***PREFACE***

*This document is the DMID eCTD compliant protocol template for developing DMID-sponsored interventional clinical research protocols. eCTD Section headings and template text should be included in your protocol as provided in the template. Font should be Times New Roman 12. Text should be formatted using Normal style. Bulleted lists should be formatted using Bullet (listing) style.*

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***eCTD formatting questions should be sent to DMID-RASeCTD@tech-res.com, with the RAS in cc.***

*This template provides general content applicable to all clinical trials evaluating an investigational product. Where specific examples are provided, they are often from the vaccine area. The template should be amended as necessary for investigational device trials.*

*The Protocol Template includes suggested template language as well as sections that will need to be entirely study-specific. The standard template language should be used unless it is not applicable to the study. Instructions for modification can be found in this guidance document.*

*The template also includes language that should be used as presented. This guidance identifies those sections. Please follow the guidelines in this guidance document for instructions concerning study-specific sections.*

*Note that instructions and explanatory text are indicated by blue italics. Example text is* ***optional****, and should be customized with* ***appropriate protocol-specific text*** *as applicable.*

*Throughout this protocol template, there may be subject headings that do not apply to your particular study. In such instances, please delete.*

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

*Cross Reference Feature-How do I refer to another section, table, or figure?*

*Place the cursor where you would like to insert the reference. Navigate to the “References” tab and click on the “Cross-reference” option under the Captions group. In the reference type field select Table, Figure or Heading from the drop-down menu. In the Insert reference to field, choose “Only label and number” when linking to Tables and Figures, and “Heading text” and/or “Heading number” when linking to specific section Headings. Select the entity you would like to insert and click Insert.*

*Refer questions regarding use of this protocol template to the appropriate DMID Clinical Project Manager.*

*References:*

[*International Conference on Harmonization (ICH) E6, Good Clinical Practice,*](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf) *Section 6, “Clinical Trial Protocol and Protocol Amendments”*

[*FDA Guidance for Regulations Relating to Good Clinical Practice and Clinical Trials*](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm)

[*Selected FDA GCP/Clinical Trial Guidance Documents*](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219433.htm)

[*Guidance for Industry: E9: Statistical Principles for Clinical Trials*](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073137.pdf)

[*Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination*](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf)

[*CDISC Standards and Implementations*](http://www.cdisc.org/standards-and-implementations)

[*Clinical Trials.gov (reporting requirements)*](https://clinicaltrials.gov/ct2/manage-recs)

TITLE

DMID Protocol Number: *(Include the protocol number in the header)*

DMID Funding Mechanism: *(e.g., grant #, contract #)*

 Pharmaceutical Support: *(Include only if applicable)*

Other Identifying Numbers: *(Include only if applicable)*

IND Sponsor: *(if applicable. Do not include IND number)*

Lead Principal Investigator:

DMID Clinical Project Manager:

Draft or Version Number: *(Include the version number in the header; refer to DMID Document Version Control Guidelines for assigning version numbers)*

Day Month Year
*(Write out the month and use international date format, e.g., 29 February 2016)*

Statement of Assurance

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally-funded human subjects research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be subject to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution’s IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

Statement of Compliance

*Refer to:*

*http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf*

*https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf*

*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html*

*Provide a statement that the trial will be conducted in compliance with the protocol, International Conference on Harmonisation E6: Good Clinical Practice: Consolidated Guideline (ICH E6) and the applicable regulatory requirements.*

*Text will be slightly different for Investigational Drug Exemption.*

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

* United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
* Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
* International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
* Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
* National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
* National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
* Applicable Federal, State, and Local Regulations and Guidance

Signature Page

*This section should not be changed without DMID concurrence.*

*The local investigator who is responsible for the study implementation at his/her specific site (i.e., the individual who signs the Form FDA 1572, Investigator Agreement, or the Investigator of Record form) must sign the signature page for each version of the protocol approved by DMID and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), as applicable.*

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor’s approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

|  |
| --- |
| Site Investigator Signature:*\** |
| Signed: |  | Date: |  |
|  | *Name**Title* |  |  |

*\* The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; i.e., if it is an Investigational New Drug study, the individual who signs the Form FDA 1572 or, if it is a non-IND study, the individual who signs the Investigator of Record form.*

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List of Abbreviations

|  |  |
| --- | --- |
| AE | Adverse Event/Adverse Experience |
| BLA | Biologics License Applications |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CMS | Clinical Material Services |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR  | Clinical Study Report |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DMID | Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| FWA | Federal Wide Assurance |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator’s Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committeeof Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IEC | Independent or Institutional Ethics Committee |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| JAMA | Journal of the American Medical Association |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| N | Number (typically refers to subjects) |
| NDA | New Drug Application |
| NEJM | New England Journal of Medicine |
| NIAID | National Institute of Allergy and Infectious Diseases, NIH, DHHS |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| OHSR | Office for Human Subjects Research |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SMC | Safety Monitoring Committee |
| SOP | Standard Operating Procedure |
| US | United States |
| WHO | World Health Organization |

*Please modify list to include your protocol-specific terms.*

Protocol Summary

|  |  |
| --- | --- |
| **Title:** | *Include type of trial (e.g., dose-ranging, observational, double blind)* |
| **Design of the Study:** | *Include succinct, 3 sentences or less, description of study design to provide an overview of the study design, including study arms, sample size and schedule of interventions (e.g., vaccine administration).* ***OR****Describe the study type in a single sentence; e.g., randomized, double-blind, placebo controlled, prospective cohort, etc.* |
| **Study Phase:** | *1,2,3,4* |
| **Study Population:** | *Include sample size, gender, age, general health status, geographic location* |
| **Number of Sites:** | *1 or up to n, list here*  |
| **Description of Study Product or Intervention:** | *Describe the study product, include dose and route of administration (bullets)* |
| **Study Objectives:** | *Copy objectives from the appropriate sections of the protocol.* Primary:Secondary:Exploratory:* *Include only if applicable, or delete*
 |
| **Duration of Individual Subject Participation:** | *Provide the estimated duration of time (days, weeks, or months) for a subject to complete their participation in the study.* |
| **Estimated Time to Last Subject/Last Study Day:** | *Provide the proposed timeframe from study activation to the last subject’s last study day (defined as the time point the final subject will be contacted by the study site), as described in the protocol.* |

*The schematic should provide an overview of the study design. Examples are provided:*

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

Table : Treatment Arms

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

*Instructions for progressing to next phase (include only if applicable, or delete):*

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

*Example #2: Flow diagram*

Figure : Schematic of Study Design

Total N: Obtain informed consent. Screen subjects by criteria; obtain history document.

Randomize

Perform pregnancy test; collect blood for assays;

**Administer Study Product/Intervention**

Clinical and AE assessment

Clinical and AE assessment

**Assessment of Final Study Outcome Measures**

Prior to Enrollment

Time Point or Study Visit 1

Time Point or Study Visit 2

Time Point or Study Visit 3

Time Point or Study Visit

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

# Key Roles

*Refer to ICH E6, Section 6.1*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

*Provide names and contact information for the individuals/institutions listed below. Other individuals/institutions, such as the Study Site Investigators, DMID Medical Monitor, DMID Medical Officer, DMID Scientific Lead, Safety and Pharmacovigilance Contractor, Study Monitor, Study Product Repository, Clinical Laboratory(ies), or other medical or technical departments should be listed in the study Manual of Procedures (MOP).*

|  |  |
| --- | --- |
| **Lead Principal Investigator:****DMID Clinical Project Manager:** | *Site investigator responsible for conducting the study. A study can have only one Lead Principal Investigator.**Name, degree, title**Institution Name**Name, degree, title**Institution Name* |
|  |  |
| **Statistical and Data Coordinating Center:** | *Institution Name* |

# Background and Scientific Rationale

## Background

*Refer to ICH E6, Section 6.2*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

*Include:*

* *The name and brief description of the study intervention/investigational products(s).*
* *A summary/background of the disease/condition that the study intervention/investigational product(s) intends to examine.*
* *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance, including any reproductive toxicology studies.*
* *A summary from relevant clinical trials including incidence and type of reported adverse events thus far.*
* *Discussion of important literature and data that provide background for the trial (cite reference citations and list in the References Section 16).*
* *Applicable clinical, epidemiological, or public health background or context of the study.*
* *Importance of the study and any relevant treatment issues or controversies.*
* *If you need to PASTE content from elsewhere…*

## Scientific Rationale

### Purpose of Study

*Include a statement of the hypothesis. Include the purpose of the study, the name(s) of the intervention(s) (e.g., vaccine, drug, biologic, device) being evaluated, a description of and justification for the route of administration, dosage/dosage regimen, treatment period(s), and selection of study population.*

### Study Population

* *Include a description of and justification for the study population selection. The study population should be commensurate with the stage of the study and the development stage for the study product.*
* *Identify if the study will include subjects at international sites.*
* *Include from where the study population will be drawn (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public).*
* *If the study intends to enroll pregnant women, children/neonates, prisoners, or other potentially vulnerable populations, refer to the applicable section of 45 CFR Part 46, Subpart B, C, and D. Note that these regulations apply if any subjects are members of the designated population even if it is not the target population.*
* *If any of the following are excluded, explain why they are excluded and any future plans to include in other studies: women, minorities, and/or children.*

## Potential Risks and Benefits

*Refer to 45 CFR Part 46.116 (a) (2) and (3)*

*(http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf).*

*Include a discussion of known risks and benefits, if any, to human subjects. For each study product/intervention, including comparators, describe potential risks and benefits. Identify any alternative treatments. Include description of potential risks for protocol-specified treatments that are not designated study treatment/intervention.*

### Potential Risks

*If a package insert is available, it should be used as the primary source of risk information. If the product is investigational, the Investigator’s Brochure (IB) should be the primary source of the risk information. In addition, literature searches can also provide relevant risk information. If the risk profile cannot be described from any of the above sources, the risk information discussion will result from the literature search and review.*

* *Include a discussion of known or potential risks from the study product(s) or research-related procedures, if any, to human subjects. Include risks for procedures required to complete a study procedure (e.g., sedation, insertion of a tube, pre-medications, hydration, etc.).*
* *Include a review of relevant literature, which should be referenced and included in the References section.*
* *Describe in detail any physical, psychological, social, legal, economic, or any other potential risks to subjects, including immediate risks, long-range risks, and the rationale for the necessity of such risks.*
* *Describe risks seen in animal studies separately from risks seen in studies with humans. Include dose levels utilized in animal studies and dose levels in human studies. Include a separate section for unexplained deaths in animals and humans if applicable.*
* *Describe why alternative procedures may not be feasible.*
* *Describe why the value of the information to be gained outweighs the risks involved.*

