PREFACE

This document is the DMID protocol template, which is required for DMID-sponsored clinical studies that pose greater than minimal risk to study subjects. Note that international trials, special populations (eg, children, pregnant women, elderly), and most procedures greater than a routine blood draw in an adult, are considered greater than minimal risk.

Minimal risk is defined by 45 U.S. Code of Federal Regulations (CFR) 46.102 (i) as follows:

> *"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."*

Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102

Note that instructions and explanatory text are indicated by italics and should be replaced in your protocol document with appropriate protocol-specific text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template.

Refer questions regarding use of this protocol template to the appropriate DMID Protocol Champion or Clinical Affairs Specialist.

TITLE

***DMID Protocol Number:**
**(Protocol number required – Protocol Champion must complete attached form)*

Sponsored by:
National Institute of Allergy and Infectious Diseases (NIAID)

DMID Funding Mechanism:

Industrial Support Provided by: *(if applicable)*

Principal Investigator:

***DMID Protocol Champion:**
**(Protocol Champion must complete attached form to generate Protocol Number)*

DMID Medical Monitor: *(if applicable)*

DMID Clinical Affairs Specialist: *(if applicable)*

DMID Regulatory Affairs Specialist: *(if applicable)*

Draft or Version Number: *(see DMID SOP for assigning version #s)*

Day Month Year
(Write out the month and use international date format, e.g., 23 January 2004)

This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

Statement of Compliance

Provide a statement that the trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) and the applicable regulatory requirements. An example is provided below:

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

- *U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)*
- *ICH GCP E6*
- *Completion of Human Subjects Protection Training*
- *NIH Clinical Terms of Award*

Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.
http://www.fda.gov/cder/guidance/959fnl.pdf
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html
http://cme.cancer.gov/c01/

SIGNATURE PAGE

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

Site Investigator:*

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; ie, if Investigational New Drug study, the individual who signs the Form FDA 1572.*

Table of Contents

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List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PI	Principal Investigator
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

This list should be expanded to include protocol-specific terms.

Protocol Summary

Limit to 1-2 pages
Put key words in boldface in Protocol Summary.

Title:

Population: *Include sample size, gender, age, general health status, geographic location*

Number of Sites: *3 or fewer, list here; otherwise, list only in an Appendix and in Section 1*

Study Duration: *State duration of study*

Subject Duration: *State duration per subject*

Objectives:
Include primary/secondary outcome measures and method by which outcome will be determined; copy objectives and clinical/laboratory outcome measures from the appropriate sections of the protocol. Include a sentence or two about efficacy and safety assessments.

Primary:

