## 15. REFERENCES

List all references cited within the protocol. Each reference must include the title, names of all authors, book or journal, volume number, page numbers, and year of publication. For information not publicly available (e.g., manuscript drafts or local government/regulatory treatment guidelines not available on the Internet), please include copies as accompanying documents.

## 16. APPENDICES

Appendices may include:

- *Informed Consent or Sample Informed Consent*
- *Schedule of Events* (see Attachment A)
- *Biosafety Precautions*
- *Repository Instructions*
- *Toxicity Grading Scales*
- *Specimen Handling*
- *Protocol team roster contact information*

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## APPENDIX A

### SAMPLE SCHEDULE OF EVENTS

		Follow-Up Schedule						Study Completion	Premature Discontinuation of Study Treatment (or of Study)
Procedures		Screening	Baseline	Time Point or Study Visit 1	Time Point or Study Visit 2	Time Point or Study Visit 3	Time Point or Study Visit 4, etc.		
Assessment of Eligibility Criteria		X	X						
Review of Medical History		X	X						
Review of Concomitant Medications		X	X	X	X	X	X	X	X
Study Intervention			X						
Physical Exam	Complete	X						X	X
	Symptom-Directed		X	(X)	(X)	(X)	(X)		
	Reactogenicity		X	X					
	Vital Signs		(X)	(X)	(X)	(X)	(X)		
Assessment of Adverse Events				(X)	(X)	(X)	(X)	X	X
Chemistry		X	X	(X)	(X)	(X)	(X)	X	X
Hematology		X	X	(X)	(X)	(X)	(X)	X	X
Urinalysis		X	X	(X)	(X)	(X)	(X)	X	X
Immunology			X		(X)		(X)	X	X
Virology		X	X		X		X	X	X
Other procedures			(X)		(X)		(X)	(X)	(X)

(X) – As indicated/ appropriate.

Provide a list of tests to be done, e.g.:

Hematology – Hemoglobin, hematocrit, WBC and differential count, platelet count

Biochemistry – Sodium, potassium, chloride, urea, creatinine, glucose, uric acid, bicarbonate, amylase, lipase, albumin, total bilirubin, cholesterol, triglycerides, and CPK, as appropriate for the study. Note that this list is an example; specify list of tests applicable for the protocol.

Urinalysis – Protein and glucose, as appropriate for the study

Immunology – Specify specimen types for non-standard laboratory assays

Other – Other procedures that are done to evaluate outcome measures (e.g., photographs, X-rays)

Study Intervention – Modify as appropriate if intervention is administered more than once throughout the study

Specify time points for follow-up in days, weeks, or months, as appropriate for protocol.

At baseline, all procedures should be done before study intervention.

Indicate volume of blood if frequent or large phlebotomies are part of the protocol over two months.

Information outlined in the Procedures/Evaluations/Timing, Section 7 should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix A. The description of the procedures/evaluations and the sequence of procedures/evaluations can either be written as separate sections or combined into one section, as appropriate or as preferred. Investigators must decide on the best presentation of study evaluations.