### Potential Benefits

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

* *Describe known direct benefits, if any, to human subjects or state that there is no anticipated direct benefit.*
* *Discuss any potential benefit to society by adding to generalized knowledge or any other immediate or long-term benefit(s) for the study population.*

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

# Study Design, Objectives and EnDpoints or Outcome Measures

## Study Design Description

*Refer to ICH E6, Section 6.4*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

*The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.*

*Describe the trial design, including the rationale for design features:*

* *A description of the type/design of trial to be conducted (e.g., placebo-controlled, double-mask, parallel design, open-label, dose-escalation, dose-ranging).*
* *A brief description of the study population (e.g., healthy/sick, inpatient/outpatient).*
* *A description of any randomization procedures.*
* *A description of any blinding procedures (e.g., single-blind, double-blind, how blind is maintained).*
* *Single or multicenter.*
* *Number and description of study groups/arms including sample size (including a table and/or schematic, if appropriate).*
* *The expected duration of subject participation.*
* *Identification of the study product and specifics of administration of other study products (e.g., placebo),* *including dosage, dosage regimen, and dose escalation.*
* *Identification of any protocol-required medications/treatments other than study product(s) and the timeframe for administration.*
* *A description of the sequence and duration of all trial periods, including follow-up (specify individual subjects, not the entire trial).*
* *Changes in scheduling, such as dose adjustments for weight or laboratory results.*
* *Other protocol-specific details, such as collecting samples, centralization of evaluations (e.g., central laboratory or central reading center for clinical scans).*

Schematic of Study Design - See Figure 1 and Table 1

## Study Objectives

*A detailed description of the primary and secondary, exploratory (if applicable) objectives of the study is included in this section. For each of the following categories, provide a detailed description of the objectives of the study to be measured during the trial. These typically include:*

* *Statement of purpose, e.g., to assess, to determine, to compare, to evaluate.*
* *General purpose, e.g., efficacy, safety, immunogenicity, pharmacokinetics.*
* *Specific purpose, e.g., dose-response, superiority to placebo.*

### Primary

* *Describe the study’s primary objective.*

### Secondary

* *Describe the study’s secondary objectives.*

### Exploratory

*Do not include this section if not applicable, otherwise delete.*

*Exploratory objectives are those where the study may not have sufficient statistical power to evaluate.*

*Any analysis that is likely to be longer than 12 months after the last subject’s last study day should be considered an exploratory endpoint or as an endpoint for a separate protocol or sub-study.*

## Study Endpoints or Outcome Measures

*Describe the methods for assessing the effects of the study treatments. Provide succinct but precise descriptions of the measures used to determine the endpoints or outcomes stated in the study objectives. Outcome measures or endpoints must be consistent with the study objective(s) and methods for collecting data. A particular study objective can have more than one corresponding outcome measure or endpoint supporting it. Describe how and by whom the outcome or endpoint will be ascertained, as appropriate. Include the study days at which samples will be obtained and the specific laboratory tests to be used as well as other procedures/observations used to assess outcomes. Prioritize the endpoints or outcome measures.*

*Each endpoint or outcome measure must have a name, a metric, and a time point (see examples below), and either the number of subjects or number of events or proportion of subjects or events may be reported. Note that rates cannot be reported to the National Library of Medicine’s (NLM) Clinicaltrials.gov. Consider including the name of the intervention or specific doses to be studied, if applicable.*

*Examples:*

* *Geometric Mean Titers (GMT) by Hemagglutination Inhibition Assay (HAI) of antibodies to the antigens contained in investigational product ‘X’ and investigational product ‘Y’ before and following vaccination with the respective vaccine [Time Frame: Day 1 (pre-vaccination) and Day 21 after vaccination].*
* *Number of participants reporting solicited local injection site and solicited systemic reactions following vaccination with investigational product ‘X’ [Time Frame: Day 1 (post-vaccination) and Day 21 after vaccination].*

*Refer to ICH E6, Sections 6.7-6.8*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

*If the endpoint is based on an FDA guidance, include.*

*An outcome measure is “an observation variable recorded for [subjects] in the trial at 1 or more time points after enrollment for the purpose of assessing the effects of the study treatments” (Meinert CL. Clinical trials: design, conduct, and analysis. Oxford: Oxford University;1986).*

* *Can separate out bullets below into efficacy, safety, immunogenicity and pharmacokinetics based on study design*

### Primary

*Outcome measures should be prioritized. Generally, there should be just* ***1*** *primary method for measuring outcomes, with evidence that this method will provide a clinically relevant, valid, and reliable measure of the primary objective (e.g., laboratory procedures, safety assays).*

*Note: As applicable, Basic Results reporting in Clinicaltrials.gov is required for the primary outcome measure within 12 months of the primary completion date. As specified in* [*US Public Law 110-85, Title VIII, Section 801*](https://clinicaltrials.gov/ct2/manage-recs/fdaaa)*, the primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. Contact the protocol Clinical Project Manager for the study for any questions concerning Clinicaltrials.gov requirements.*

*

### Secondary

*Include secondary outcome measures. Discuss their importance and role in the analysis and interpretation of study results. These results must also be reported to the NLM within the required timeline.*

*

### Exploratory

*Do not include this section if not applicable. Only include if applicable, or delete.*

# Study Intervention/Investigational Product

*Note: If multiple products are to be evaluated in the study, each product should be listed within subsections 4.1.1, 4.1.2, 4.2. and 4.4. The product name should be listed and underlined, followed by the appropriate information for that product. Describe placebo or control product(s), and as appropriate, protocol-required medications other than study product, rescue medications, etc. See below for examples.*

## Study Product Description

*Information in this section can usually be obtained from the IB or the package insert. Briefly describe the chemical classification and physical characteristics/appearance of the active ingredient or component of the study product(s). For vaccines or biologics, this section may include a brief discussion of the pharmacology and manufacturing processes. Refer to IB or package insert .*

### Formulation, Packaging, and Labeling

*Describe the formulation, dosage form, and strength or concentration for each study product to be supplied for the study. Include a brief description of the appearance of each study product. Limit discussion of any inactive ingredients or components of the study product related to its formulation to a brief narrative and do not include specific quantities or concentrations of inactive ingredients unless significant or clinically relevant. Any product(s) required for preparation or delivery of the active product or placebo should be described in separate sections, as well as their purpose (e.g., WFI for reconstitution, 0.9% NaCl piggyback solutions for dilution and administration, etc).*

*Include the type of packaging container, package size, or delivery system for the individual unit that will be supplied.*

*Include the following statement for all IND studies: “The study product will be labeled according to manufacturer or regulatory specifications and include the statement “Caution: New Drug – Limited by Federal Law to Investigational Use.”*

Product 1 Name: Active Product(s) and Components

*Describe each product separately.*

Product 2 Name: Placebo

*Describe each placebo separately.*

*Include only if applicable, or delete*

### Product Storage and Stability

*Describe all necessary storage conditions, including specific temperature numerical ranges and container requirements, and any permissible excursions. Describe any special handling precautions. Provide additional information regarding stability, storage conditions, and expiration or hold times for study products in which multi-dose vials are entered (i.e., the seal is broken), for reconstituted or diluted study product, or for any final preparations of study product. The storage conditions for any product(s) required for preparation or delivery of the active product or placebo should be described in separate sections.*

*The following standard format may be used for storage temperature information:*

*[Insert name, strength, and dosage form of study product] must be stored between [xx°C to xx°C (xx°F to xx°F); excursions between xx°C-xx°C (xx°F-xx°F) are permitted.]*

*(Note: A specific numerical range must be included when describing temperature storage conditions. For example, “store at room temperature” or “under refrigeration” is not acceptable without reference to a specific numerical range.)*

Product 1 Name: Active Product(s)

*Describe storage conditions for each product separately.*

Product 2 Name: Placebo

*Describe storage conditions for each placebo separately.*

*Include only if applicable, or delete.*

## **Acquisition/Distribution**

*Identify who is providing study product(s) and other study product-related items, such as diluents or other vehicles for preparation for use in the study and from where the clinical research sites can obtain these study products. If sites will be responsible for obtaining any study-related products locally or at the site level, this section must also specify this information. Provide shipping instructions to the clinical research site in the MOP.*

Product 1 Name: Active Product(s)

Product 2 Name: Placebo

*If applicable keep, or delete.*

## Protocol-Specified Medications/Treatments other than Study Products

*This section is optional. Include only specific medication or treatments that are required during the protocol in addition to the study product. Do not include standard of care or therapies required as part of eligibility prior to participation or enrollment into the protocol (these should be described in the inclusion/exclusion criteria section of the protocol and their use in the clinical evaluations section of the protocol).*

*Include only if applicable, or delete.*

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

*List investigational agents, route, doses, and frequency of administration. Include thawing, diluting, mixing, and reconstitution/preparation instructions, as appropriate. Include any specific instructions or safety precautions for dispensing or administration of study products or masking of the product or the administrator. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc.*

Product 1 Name: Active Product(s)

Product 2 Name: Placebo

*Include if applicable, or delete.*

*A tabular format may be useful. Modify the example table below as applicable.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Product Name* | *Dose* | *Route* | *Frequency of Administration* | *Duration of Therapy* |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

## Pre-determined Modification of Study Intervention/Investigational Product for an Individual Subject

*If applicable, include procedures for modifications of study product dose or regimen for a study subject due to pre-determined factors, such as toxicity, abnormal laboratory values, events of concern, acute febrile illness, or specify other events or values per protocol.*

*Include procedures to follow if a dose is not tolerated, e.g. emesis after administration of an oral dose.*

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

*Provide plans for how the study intervention/investigational product(s) or device(s) will be distributed including participation of a drug storage and distribution center, frequency of product distribution, amount of product shipped, and plans for return of unused product. Include information regarding the disposition of used study product, and if any study product may be destroyed upon completion of monitoring accountability verification.*

*Modify template language as appropriate for the study. Details should be provided in the MOP.*

***Optional Example text:*** *customize with* ***protocol-specific text,*** *as applicable*

[Product] will be stored and shipped from the DMID contract Clinical Material Services (CMS) to the Clinical Sites. Once received, [product] will be stored in and dispensed by the Investigational Pharmacy. Unused product may be destroyed.

The Food and Drug Administration (FDA) requires accounting for the disposition of all investigational products. The Investigator is responsible for ensuring that a current record of product disposition is maintained and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition, as required by federal law, consist of the date received, date administered, quantity administered, and the subject number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records must be available for inspection by the DMID monitoring contractors, and is subject to inspection by a regulatory agency (e.g., FDA) at any time. An assigned Study Monitor will review the pharmacy records.

Unused reconstituted investigational product vials will be stored at [xoC±xoC, /room temperature] in the Investigational Pharmacy until clinical trial accountability is completed. At study termination, all unused investigational product will be disposed in accordance with the MOP following complete drug accountability and monitoring.

# Selection of Subjects and Study Enrollment and Withdrawal

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

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

*If the study intends to enroll children, pregnant women, prisoners, or other vulnerable populations, refer to applicable section of 45 CFR Part 46, such as Subpart B – Additional Protections Pertaining for Pregnant Women, Human Fetuses, and Neonates Involved in Research; Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects; Subpart D – Additional Protections for Children Involved as Subjects in Research. Please refer to these regulations and Office for Human Research Protections (OHRP) guidelines when choosing the study population.*

*Note that these regulations apply if any subjects are members of the designated population even if it is not the target population. For example, if a subject becomes a prisoner during the study or becomes pregnant and continues in the study, the respective Subpart will apply.*

* *If women, minorities, or children will not be recruited, explain why not. Provide justification for Exclusion in Ethics/Protection of Human Subjects, Section 9.4 Refer to: http://grants2.nih.gov/grants/funding/women\_min/women\_min.htm.*
* *Indicate from where the study population will be drawn (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public). Where appropriate (single center studies), include names of hospitals, clinics, etc.*
* *Identify strategies for subject recruitment and retention, including a discussion of recruitment strategies specifically for achieving NIH gender/minority guidelines. As appropriate, include names and types of facilities (e.g., hospitals, clinics, etc.) from where the study subjects will be recruited. Include other recruitment strategies, such as existing cohorts, as applicable.*
* *If subjects require screening: distinguish between recruitment procedures (e.g., discussing the study with them, reviewing records when appropriate prior to consent) vs screening and/or enrolling subjects (e.g., obtaining informed consent and obtaining samples).*
* *Select screening laboratory tests carefully, if they will be used (laboratory parameters selected should be related to evaluation of safety, with ranges based on toxicity criteria).*

*If males and females of reproductive potential will be enrolled, provide specific contraception requirements (e.g., licensed hormonal methods).*

***Optional Example text****: customize with* ***protocol-specific text,*** *as applicable*

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed toward the DMID Medical Officer.

## Eligibility Criteria

*Eligibility Criteria:*

* *The risks of the study product/intervention should structure the development of the inclusion/exclusion criteria.*

*Provide a definition of subject characteristics required for study entry. 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).*

*For studies with more than one set of criteria (for example, different eligibility requirements for different study cohorts), specify the inclusion/exclusion criteria for each cohort.*

***Each inclusion/exclusion criterion must be ≤ 200 characters, including spaces****. If more than 200 characters are necessary to explain the criterion, use an asterisk and add a footnote as described below. Include qualifiers and parentheticals as footnotes to the criterion. For example:*

*Criterion: “Females of childbearing potential must agree to use an efficacious method of birth control\* within two months of vaccination and during the entire study.”*

*Footnote to the Criterion: \*Acceptable methods of birth control include the following: birth control pills, injection hormonal contraceptive, implant hormonal contraceptive, hormonal patch, IUD, sterilization by hysterectomy or tubal ligation, spermicidal products and barrier methods (such as cervical sponge, diaphragm, or condom), abstinence, monogamous with a vasectomized partner.”*

*Eligibility criteria should be numbered sequentially.*

### Subject Inclusion Criteria

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

*Examples of inclusion criteria include the following: informed consent obtained and signed, age, presence or absence of a medical condition/disease, required laboratory result, 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 capability will be enrolled, include details of allowable contraception methods for trial (e.g., licensed hormonal methods).*

*The ICH M3 footnote on highly effective contraception:*

*A highly effective method of birth control is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner. For subjects using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.*

*ICH Guidance for Industry M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (June 2009).*

### Subject Exclusion Criteria

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

*Examples include the following: medical condition or laboratory finding that precludes participation, recent (with time frame) febrile illness that precludes or delays participation, pregnancy or lactation, characteristics of household or close contacts (e.g., household contacts who are immunocompromised), known allergic reactions to components of the study product(s), treatment with another investigational drug (with time frame), history of drug/alcohol abuse, disallowed concomitant medications(include the timeframe; e.g. 30 days prior to enrollment), etc.*

## Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

### Withdrawal from the Study or Discontinuation of the Study Product

*Modify the standard language as appropriate for the study. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB/IEC-approved consent form with the revised procedures.*

*As applicable, identify specific criteria for not providing subsequent doses of study product for multi-dose regimens. If appropriate, provide distinct discontinuation criteria for subjects and cohorts, listing both sets of criteria separately.*

*Write N/A for a single dose study.*

*Also note that subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason.*

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Subjects may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also withdraw a subject from receiving the study product for any reason. Follow-up safety evaluations will be conducted, if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs).

The reasons, might include, but are not limited to the following:

* Subject no longer meets eligibility criteria
* Subject meets individual halting criteria (reference to section 8.5.2)
* Subject becomes noncompliant
* Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses
* Subject lost to follow-up
* Subject becomes pregnant, if applicable
* Determined by a physician’s discretion to require additional therapy not indicated in the protocol to ensure subject’s health and well-being (or treatment failure, if applicable)

The investigator should be explicit regarding study follow-up (e.g. safety follow-up) that might be carried out despite the fact the subject will not receive further study product. If the subject consents, every attempt will be made to follow all AEs through resolution. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB/IEC-approved consent form with the revised procedures.

The investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study.

### Subject Replacement

*Clearly describe whether and how there will be replacement of subjects who discontinue study product administration and withdraw from the study, and criteria for replacement.*

***Optional Example text****: customize with* ***protocol-specific text,*** *as applicable*

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product will not be replaced. Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF but before administration of the study product may be replaced.

### Study Termination

*List actions by the investigator for discontinuation of the study in this section. List other possible reasons for discontinuation of the study, if applicable.*

***Optional Example text****: customize with* ***protocol-specific text,*** *as applicable*

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/IEC.

# Study Procedures

*Information, including the visit number, study day number, day (after intervention), and window of assessment outlined in this section should refer to and be consistent with the information in the Schedule of Events in Appendix A and in Section 7.*

## Screening

*This section must include instructions for obtaining signed informed consent.*

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

*If a separate screening consent will not be used, the study consent must be signed prior to screening.*

*Explain the circumstances for enrollment of subjects with parental permission (and assent, if applicable) or consent by a legally authorized representative.*

## Enrollment

*List the sequence of events that should occur during enrollment. Include obtaining signed informed consent if not already obtained prior to screening or if there is a separate consent form from the screening consent.*

*List evaluations/procedures necessary to assess or confirm whether a subject still meets the eligibility criteria and may be enrolled.*

*List assessments that are required at baseline for subsequent comparison with outcome measures after study intervention (e.g., baseline signs and symptoms prior to vaccination).*

*List any special conditions (e.g., results of the pregnancy test must be negative and available prior to administration of study product).*

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

*Reference Section 10 for randomization, if applicable.*

## Planned Study Visits

*List all visits that occur after enrollment. For each study visit, state the expected duration (minutes, hours, or days) of subject participation.*

*Discuss the sequence of events that should occur during the study visit. Include, as applicable, administration of study intervention/ investigational product, counseling, review of solicited events, reactogenicity, collection of concomitant medication information, assessments of AEs, etc.*

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

*Study Day 1 usually indicates the day of first receipt of study intervention. [Note: for some studies, Day 1 may pertain to another study event or intervention.] The Study Schedule cannot include any labels referencing Day 0. Any study days that occur prior to Day 1 should be labeled with negative study day numbers, beginning with -1 for the day prior to Day 1. Provide windows around the study day where appropriate. For clinic visits occurring on a single day but with multiple data collection time points (e.g. PK study), the study day numbering format should be 1A, 1B, 1C and so forth where study day 1A captures the data associated with the first time point for that day; 1B captures the data associated with the second time point for the same day; and 1C captures the data associated with the third time point for the day.*

### 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 AEs, etc.*

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

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

### Final Study Visit

*Define when the final study visit should occur and any special procedures/evaluations or instructions to the subject. Describe provisions for follow-up of ongoing AEs/serious adverse events (SAEs).*

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

### Early Termination Visit

*If needed keep, or delete.*

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

## Unscheduled Study Visits

*Specify how unscheduled visits(s) will be handled and documented.* *Supplemental study visits will be assigned a trailing alpha letter after the study day number. For example, if a subject has an unscheduled study day that occurs between study day 1 and study day 2, the study visit day would be numbered as study day 1S.*

## Protocol Deviations

*Describe plans for detecting, reviewing, and reporting deviations from the protocol. DMID does not approve planned deviations.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions should be developed by the site and implemented promptly. It is the responsibility of the site Principal Investigator and other study personnel to use continuous vigilance to identify and report protocol deviations. All individual protocol deviations will be addressed in subject study records. All protocol deviations, either individual, product, or site-specific will be collected and the record stored in a sponsor-determined location. Protocol deviations must be sent to the local IRB/IEC per its guidelines. The site Principal Investigator and other study personnel are responsible for knowing and adhering to their IRB/IEC requirements.

***OR***

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or the site personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID per the DCC protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in study subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site principal investigator and personnel are responsible for knowing and adhering to their IRB requirements.

# Description of Clinical and Laboratory Evaluations

*Information outlined in this section should be consistent with the information in the Schedule of Events in Appendix A.*

## Clinical Evaluations

*List all clinical evaluations to be done during the protocol, and including special instructions, if any.* *Differentiate screening and baseline procedures from those taken after the intervention, as appropriate.*

***Optional******Examples****: customize with* ***protocol-specific text,*** *as applicable*

* *Medical history (describe what is included for history, e.g., time-frame considerations, whether history will be obtained by interview or from medical records).*
* *Medications history (e.g., describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter). Assessment of eligibility should include a review of permitted and prohibited medications.*
* *Physical examination (list the vital signs [including height and weight] and organ systems to be assessed; address in the MOP whether it is an actual measurement or subject's self- report); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur. If an adverse event occurs, describe if a full physical examination should be done.*
* *Reactogenicity assessments (e.g., pain, tenderness; describe rating scale).*
* *Review of memory cards/aids.*
* *Counseling procedures.*
* *Criteria for dose adjustment.*
* *Rescue therapy.*

### Research Procedures

*If applicable keep, or delete*

*List procedures required to assess the study product. Provide specific instructions or precautions, if applicable.*

*Examples:*

* *Medical history: Describe what is included for history, e.g., time-frame considerations, whether history will be obtained by interview or from medical records.*
* *Physical examination: List the vital signs [including height and weight] and organ systems to be assessed. Address whether it is an actual measurement or subject's self-report; if applicable, discuss what constitutes a targeted physical examination and at which study days it may occur. If an adverse event (AE) occurs, describe if a full physical examination should be done.*
* *Solicited events, also called reactogenicity assessments in vaccine studies): Refer to the Assessment of Safety section*
* *EKG, Sonographies, X-Rays, etc.*

*If a protocol requires specialized testing or diagnostics, specific guidelines for interpretation must be described in the protocol. The protocol must identify which test is to be performed, what information will be transmitted to the PI, and what criteria will be used for eligibility.*

### Assessment of Concomitant Medications/Treatments other than Study Product

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

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

*If applicable, describe how concomitant medications/treatments other than study product, including specific medications/treatments required during the study (e.g., contraceptive measures, medications related to eligibility) will be assessed. Explain any counseling related to concomitant medications/treatments that may occur during study visits. If this section is not applicable, do not include this section in the protocol.*

### Assessment of Subject Compliance with the Study Visit Schedule

*If applicable, include plans for assessing the subject’s compliance with the protocol. If this section is not applicable, do not include this section in the protocol.*

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

*Include plans for compliance assessment (e.g., questionnaires, direct observation, pill counts) in this section. If there is a possibility of vomiting the product, include instructions for re-dosing.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

Subjects will be directly observed at the time of dosing by a member of the clinical research team who is licensed to administer the study product. Administration will be documented on [cite source document] and entered into the eCRF.

### Non-Research Standard of Care

*Include only if applicable, or delete. Describe any specific medical care, including diagnostics or treatment that is indicated whether or not the subject participates in the research study. If all procedures are research procedures and this section is not applicable, do not include this section in the protocol. Include rescue medications or standard of care treatments as a result of the intervention (e.g., treatment in challenge studies).*

## Laboratory Evaluations

*List all laboratory evaluations. Differentiate screening laboratory specimen collection from those taken after vaccination/study product administration, as appropriate. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods (e.g., use consistent laboratory method throughout study) to provide for appropriate longitudinal and cross-comparison. If more than one laboratory will be used, specify which evaluations will be done by each laboratory, including whether tests will be done at a central laboratory or the local site laboratory.*

*Please note that only the laboratory tests indicated in the toxicity tables will count toward halting criteria.*

### Clinical Laboratory Evaluations

***Optional******Examples****: customize with* ***protocol-specific text,*** *as applicable*

* *Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
* *Biochemistry: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).*
* *Serology: Hepatitis A, Hepatitis B and Hepatitis C, HIV, West Nile Virus, Syphilis Treponemal.*
* *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.*

### Research Assays

*List assays required to assess the study product. Include estimated volume and type of specimen needed for each test. Identify the laboratory(ies) that will perform the assay. If more than one laboratory will be used, specify which assays will be done by each laboratory.*

*Examples:*

* *Immunology assays*
* *PK studies*

#### Laboratory Specimen Preparation, Handling, and Storage

*Specify special instructions for the preparation, handling, and storage of specimens. Include when assays are to be performed (e.g., in batches, annually, or at study completion). As appropriate, details should include required storage temperatures, aliquots of specimens, where they will be stored, and how they will be labeled.*

#### Laboratory Specimen Shipping

*Describe the frequency with which specimens are to be shipped. Contact information for laboratory personnel and detailed shipping information should be included in the study MOP.*

*Reference: International Air Transport Association (IATA)*

# Assessment of Safety

## Assessing and Recording Safety Parameters

*Reference safety parameters that are outcome measures. Include other parameters if not primary study outcome measures.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

Safety will be assessed by the frequency and severity of: *[insert description]*

### Adverse Events (AEs)

*Refer to ICH E6, Section 1.2*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

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

* *Identify the time period for documenting AEs (e.g. “from the first intervention, Study Day X, through Study Day Y”). The start and stop date of each reported AE must be recorded in the appropriate data collection record. Describe the time period for collection (e.g., Days 1-28, note the SAE collection period should be documented as beginning on Day 1 the day of dosing) and follow-up of AEs.*
* *Describe which AEs will be collected as solicited events (in vaccine trials, note that each solicited event will be captured in only 1 format [e.g., in a reactogenicity case report form {CRF} or as an AE]). Plan the reporting and data collection system to avoid double capture.*
* *Describe how unsolicited events will be captured.*

*Refer to 21 CFR 312.32 IND safety reporting.*

*Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs, including solicited local (injection site) and systemic (subjective and quantitative) reactions, will be captured on the appropriate data collection form and eCRF. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

If an event meets both the criteria of a study endpoint and an adverse event, the event will be reported either as a study endpoint or as an adverse event (not both).

#### Adverse Events Grading

*Describe how decisions will be made regarding determining relatedness and grading severity.*

*Include protocol-defined grading systems used to grade solicited local and systemic (subjective and quantitative) reactions. The Toxicity Table should be included in the protocol itself or attached in Appendix B.*

*The table of CDISC definitions and DMID’s interpretation guide for grading AEs that do not appear in the Toxicity Table, must be included. For all other protocols, this table is recommended but not required. However, all grading tables must be CDISC-compliant.*

*Reference: CDISC Standards and Implications*

 *The following criteria can be used to complete the table.*

* *Mild grading*
	+ - *Transient: Duration less than 48 hours*
		- *Therapeutic Intervention: An action to alleviate the adverse event that does not require a medication or medical procedure, such as a change in diet, or application of cool pack or warm compress, or rest*
* *Moderate grading*
* *Therapeutic Intervention: Use of non-narcotic pain reliever or over-the-counter medication*
* *Severe grading*
* *Activities of Daily Living (ADLs): Negative impact on ADLs, such as missed work, unable to do housework or exercise*
* *Significantly Affects Clinical Status: A medically attended event – clinical care was sought from a healthcare professional*
* *Intensive Therapeutic Intervention: Required prescription medication, or intravenous fluids or medical procedure*

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

**Severity of Event:**

AEs will be assessed by the investigator using a protocol-defined grading system (toxicity table included as an appendix). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

* Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject’s usual activities of daily living.
* Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
* Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

**Relationship to Study Product:** The assessment of the AE’s relationship to study product will be done by the licensed study physician indicated on the Form FDA 1572 and the assessment will be part of the documentation process. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

* Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
* Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

### Reactogenicity

*For Vaccine Studies and Some Therapeutic Trials, delete if not applicable.*

Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. The following Toxicity Grading Scales will be used to grade solicited local (injection site) and systemic (subjective and quantitative) reactions:

*(Insert local injection site reactogenicity grading table here):*

* Mild (Grade 1): [*insert description*]
* Moderate (Grade 2): [*insert description*]
* Severe (Grade 3): [*insert description*]

*Example ‘functional scale’ text for assessing reactogenicity or other parameters not specifically listed in the toxicity table:*

1 = Mild (awareness of a symptom but the symptom is easily tolerated)

2 = Moderate (discomfort enough to cause interference with usual activity)

3 = Severe (incapacitating; unable to perform usual activities; requires absenteeism or bed rest)

### Serious Adverse Events (SAEs)

*Refer to 21 CFR 312.32 IND safety reporting and 21 CFR 312.64 Investigator reports*

*Refer to ICH E6, Section 1.50*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

*21CFR 312.32: Definitions for serious and serious suspected adverse reaction*

*Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.*

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes:

* Death,
* a life-threatening adverse event1,
* inpatient hospitalization or prolongation of existing hospitalization,
* a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
* a congenital anomaly/birth defect.
* Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

1 Life-threatening adverse event. An AE is considered “life-threatening” if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

SAEs will be:

* Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 or by the Institution as the site Principal Investigator or Sub-Investigator.
* Recorded on the appropriate SAE data collection form and eCRF.
* Followed through resolution by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site Principal Investigator or Sub-Investigator).
* Reviewed and evaluated by DMID, an Independent Safety Monitor (ISM) (as deemed necessary), the DSMB or SMC (periodic review unless related), and the IRB/IEC.

## Specification of Safety Parameters

*Reference safety parameters that are outcome measures. Include other parameters if not primary study outcome measures.*

Safety will be assessed by the frequency and severity of: *[insert description]*

### Solicited Events

*Describe the methods and timing for assessing, recording, and analyzing solicited safety parameters, such as reactogenicity. Include the type and duration of the follow-up of subjects.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

Solicited events are AEs that are common and known to occur following administration of study product.

### Unsolicited Events

*Describe the methods and timing for assessing, recording, and analyzing unsolicited safety parameters. Include procedures for eliciting reports of and for recording and reporting AEs and intercurrent illnesses. Describe procedures for follow-up of subjects.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

Unsolicited events are any other AEs that occur following administration of study

### New-Onset Chronic Medical Conditions (NOCMCs)

*Include only if applicable, or delete*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

NOCMCs are defined as any new ICD-10 diagnosis that is applied to the subject during the duration of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

### Medically-Attended Adverse Events (MAAEs)

*Include only if applicable, or delete*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

For each unsolicited AE experienced, the subject will be asked if he/she had received medical attention, defined as hospitalization, an ER visit, or an otherwise unscheduled visit to or from medical personnel for any reason. AEs characterized by such unscheduled medical care will be designated as MAAEs.

### Potentially Immune-Mediated Medical Conditions (PIMMCs)

*Include list of PIMMCs as an Appendix only if applicable, or delete*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

PIMMCs constitute a group of AEs that includes diseases which are clearly autoimmune in etiology and other inflammatory and/or neurologic disorders which may or may not have autoimmune etiologies. PIMMCs currently in effect are presented in Appendix X: List of PIMMCs.

### Dose Escalation Criteria

*Include only if applicable, or delete*

*Describe the dose escalation criteria for the cohort studies and the enrollment of sentinel subjects.*

#### Cohort Studies

*Include only if applicable, or delete*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

For cohort studies that do not require SMC meeting to advance to the next cohort, the Principal Investigator(s), DMID Medical Monitor and DMID Medical Officer will confirm that cohort data has not met pre-defined objective criteria.

Criteria 1: Clinical (AE)

Criteria 2: Laboratory (AE)

Criteria 3: PK data, if applicable

If dose escalation criteria are not met, the SMC will review the study data and provide guidance on how to proceed. The dose escalation data reviews will include blinded data but if necessary for safety considerations, unblinding of certain results can occur.

#### Sentinel Subjects

*Include only if applicable, or delete*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

For studies with sentinel subjects that do not require SMC meeting to enroll the remaining subjects in the same cohort or arm, the Principle Investigator(s), DMID Medical Monitor and DMID Medical Officer will confirm that sentinel subject(s) data has not met pre-defined objective criteria.

Criteria 1: Clinical (AE)

Criteria 2: Laboratory (AE)

Criteria 3: PK data, if applicable

If the predefined criteria for sentinel subject are met, the SMC will review the study data and provide guidance on how to proceed. The sentinel subject data reviews will include blinded data but if necessary for safety considerations, unblinding of certain results can occur.

## Reporting Procedures

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

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

*Include statement that all relevant follow up SAE information must be provided to the sponsor within 24 hours of becoming available to the study site.*

*Include language that SAEs may be reported post trial if related to the study - these reports will be regarded as a trial report.*

*Include specific details of reporting procedures for:*

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

*(Refer to Report of Council for International Organizations of Medical Sciences [CIOMS] Working Group V, Appendix 8 for examples of narrative information for AE reports.)*

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

* *Time frame for collecting and reporting AEs and SAEs.*
* *Identification of additional protocol-specific parameters (safety issues) that need to be reported in an expedited fashion – either to the investigator, sponsor, or regulatory body.*
* *Document AEs from the first study intervention, Study Day X, through Study Day X.*
* *Document SAEs from the first study intervention, Study Day X, through Study Day X.*

### Reporting Serious Adverse Events

*Include specific details of reporting SAEs, including any specific reporting procedures for deaths and life-threatening events. Identify which forms should be completed, how reports will be distributed, and what follow-up is required, including surveillance period for follow-up.*

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

**Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:**

**DMID Pharmacovigilance Group**

**Clinical Research Operations and Management Support (CROMS)**

**6500 Rock Spring Dr. Suite 650**

**Bethesda, MD 20817, USA**

**SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)**

**SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)**

**SAE Email Address: PVG@dmidcroms.com**

In addition to the SAE form, select SAE data fields must also be entered into the DCC system. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the ISM (as deemed necessary) when they are provided to the DMID Pharmacovigilance Group. The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site principal investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site principal investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

### Regulatory Reporting for Studies Conducted Under DMID‑Sponsored IND

*Select the appropriate template language for studies conducted under DMID-Sponsored IND or studies not conducted under DMID-Sponsored IND.*

*Modify the template language, as appropriate, to include reporting to regulatory agencies other than the U.S. FDA.*

 *The acronym SUSAR typically means "suspected, unexpected, serious adverse reaction," although the exact order of the words may vary, such as "serious unexpected suspected adverse reaction" and "suspected serious unexpected adverse reaction." The term is often used to identify serious adverse reactions that require reporting to a regulatory authority. The specific requirements for reporting would depend on the regulatory agency(ies) involved.*

*Some international examples of this term are by the Medicines and Healthcare Products Regulatory Agency (United Kingdom), in Part 5 (Regs 32, 33, 34 and 35) of the Medicines for Human Use (clinical Trials) Regulations 2004: SI 2004/1031 and the European Union in the Directive 2001/20/EC of the European Parliament and the Council of the European Union relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.*

*Reference:*

*21 CFR Part 312.32*

*21 CFR Part 812.150*

*www.mhra.gov.uk*

Following notification from the site Principal Investigator or appropriate sub-investigator, DMID, as the IND sponsor, will report any suspected unexpected serious adverse event. DMID will report an AE as a suspected unexpected adverse event only if there is evidence to suggest a causal relationship between the study intervention and the AE. DMID will submit an IND safety report to the FDA and will notify all participating site Principal Investigators (i.e., all Principal Investigators to whom the sponsor is providing drug under its IND(s) or under any Principal Investigator’s IND(s)of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor’s initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as “not related” to study product(s), will be reported to the FDA at least annually in a summary format.

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

The Suspected Unexpected Serious Adverse Reaction (SUSAR) report is equal to an IND Safety Report. The difference is the regulatory agency and the country(ies) the study is conducted in.

For studies conducted in Europe or the United Kingdom, the IND safety report called SUSAR will be submitted on a CIOMS form. The FDA will accept the CIOMS format as well.

If the US IND holder conducts studies internationally, the sponsor is required to submit both SUSAR and IND safety reports (CIOMS form, 3500A).

### Regulatory Reporting for Studies Not Conducted Under DMID‑Sponsored IND

*If a study is not being conducted under an IND, it may be appropriate to name alternative ways to report AEs (e.g., MEDWATCH, VAERS). DMID should be copied simultaneously when an alternate method of reporting is utilized.*

*If applicable, keep or delete.*

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

### Reporting Other Adverse Events

*If applicable, keep or delete.*

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

### Reporting of Pregnancy

*If applicable, keep or delete*

*State the study pregnancy-related policy and procedure. Pregnancy is not an AE, but is a collectable event. Include mechanisms for reporting to sponsor, IRB/IEC, and others as applicable. Provide appropriate modifications to study procedures (e.g., discontinuation of study product while continuing safety follow-up, following pregnant women to pregnancy outcome).*

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

*Refer to ICH E6, Section 6.8*

*(https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf)*

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

AEs will be assessed, and followed from initial recognition of the AE through end of the protocol defined follow-up period.

SAEs will be followed up through resolution even if duration of follow-up goes beyond the protocol-defined the follow-up period.

Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

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

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

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

*Define the circumstances in which abnormal laboratory values will be reported as AEs/SAEs. Generally, in healthy people, a grade 3 abnormality is an SAE. In sick populations, define in terms of a change from baseline and disease progression.* *Include specific details of the protocol-specific reporting procedures, including which forms should be completed, how reports will be distributed, and what follow-up is required.*

## Halting Rules

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

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

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

*Types of halting rules include:*

***Study Halting Rules***

*The protocol should define study halting criteria for the clinical trial and describe the methods and responsibilities for making decisions about dosing of subjects and stopping of the clinical trial. In the case of multicenter trials it is particularly important to define processes for immediate communication across sites. Study halting criteria are written so that individual events will lead to the stopping of dosing and enrollment until a safety data review by an independent safety committee (SMC or DSMB) can occur. These criteria must be written in a clear and objective manner so that the data center can program the criteria to monitor and immediately notify the study team when a study halting criteria has been met. Study halting criteria are events that would warrant immediate interruption of dosing as the potential risk to subjects is too great to continue without a thorough investigations prior to proceeding.*

***Dose Escalation Halting Rules***

*Dose escalation halting criteria should be pre-specified in the protocol and will be used to identify and mitigate the risk of progressing to a subsequent cohort. Administration in the next cohort should not occur before subjects in the previous cohort have been treated and data/results from those subjects are reviewed in accordance with the protocol.*

***Individual Halting Rules***

*Individual halting rules are specific criteria that would result in an individual subject to be discontinued from further dosing.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

### Study Halting Criteria

*List safety finding(s) that would discontinue study intervention. Delete if not applicable.*

 *The study will be halted if:*

 *1.*

 *2.*

*The study may also be suspended (subject enrollment and/or study interventions suspended) because of safety findings, such as an SAE or an overall pattern of symptomatic, clinical, or laboratory events that the DMID or the Safety Oversight Committee consider associated with the study product. These may appear minor in terms of individual events, but might collectively represent potential concern for safety.*

*The DMID Medical Monitor may stop enrollment and/or administration of study product if AEs that meet the halting criteria are reported.*

### Individual Halting Criteria

*List safety finding(s) that would discontinue study intervention in an individual. Delete if not applicable.*

 *The study intervention will be discontinued in an individual if:*

*1.*

 *2.*

## Safety Oversight (ISM, SMC, DSMB, as applicable)

*In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety in the study.* [*Refer to NIAID Policy on Data and Safety Monitoring Board (DSMB) Operations*](http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Documents/dsmbpolicyv5.pdf)*.*

*State who is responsible for safety oversight, i.e., ISM, SMC, or DSMB. For clarity and consistency, select the language appropriate to the committee being used (a DSMB or SMC).*

*For safety committees, include, as appropriate, pre-arranged time points for meeting (e.g., enrollment milestones, prior to next stage in protocol) and state which safety outcome measures will be monitored.*

*When an ISM is required, Example text:*

### Independent Safety Monitor (ISM)

For certain clinical trials, DMID will require an Independent Safety Monitor (ISM) to be assigned for each study site and the requirement for an ISM will be specified in the protocol. An ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. The ISM will review SAEs in real time and other AEs as needed and provide an independent assessment to DMID.

*When an ISM is not required, Example text:*

**For this clinical trial an ISM is not required**.  However, at each participating site, **upon DMID Medical Monitor request,** the principal investigator (PI) will identify a physician with relevant expertise, to act as a Secondary Medical Assessor (SMA). The SMA will examine a subject and/or medical records and provide a medical assessment (or second medical opinion) to the DMID of the safety event in question. The PI will send to the DMID MM, a summary of the event and include the PI and SMA assessments.

Note: In the case that DMID has requested this type of evaluation multiple times, DMID may request the site(s) identify an ISM to assist DMID with safety oversight.

### Data and Safety Monitoring Board (DSMB)

*Example text:*

Safety oversight will be conducted by a DSMB that is an independent group with expertise to interpret data from this study and will monitor subject safety and advise DMID. The DSMB members will be separate and independent of study personnel participating in this study and should not have scientific, financial or other conflict of interest related to this study. DSMBs must consist of at least three voting members, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise.

The DSMB will operate under the rules of a DMID-approved charter that that defines the data elements to be assessed and the procedures for data reviews and will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs.  The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time.

As defined in the charter, the DSMB will review data at specified times during the course of the study for subject and overall study progress, and will conduct ad hoc reviews as appropriate when a halting rule is met or for immediate concerns regarding observations during this study.

*Example Text:*

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

**OR**

Additional data, interim statistical reports, or the unblinding of a treatment assignment may be requested as deemed necessary for the DSMB review of subject safety or any concerns with the study. After each meeting, the DSMB will make recommendations to DMID whether the study (or intervention for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be modified and then proceed, or be terminated.

### Safety Monitoring Committee (SMC)

*Example text:*

An SMC comprised of individuals independent of the study, with relevant expertise, to advise DMID and the study investigators, will be established by DMID. SMC members will be separate and independent of study personnel participating in this study and should not have scientific, financial, or other conflict of interest related to the study. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this study. The SMC will operate under the rules of a DMID-approved charter. DMID or the SMC chair may convene the SMC at specified times during the course of study as defined in the SMC Charter or on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of the study.

After each meeting the SMC will make recommendations to DMID whether the study (or intervention for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be modified and then proceed, or be terminated.

***OR***

This clinical study will utilize an SMC, which is an independent group of experts that advises the DMID. The primary responsibility of the SMC is to monitor subject safety. The SMC is external to the DMID and comprises at least 3 voting members. The SMC will consist of members with appropriate phase 1 study expertise to contribute to the interpretation of the data from this trial. Its activities will be delineated in a SMC charter that will describe the membership, responsibilities, and the scope and frequency of data reviews. The SMC will operate on a conflict-free basis independently of the study team. The DMID or the SMC may convene ad hoc meetings of the SMC according to protocol criteria or if there are concerns that arise during the study.

As defined in the charter, the SMC will review data at specified times during the course of the study for subject and overall study progress, and will conduct ad hoc reviews as appropriate when a halting rule is met or for immediate concerns regarding observations during this study.

# Human Subjects Protection

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

## Institutional Review Board/Independent Ethics Committee

*Modify the template language as appropriate for the study. The language should indicate if the study has a single IRB or multiple IRBs.*

*References:*

*45 CFR 46*

*21 CFR 56*

*OHRP: Register IRBs and Obtain FWAs*

*FDA Guidance: Centralized IRB Review Process in Multicenter Clinical Trials (2006)*

*NIH Policy: Use of Single IRB for Multi-site Research (2016)*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

Each site principal investigator will obtain IRB approval for this protocol to be conducted at his/her research site(s), and send supporting documentation to the DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. The IRB/IEC must be registered with OHRP as applicable to the research. DMID must receive the documentation that verifies IRB/IEC-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects, and may cease if annual review is no longer required by applicable regulations and the IRB/IEC. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

***(For U.S. multi-centered studies using a single IRB, add the following):***

A single IRB of record, *(name of IRB)*, will be accountable for compliance with regulatory requirements for this multi-centered study, at participating sites. [*Specify: Written agreements between the single IRB and participating sites; A written policy*] will be required. The [*specify: agreements; policy*] will set forth the specific responsibilities of the IRB and each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the DMID or regulatory authorities upon request.

***(For minors in the study, add the following):***

The IRB/IEC will determine that adequate provisions are made for soliciting the permission of each child's parent(s) or legal guardian, including whether permission of one parent is sufficient for research or whether permission is to be obtained from both parents. ***(For minors reaching age of majority during participation in the study, add the following):*** The IRB/IEC will determine how consent from subjects will be obtained when participation in the study is ongoing, and the subject has reached the age of majority.

## Informed Consent Process

*Informed consent, or IRB/IEC approved waiver of consent or altered consent process, is required for all subjects participating in a DMID-sponsored clinical trial, in compliance with applicable regulations and guidelines, including but not limited to 45 CFR 46, 21 CFR 50, 56, 312/812 for FDA-regulated studies, and ICH E6 Guidelines. Prior to the beginning of the trial, the investigator should have the IRB/IEC’s written approval, favorable opinion of the written informed consent form(s), and any other written information to be provided to the subjects.*

*References:*

*45 CFR 46*

*21 CFR 50*

*21 CFR 56*

*Describe procedures for obtaining and documenting informed consent of volunteers. Identify different consent forms that are needed for the study (e.g., screening, study participation, future use of specimens, extra blood for additional research, parental/legal guardian permission form, and assent form for minors). If applicable, describe provisions for special populations, e.g., non-English speakers, illiterate individuals, vulnerable populations). If a separate screening protocol and consent will be used it should be stated here. Clinical consent forms that are needed specifically for the clinical trial (e.g., screening for human immunodeficiency virus, plasmapheresis, anesthesia) should also be listed here.*

*Describe the consent process for providing the study subject with information about data sharing, either specific information about a study subject’s individual-level data and/or study metadata and whether through unrestricted or controlled-access repositories, as applicable.*

*For studies that are subject to the requirements of the FDA regulations, the informed consent documents should meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25(a), each of the six elements of 21 CFR 50.25(b) that is appropriate to the study, and 21 CFR 50.25 (c) for applicable clinical trials. IRBs have the final authority for ensuring the adequacy of the information in the informed consent document.*

*Note: Provide each institution with an informed consent form template for subject participation. Each institution may format the consent form according to its institutional guidelines.*

*Written documentation of informed consent is required prior to starting an intervention or administering study product. Once signed, a copy of the informed consent document will be given to the subjects for their records.*

*When the consent interview is conducted in English, the consent document should be in English. When the study subject population includes non-English speaking people or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB should require a translated consent document to be prepared and assure that the translation is accurate.*

***Optional Example text****: customize* ***with protocol-specific text****, as applicable*

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual’s trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The explanation will be organized, and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential subjects face-to-face. The key information about the purpose of the study, the procedures and experimental aspects of the study, risks and discomforts, any expected benefits to the subject, and alternative treatment will be presented first to the subject.

Subjects will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject’s participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures.

Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the subject’s participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The extent of the confidentiality of the subjects’ records will be defined, and subjects will be informed that applicable data protection legislation will be followed. Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject’s original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject is authorizing such access.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject’s identity will remain confidential. Subjects will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this research trial, and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved and subjects will be asked to read and review the consent form. Subjects must sign the informed consent form prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the informed consent form will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site Clinical staff may pre-screen via chart review and refer potential subjects to the Research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site principal investigator to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all informed consent forms that they sign.

### Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

*If applicable, keep or delete.*

*Modify the template language as appropriate for assent of minors in this study. Describe any specific requirements for assent of minors in this study.*

*Children are considered to be vulnerable persons who, as research subjects, require additional protections beyond those afforded to competent adult persons. Safeguards are included in the federal regulations 45 CFR 46 subpart D, 21 CFR 50 subpart D for FDA regulated studies, and ICH E6 Guidelines.*

*For FDA-regulated studies, waiver of consent/parental permission is not applicable for use of the test article. For research in which 21 CFR Section 50.54 applies, additional federal panel of experts review must be conducted.*

*When a study includes subjects who may be enrolled in the trial only with the permission of the subject’s parent/legal guardian (e.g., young age of minors or those who are cognitively impaired), the subjects should be informed about the trial to the extent compatible with their understanding. If capable, the minor should sign and date the assent form. An IRB-approved assent form, describing (in simplified terms) the details of the study intervention/product, study procedures, and risks may be used. Assent forms do not substitute for the consent/permission form signed by the subject’s legally authorized representative. Any minor assent form must be linked to an IRB-approved parental permission form that is signed by the parent/ legal guardian of the minor child authorized per state/local regulations.*

***Optional Example text****: customize with* ***protocol-specific text****, as applicable*

Investigators will follow IRB/IEC requirements for enrollment of minors in this study. Minors will be informed about the study to the extent understandable to the minor. Investigators or designee will conduct the consent process with the parent(s)/legal guardian, who will be given an IRB/IEC-approved permission form, which may be referred to as a consent form, to read, review, and sign prior to any study procedures. The parent(s)/legal guardian will be provided meaningful study information including a statement that this study involves research, the child may not benefit from the trial, and the study involves risk. The required elements will be clearly presented, including the purpose of the study, the experimental procedures, the potential risks and discomforts, known adverse effects, possible benefits of the study for the subject, alternative therapies that may be beneficial, use and disclosure of private information, and other elements that are part of obtaining proper consent. The subject’s parent(s)/legal guardian will be allowed sufficient time to discuss questions with the investigator.

The investigator or designee will describe in simplified terms the details of the study intervention/product, study procedures, risks and discomforts, benefits, and other consent elements, as appropriate. A separate IRB/IEC-approved assent form will be used for the minor, who may read and sign the form, or have it read to him/her prior to participation in study procedures. Assent may be obtained verbally or waived when approved by the IRB/IEC as appropriate to age. If a child declines to participate in the trial when assent is required by the IRB/IEC, the subject will not be enrolled even though the parents have provided permission.

To ensure that consent is an ongoing process throughout the subject’s participation in the study, the investigator and staff will review information as needed with the subject and the parent(s)/legal guardian and confirm that assent and permission are continuing. The permission and assent documents will be updated when new information is acquired that may impact the decision to continue in the study, and the subject’s assent and the parent(s)/legal guardian’s permission will be obtained, as applicable.

***(For minors reaching age of majority during participation in the study, add the following):*** The subject who reaches the age of majority will be consented at the next visit prior to study procedures. When no further visits are planned but the subject’s participation is ongoing, the consent will be obtained via IRB/IEC-approved processes.

### Other Informed Consent Procedures

*Special Populations*

*If applicable, describe provisions for special populations, e.g., illiterate individuals, vulnerable populations).*

*Use of a Legally Authorized Representative (LAR) - Modify the template language as appropriate for the study.*

*Illiterate Subjects - Describe in detail how illiterate subjects will be consented*.

*If the protocol will enroll vulnerable subjects who cannot freely provide consent for oneself, consider requesting a Human Subjects Protection Specialist (HSPS) consultation.*

*Include text below as applicable:*

**Use of a Legally Authorized Representative (LAR)**

Potential subjects for this study are adults but may be unable to provide legally effective informed consent due to their health status (*i.e*., dementia, intubated, sedated). The subjects may be enrolled in the study if consent is obtained from the LAR. The investigator will be familiar with the local IRB/IEC policy regarding the priority list of LAR and whether enrollment in a study is permitted by an advanced directive *(e.g*., living will, durable power of attorney for proxy consent). Additionally, subjects will be informed about the study to the extent compatible with the person’s understanding and assent may be obtained when applicable, and enrollment declined if the subject refuses participation.

If a LAR originally provides legally effective informed consent and the subject’s condition improves, the subject will also be informed about the study as soon as is feasible and will be re-consented. The subject may continue in the study only if the subject’s consent is provided.

**Illiterate** **Subjects**

If illiterate**,** subjects will be consented according to the following procedures:

**Human Genetic Testing**

*Describe the consent process for providing the study subject with information about data sharing. Modify the template language to provide specific information about how a study subject’s individual-level data and study metadata will be shared and whether through unrestricted or controlled-access data repositories. Consider sample text from the NIH/NHGRI,* [*Informed Consent for Genomic Research*](https://www.genome.gov/27026588/informed-consent-for-genomics-research/)  *<*[*https://www.genome.gov/27026588/informed-consent-for-genomics-research/*](https://www.genome.gov/27026588/informed-consent-for-genomics-research/) *>.*

The rights and privacy of human subjects who participate in genomic or phenotypic research studies will be protected at all times. The consent process, including relevant language in the ICF will provide an explanation of the potential risks to the individual study subjects and their families. The consent will include whether individual subject data will be shared through openly accessible public (unrestricted) databases or NIAID-designated controlled access data repositories. Clinical metadata, genomic, or other datasets or a subset of the clinical and other metadata that may potentially identify human subjects will not be released in unrestricted databases. Subjects will be informed that the evolution of genomic technology and analytical methods raises the risk of re-identification, even when specimens are de-identified.

## Consent for Future Use of Stored Specimens and Data

*Specify whether future use specimens from residual samples (after the protocol assays are completed), will be stored de-identified or with coded (identifiable)labels.*

*Specify whether extra amounts or types of specimens are to be obtained for other research not specific to the protocol. Describe whether an IRB will review the studies with the extra specimens. Describe the process for informed consent to store, share, and use specimens not collected specifically for the current study; include descriptions for all basic elements of consent.*

*Include the provisions for consent and the options that are available for the volunteer to agree to the future use of his/her specimens. Specify the location(s), if other than the clinical site, where specimens will be maintained, how long they will be maintained, and who will have access to the specimens and codes. Identify to whom specimens will be released and for what kind of research. Describe whether or not specimens will be identifiable and whether coded, bar-coded, or delinked (anonymized) and if an IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens. Explain whether subject’s will or will not be contacted for secondary research use. Include a statement that genetic testing will not be performed, if required by the IRB.*

*Identify whether stored specimens may be used for future genomic research. Refer to the NIH Genomic Data Sharing (GDS) Policy and the NIAID/DMID Data Sharing and Release Guidelines for further information.*

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Residual samples/specimens are those that are left over after protocol-specified testing and this study has been completed. Subjects will be asked for permission to keep any remaining (residual) specimens (serum and PBMCs) derived from venous blood samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. These residual specimens will be stored coded indefinitely at <*Specify: name of facility, a DMID-contracted storage facility, or for general location: a central clinical storage facility with IRB oversight*>. Specimens may be shared with <*Specify if known where the specimens are to be sent, e.g. name of industry, specific research labs, etc, or investigators at the participating site and with other investigators at [specify:U.S. or international] institutions>*. The recipients of specimens will be informed that these specimens have a NIH certificate of confidentiality. The information provided to a recipient <*Select: will not contain direct identifiable information, will contain identifiable information for contacting the subject for consent>*. <*For specimens collected without a specific purpose, add:* Use of the specimens will require review by an IRB.>

**Non-protocol Extra Samples**

Additional venous blood samples for serum and PBMC specimens will be collected during this study specifically for the purpose of <*specify: concurrent research or future research use*>, from subjects who consent to collection of those specimens. <*Explain whether a separate consent form or informed consent within this study consent includes collection of extra samples*.> <*Specify the type, amount, and frequency or number of times that blood, or specimens, are collected. For example:* An extra 10 mL venous blood sample will be collected four times.> <*Describe types of known or anticipated research, e.g.* Research <*will/may*> include *detailed systems biology analyses, non-traditional immune assay development, assessing innate immune factors*>. These samples/specimens collected during this trial specifically for the purpose of future research will be stored coded indefinitely at <*Specify: name of facility, a DMID-contracted storage facility, or for general location: a central clinical storage facility with IRB oversight*.> Specimens may be shared with <*Specify if known where the specimens are to be sent, e.g. name of industry, specific research labs, etc, or investigators at the participating VTEU site and with other investigators at [specify: U.S. or international] institutions>*. The recipients of specimen will be informed that these specimens have a NIH certificate of confidentiality. The information provided to a recipient <*Select: will not contain direct identifiable information, will contain identifiable information for contacting the subject for consent>*. <*For specimens collected without a specific purpose, add:* Use of the specimens will require review by an IRB.>

Residual specimens will be available upon the completion of this trial. Extra samples/specimens collected during this study may be requested from DMID and shipped from the DMID CMS while this study is ongoing or after the study, after IRB review.

There are no benefits to subjects in the collection, storage and subsequent future use of their samples/specimens. Future use samples/specimens will not be sold or used directly for production of any commercial product. <*Remove if not applicable:* No genetic tests will be performed on samples/specimens.> Each sample/specimen will be encoded (labeled) only with a barcode and a unique tracking number that connects to a code key at the study site. Restricted access to the code key is maintained by the principal investigator to protect subject confidentiality. Reports from future research studies performed using subjects’ samples/specimens will NOT be kept in their health records.

Subjects may be given the option to decide if they want their **residual** specimens to be used for future research or have these specimens destroyed at the end of this trial. The subject’s decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to the future use of **residual** specimens and subsequently changes his/her decision, any data from a previously collected specimen may still be used for future research.

**When Protocol Purpose Includes Extra Samples**

Subjects will **not** be given the option to decide if they want extra samples/specimens collected during this trial **specifically for the purpose of future research**. These samples/specimens are protocol-required; thus, subjects will be asked to consent to the future use of these samples/specimens as a condition of their study participation.

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

*It is the policy of NIH per the NIH Revitalization Act of 1993 and NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects 1998, that women, members of minority groups and their subpopulations and children must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. If the study intends to exclude any special populations, justify their exclusion in the context of the study design.*

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Children and/or women will be excluded from this trial for [specify reasons].

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Special populations, e.g., non-English speakers, children, illiterate or non-writing individuals and vulnerable populations will not be enrolled in this study [specify reasons].

## Subject Confidentiality

*Per DMID, the sponsor’s requirements and CFR 312.58 and CFR 312.68 (for FDA-regulated studies), include procedures for maintaining subject confidentiality, any special data security requirements, record retention per the sponsor’s requirements including a description of those entities having access to records, such as DMID/Sponsor/IND representatives, IRB/REC, monitors, and governmental/regulatory agencies such as the FDA or OHRP.*

*For genomics-related studies where a genome-wide association study (GWAS) or genome sequencing is applicable, add the following language: “Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and re-identified data could potentially be used to discriminate against or stigmatize participants, their families, or groups. In addition, there may be unknown risks.”*

*Note: If only sequencing the organism, GWAS does not apply.*

*Reference: NIH Guidance for Consent for Future Research Use and Broad Sharing of Human Genomic and Phenotypic Data Subject to the NIH Genomic Data Sharing Policy.*

***Optional Example text****: customize with* ***protocol-specific*** *text, as applicable*

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject’s clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

## Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject’s consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, *or* for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

## Costs, Subject Compensation, and Research Related Injuries

*The description should be clear as to the extent of cost to participate, compensation to subjects, and research related reimbursement that will be made available by the site. The Terms of Award, other agreements should be consistent with language tailored specifically for this study.*

*Specify how the site will handle injuries that occur during the study and any applicable treatment coverage (e.g., clinical trial insurance, indemnification by pharmaceutical partner). Include any requirements by the site or any local requirements.*

*Note: NIAID is prohibited from providing indemnification by 31 U.S.C. § 1341, the Anti-Deficiency Act.”*

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject’s insurance or third party. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB’s policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH to the subject, [*insert language according to overriding agreements, or insert: or by the participating site*] for any injury suffered due to participation in this trial.

# Statistical Considerations

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

*Frame the objectives/goals of the study in terms of statistical hypothesis testing and/or estimation; provide the statistical and clinical justification for the sample size with sufficient detail to permit verification.*

*Describe the analysis populations and planned interim and final analyses for the primary and secondary study endpoints.*

*Retain required elements but customize, as necessary, to meet the requirements of the study or to improve organization and clarity*

## Study Hypotheses

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

*If the study does not include formal hypothesis testing, specify the precision that is required for estimation of key study outcomes, if applicable.*

*State if the study is exploratory (i.e., is generating a new hypothesis rather than confirming the existing hypotheses) or if there is no hypothesis to be formally tested.*

## Sample Size Considerations

*Provide the rationale for the sample size, including any statistical and/or clinical justification. State if the sample size was not chosen based on any statistical criterion (e.g., if the sample size was not chosen based on any statistical or clinical justification, but rather on logistical or feasibility reasons). If the study is a Phase I study, state briefly the rationale for the sample size (e.g., sample size was chosen based on previous experience with similar Phase I studies). Provide all information needed to validate the calculations, and to judge the feasibility of enrolling and following the necessary numbers of subjects.*

*Specify all of the following for the primary outcome measures, and for any secondary outcomes for which sample size calculations are performed:*

* *Outcome measure used for calculations (almost always the primary variable).*
* *Test statistic or rule used to decide whether to reject the null hypothesis in favor of the alternative hypothesis.*
* *Null Hypothesis: Use numerical values to express the null hypothesis of the treatment being ineffective. For example: an absolute difference in response rates between arms of zero.*
* *Effect size or alternative hypothesis – a difference that the investigator believes to be both clinically relevant and plausible – preferably supported by historical or pilot data.*
* *Type I error rate (also known as significance level) – what risk is acceptable for concluding that the treatment is effective when in reality it is ineffective as specified in the null hypothesis?*
* *Type II error rate (equal to one minus statistical power) – what risk is acceptable for concluding that the treatment is ineffective when in reality it is effective as specified in the alternative hypothesis? For each study arm, the assumed proportion for a dichotomous outcome, standard deviation for a continuous outcome, or median survival for a time-to-event outcome, justified and referenced by historical data.*
* *Any other parameters relevant to the design and sample size calculations such as assumed dropout rates, withdrawal rates, cross-over to other study arms, missing data rates, etc. justified and referenced by historical data.*
* *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.*
* *If not all randomized subjects will be included in the analysis population for the primary analysis, describe the required adjustment to the sample size to maintain statistical power.*
* *Approach to handling withdrawals and protocol violations, i.e., whether subjects will be included in the “intent-to-treat” population.*
* *Statistical method used to calculate the sample size, with a reference for the method and for any software utilized.*
* *Method for adjusting calculations for planned interim analyses, or any other planned adaptations to the study design, 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*.

## Treatment Assignment Procedures

*This section should describe the methods of assigning subjects to study group including randomization procedures (if applicable to the study design). It should include a description or a table that describes how study subjects will be assigned to study groups, without being so specific that 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).*

### Randomization Procedures

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

### Masking Procedures

*State whether the treatment arms will be masked if more than 1 treatment. Plans for maintaining appropriate masking for the study should be discussed. Refer to unmasking procedures described in the Manual of Procedures.*

## Planned Interim Analyses

*Include if applicable, or delete.*

*Any planned interim analyses or release of endpoint data should be pre-specified in the protocol, including but not limited to, formal comparison of safety or efficacy data between treatment arms. For example, state if accumulated study data for a study that is not yet complete will be reviewed by a DSMB or similar committee. If interim analyses will be reviewed by a DSMB or similar committee, describe its composition, how often it will meet, and that it advises DMID.*

*If data will be released to the study sponsors before the study is complete, describe if the data will be used to make decisions about the conduct of the current trial, or will only impact the design of future studies. For any planned interim analysis or data release, describe the level of blinding, the timing relative to the completion of enrollment and follow-up assessments, and to whom the information will be provided and for what purpose. Describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing.*

*All interim analyses must follow the DMID Expanded Distribution of Clinical Research Endpoint Data Policy.*

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

### Interim Safety Review

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

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

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

### Interim Immunogenicity or Efficacy Review

*State which immunogenicity or efficacy outcome measures will be monitored and the frequency of monitoring.*

*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 immunogenicity or efficacy event rates and the associated number of participants that would be enrolled).*

*Discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I and Type II error.*

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

## Final Analysis Plan

*Elaborate on primary analyses that underlie the sample size calculation in Section 10.2 and describe secondary analyses for the primary or secondary objectives or exploratory, if applicable.*

*More details can be provided in a separate statistical analysis plan (SAP)*, *written later but prior to performing any analyses, which must be submitted to the FDA before data base lock and allow the FDA 30 days to review. Refer to DMID Statistical Analysis Plans for DMID-Funded Clinical Trials Policy. Outline the primary features of the planned analyses [the details and supporting references can be relegated to the SAP].*

*Each study outcome should contribute to the analysis of a study objective and have a planned analysis associated with it. For secondary and exploratory endpoints, it may suffice to outline the graphical methods and/or tabulated summary statistics to be used in a descriptive analysis.*

*Plans must clearly define the analysis cohorts (e.g. “intent-to-treat”, “Per Protocol”, “Modified Intent-to-Treat” etc.), preferably with inclusion and exclusion criteria, and state clearly in which population each analysis should be performed, and the rationale for that choice.*

*Describe the procedures to account for missing, unused, or spurious data. It is important to assess the sensitivity of the results to the assumptions and choice of method for handling missing data.*

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

*If a review committee(s) will be used to adjudicate analysis populations or determine endpoint cases, describe whether these issues will be adjudicated independently, and the timing relative to study unblinding.*

# Source Documents and Access to Source Data/Documents

*Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a DMID-sponsored, DMID-affiliated, or manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), DMID, 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.*

*Describe the source of data. If case report forms are used as source documents, identify what data will be recorded directly on the case report form (i.e. no prior written or electronic record of data).*

*References:*

*ICH E6, Section 4.9: Records and Reports*

*Source Documentation Standards for DMID Clinical Trials*

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate 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. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

# Quality Control and Quality Assurance

*Address the plans for local quality assurance and quality control.*

*(http://www.fda.gov/downloads/Drugs/Guidance/ucm073122.pdf).*

*All sites conducting research under DMID sponsorship are required to have a plan in place for assuring the quality of the research being conducted.*

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

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

[*Refer to the DMID Clinical Quality Management Policy, Guidelines, and Tools*](http://www.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/Pages/clinicalmgmt.aspx)*.You can access the DMID Quality Management Plan (QMP) documentation requirements and templates on the DMID-CROMS website at: http://www.dmidcroms.com.*

*The following DMID QMP documents are available on the DMID-CROMS website:*

* *DMID Quality Management Plan - Standard Operating Procedure.*
* *Quality Management Plan, version-controlled, template.*
* *Chart Review Tool, template.*
* *Regulatory File Review Tool, template.*
* *Quality Management Summary Report, template.*
* *Quality Management Plan Fact Sheet.*

Following a written DMID-accepted site quality management plan, each participating site(s) and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

# Data Handling and Record Keeping

## Data Management Responsibilities

*Refer to: http://www.fda.gov/ora/compliance\_ref/part11/.*

*Include instructions for special data-handling or record-keeping procedures required for maintaining subject confidentiality, any special data security requirements, and record retention per the sponsor’s requirements in this section.*

*Briefly describe steps to be taken to assure that the data collected are accurate, consistent, complete, and reliable and in accordance with ICH E6. The description should include reference to source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring. Details may be provided in a MOP, User’s Guide or other citable reference document.*

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

*Additional* ***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

## Data Coordinating Center/Biostatistician Responsibilities

*Describe responsibilities for data handling and record keeping as they specifically relate to the IND sponsor if applicable, the award site, clinical site, laboratory, and data coordinating center. Information should include the role in data collection, review of data, trial materials, and reports, as well as retention of source documents, files, and records. Describe coding dictionaries to be used and reconciliation processes (if applicable). At the end of the study, a copy of all datasets will be provided to DMID.*

*If data are to be generated in one location and transferred to another group, describe the responsibilities of each party.*

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study.

The data coordinating center for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

## Data Capture Methods

*Provide details regarding the type of data capture that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time of submission of CRFs.*

*Reference for electronic data capture:*

*21 CFR Part 11: Electronic Records; Electronic Signatures*

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) and reactogenicity will be collected on data collection forms by study personnel then entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the study data coordinating center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

## Types of Data

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

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Data for this trial will include clinical, safety, and outcome measures (e.g., clinical laboratory values, reactogenicity, and immunogenicity data).

## Study Records Retention

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

***Optional Example text****: customize with* ***protocol-specific******text****, as applicable*

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, laboratory test results, and study drug disposition records will be retained for 2 years after a marketing application is approved for the study product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the study product, until 2 years after the investigation is discontinued and the FDA has been notified. These documents will be retained for a longer period, however, if required by local regulations. ICFs for future use will be maintained as long as the sample/specimen exists.

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the site principal investigator when these documents no longer need to be retained. The participating VTEU sites must contact DMID for authorization prior to the destruction of any study records.

# Clinical Monitoring

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

*Site monitoring is conducted to ensure that the human subject protections, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the sponsor, ICH E6 and, when appropriate, regulatory guidelines.*

Site monitoring is conducted to ensure that the human subjects’ protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken, and will document site visit findings and discussions.

# Publication Policy

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

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

*Describe the procedures for compliance with the NIH Policy for Registration and Posting of study results on ClinicalTrials.gov.*

*References:*

*NIH Public Access Policy.*

*NIH Office of Extramural Research Grants and Funding.*

*National Library of Medicine’s PubMed Central.*

*The International Committee of Medical Journal Editors.*

*ClinicalTrials.gov.*

*Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA).*

*The following language may be used in the protocol:*

*Example text:*

Following completion of the study, the lead Principal Investigator is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine’s PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

* NIH Public Access Policy, http://publicaccess.nih.gov/
* NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov.

For this trial the responsible party is [*identify the responsible party*] which will register the trial and post results.

The responsible party [*plans / does not plan*] to request certification of delayed posting.

Refer to:

* Public Law 110-85, Section 801, Clinical Trial Databases
* 42CFR11
* NIH NOT-OD-16-149

# Literature References

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

*Examples:*

Journal citation:

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

Whole book citation:

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

Chapter in a book citation:

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

*A full listing of ICMJE style guidelines can be found at:*

*International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. JAMA. 1997;277:927-34.*

*You may also refer to:*

*http://www.nlm.nih.gov/bsd/uniform\_requirements.html.*

# Appendices

*(Note: If there is only one appendix document, Section 17 should be renamed to “Appendix.” If there are multiple documents, it can be left as “Appendices.”*

*Schedule of Events*

*Toxicity Grading Scales*

1. Schedule of Events

| Evaluation  | Screening/Enrollment Visit 1Day 1 | Visit 2 Day 5-9 (Test of Cure) | Visit 3Day 11-143(Testof Cure Results) | Unscheduled/ Early TerminationVisit5 |
| --- | --- | --- | --- | --- |
| Signed consent form | X |  |  |  |
| Confirmation of eligibility criteria | X |  |  |  |
| Medical history for assessment of specific symptoms that are potentially related to fluoroquinolone use as described in section 9, Assessment of Safety | X | X | X | X |
| Signs/symptoms | X | X |  | X |
| Concomitant medications | X | X |  | X |
| Sexual history  | X |  |  |  |
| Interim sexual history  |  | X | X | X |
| Targeted physical examination | X | X |  | X |
| Rapid urine βhCG pregnancy test (females) | X |  |  |  |
| Speculum examination (females) | X |  |  |  |
| Cervical swab for *N. gonorrhoeae* culture (females) | X2 | X2 |  |  |
| Cervical or vaginal swab for NAAT and *gyrA* assay (females)1 | X2 | X2 |  |  |
| Urethral swab for *N. gonorrhoeae* culture (males) | X2 | X2 |  |  |
| Urine specimen for NAAT and *gyrA* assay (males)1 | X2 | X2 |  |  |
| Throat swab for *N. gonorrhoeae* culture and NAAT and *gyrA* assay1 | X2 | X2 |  |  |
| Rectal swab for *N. gonorrhoeae* culture and NAAT and *gyrA* assay1 | X2 | X2 |  |  |
| Study intervention | X |  |  |  |
| Reminder to abstain from sexual intercourse or use condoms  | X |  |  | X5 |
| Reminder to bring partners in for treatment | X | X | X | X |
| Follow-up for test of cure results |  |  |  X4 |  |

1. G*yrA* assay required only if NAAT is positive.

2. Collect specimen at anatomic site of *N. gonorrhoeae* infection.

3. Follow-up for test of cure results will be by phone call.

4. For subjects *N. gonorrhoeae* culture negative and NAAT negative, no further follow-up required. Subjects who are *N. gonorrhoeae* culture positive or NAAT positive will be referred for standard of care treatment for *N. gonorrhoeae*.

5. Not required at the Early Termination Visit.

*Note: List the tests applicable to your specific protocol.*

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

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

**Biochemistry** – Sodium, potassium, chloride, urea, creatinine, glucose, uric acid, bicarbonate, amylase, lipase, albumin, total bilirubin, cholesterol, triglycerides, and creatine phosphokinase, *as appropriate for the study*.

**Urinalysis** – Protein and glucose, *as appropriate for the study*.

**Immunology** – *Specimen types for nonstandard laboratory assays*.

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

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

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

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

*Indicate volume of blood if frequent or large phlebotomies are part of the protocol over 2 months.*

1. TOXICITY TABLE

*Please note this appendix includes a severity/grading scale for clinical and laboratory adverse events.*

*Include only if applicable, or delete.*

*Modify the toxicity table as appropriate for the study. Include appropriate elements and adjust the values in the table as necessary to meet the needs of the study.*

*The sample toxicity table uses absolute values rather than increments of upper and lower limits of normal. Different laboratories have different cut-off values for normal rates, which are not static but change over time and are calibrated for the specific population. As such, there is no consistency for borderline values; the same value at one laboratory could be considered within the normal range and at another laboratory it could be considered a Grade 1 Adverse Event. In order to achieve consistency among sites, as well as among studies over time, the use of the absolute value is a better approach than upper and lower limits because the absolute values across sites, times, and methods will be the same.*

*The laboratory values used in the creation of this toxicity table come from a national laboratory company. These values change with time and as the population and methods of testing change. Because of the structure of this table, these laboratory values are starting points for protocol toxicology laboratory value discussions and decisions.*