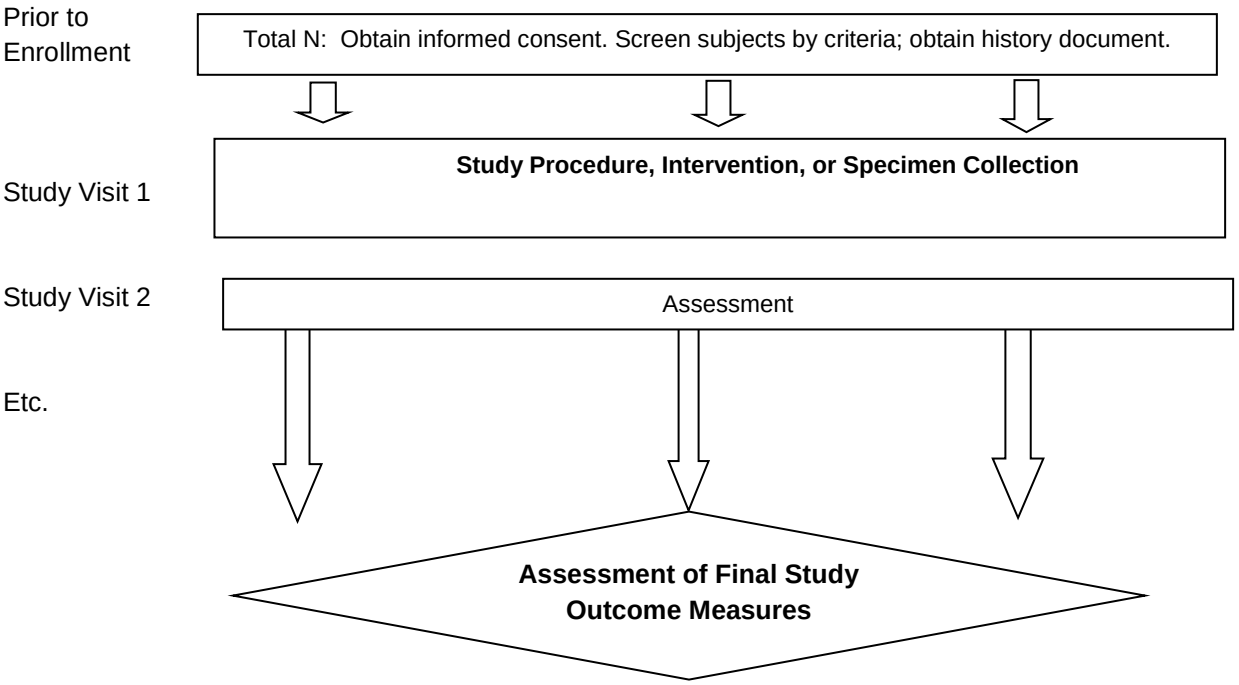
-

Secondary:

-

Schematic of Study Design: *Optional*

Example: Flow diagram



1 KEY ROLES

See ICH E6 GCP, Section 6.1
(http://www.fda.gov/cder/guidance/959fnl.pdf).

For questions regarding this protocol, contact *(insert name of appropriate DMID staff) at NIAID/DMID (insert contact information).*

Individuals: **DMID Representative**:

Principal Investigator: *Site investigator responsible for conducting the study*

Medical Monitor: (if applicable)

Provide the following information:
Name, degree, title
Institution
Address
Phone Number
Fax Number
E-mail

Institutions: *Study sites, Clinical laboratory (ies) and other medical or technical departments and/or institutions, as applicable.*

Provide the following information for each organization or institution:
Institution
Address
Contact Person
Phone Number
Fax Number
E-mail

Optional: *Consider listing, for example*
Major International Collaborators, if not included as site investigators
Protocol Data Manager, Epidemiologist, Statistician
DMID Clinical Affairs Specialist
Industry Representative(s)
Other individuals should be listed in a separate document (e.g., the Manual of Procedures) as appropriate

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

See ICH E6 GCP, Section 6.2 (http://www.fda.gov/cder/guidance/959fnl.pdf).

Include:

- *Hypothesis of study*
- *A summary of findings from studies that have potential significance to proposed study*
- *Discussion of important literature and data that are relevant to the study and that provide background for the study (reference citations are listed in Section 17)*
- *Applicable clinical, epidemiological or public health background or context of the study*

2.2 Rationale

Include a description of and justification for selection of study population.

2.3 Potential Risks and Benefits

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

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

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116

2.3.1 Potential Risks

Describe in detail any physical, psychological, social, legal, economic or any other risks to subjects that the PI foresees, as to each of the following:

- *Immediate risks*
- *Long range risks*
- *Rationale for the necessity of such risks*

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

2.3.2 Known Potential Benefits

*If the research is **beneficial** (i.e., the subject derives a direct benefit of either money or treatment from participating in the study), describe in detail any physical, psychological, social, legal, economic or any other benefits to subjects that the PI foresees, as to each of the following:*

3 OBJECTIVES

A detailed description of the objectives of the study is included in this section. These typically include:

- *Statement of purpose e.g., to assess, to determine, to compare, to evaluate*
- *Method of assessing how the objective is met, i.e., the study outcome measures*

4 STUDY DESIGN

See ICH E6 GCP, Section 6.4
(*http://www.fda.gov/cder/guidance/959fnl.pdf*).

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

- *A description of the design of the study to be conducted, including controls*
- *Approximate time to obtain specimens*
- *Expected duration of subject participation*
- *Description of subject participation (e.g., number of times and the frequency at which a subject will provide specimens)*
- *Methods for collecting specimens and data.*
- *A specific statement of the primary and secondary outcomes to be measured during the study (must be consistent with Study Objectives, as stated in Section 3)*
- *Identify structure for safety oversight per DMID guidelines (e.g., DSMB, SMC, and/or ISM, and DMID medical monitor). For DMID guidelines refer to: http://www.niaid.nih.gov/dmid/clinresearch/.*

5 STUDY POPULATION

The study population and inclusion/exclusion criteria should be clearly defined in this section of the protocol. This section should include a discussion of:

5.1 Selection of the Study Population

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

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

- *Provide the target sample size, including actual numbers to be enrolled.*
- *Include numbers of women, minorities and children expected to be recruited. If women, minorities and children will not be recruited, explain why not. Provide justification for Exclusion in Ethics/Protection of Human Subjects, Section 14.4. Refer to: http://grants2.nih.gov/grants/funding/women_min/women_min.htm*
- *Indicate from where the study population will be drawn (e.g., inpatient hospital setting, outpatient clinics, student health service). Where appropriate (single center studies), include names of hospitals, clinics, etc.*
- *Identify strategies for subject recruitment and retention.*
- *If subjects require screening: distinguish between screening subjects (e.g., discussing the study with them) vs. enrolling subjects (e.g., obtaining informed consent and obtaining samples). Note: if screening procedures are required for eligibility (e.g., laboratory tests), there must be a separate screening consent form in addition to the informed consent form for study participation.*

Eligibility Criteria

- *The eligibility criteria should provide a definition of subject characteristics required for study entry.*

Refer to OHRP Guidance Document, "Categories of Research that May be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure" Section: Research Categories, 2 (a) and (b).

http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm

- *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >32 years old as an inclusion criterion and also age ≤32 years old as an exclusion criterion).*
- *Select screening laboratory tests carefully, if they will be used.*

5.2 Inclusion/Exclusion Criteria

Provide a statement that subject must meet all of the inclusion criteria to participate in this study and then list each criterion.

Examples 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.

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 participation, pregnancy or breast feeding.

6 STUDY PROCEDURES/EVALUATIONS

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

6.1 Study Procedures

Specify the type of information the Principal Investigator will gather, along with the means for collecting and recording data.

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

Examples:

- *Specimen collection*
- *Medical history*
- *Concomitant medications*
- *Physical exam*
- *Counseling procedures.*

6.2 Laboratory Evaluations

6.2.1 Laboratory Evaluations/Assays

List all laboratory evaluations, if applicable. 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). Provide descriptions of assays to be performed.

6.2.2 Special Assays or Procedures

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

6.2.3 Specimen Collection, Preparation, Handling and Shipping

6.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

Special instructions for the collection, labeling, preparation, handling, and storage of specimens should be summarized in this section and clearly detailed in a Manual of Procedures. These instructions include required temperatures, aliquots of specimens, whether samples will be frozen, where they will be stored, how they will be labeled, etc. Include a discussion of long-term access and consent for future use. There may need to be additional considerations for biological specimens, especially biohazardous specimens that require special containment.

6.2.3.2 Specimen Shipment

State the frequency with which specimens are to be shipped and to what address. Include contact information for laboratory personnel. Include days and times shipments are allowed and any labeling requirements for specimen shipping. Also, any special instructions such as dry ice or wet ice or the completion of a specimen-tracking log are included. Place specific details in a Manual of Procedures and reference within the protocol.

7 STUDY SCHEDULE

Information outlined in the Study Schedule section should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix A and in Section 6.

The evaluations to be done must be listed individually in this section or alternatively, refer to the Schedule of Procedures/Evaluations (Appendix A).

Allowable windows should be stated for all visits.

7.1 Screening

This section must include instructions for obtaining signed informed consent.

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

7.2 Enrollment/Baseline, if applicable

If applicable, include discussion of evaluations/procedures necessary to assess or confirm whether a subject still meets the eligibility criteria and may be enrolled.

7.3 Follow-up and Final Visits, if applicable

Include discussion of evaluations/procedures. Discuss the sequence of events that should occur during the visit, if applicable. Include, as applicable, counseling, medications, adverse events, etc. Define when the final study visit should occur and any special evaluations or instructions to the subject.

7.4 Early Termination Visit, if applicable

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 participant is willing. Subjects may withdraw voluntarily from participation in the study at any time.

7.5 Criteria for Discontinuation or Withdrawal of a Subject (or a Cohort), if applicable

List possible reasons for discontinuation of a subject in this section (e.g., development of laboratory toxicities, study closure due to DSMB review, discretion of DMID).

8 ASSESSMENT OF OUTCOME MEASURES

Refer to ICH E6 GCP, Sections 6.7-6.8
(*http://www.fda.gov/cder/guidance/959fnl.pdf*).

8.1 Specification of the Appropriate Outcome Measures

8.1.1 Primary Outcome Measures

8.1.2 Secondary Outcome Measures

9 SAFETY ASSESSMENT AND REPORTING

Describe how any adverse events resulting from study procedures will be captured and reported. Describe time frame for reporting and collecting AEs and SAEs.

9.1 Definition of Adverse Event (AE)

See ICH E6 GCP, Section 1.2
(http://www.fda.gov/cder/guidance/959fnl.pdf)

An AE is any untoward medical occurrence in a subject undergoing a study related procedure and believed reasonably to be caused that study related procedure. Include time period of collection.

9.2 Definition of Serious Adverse Event (SAE)

See ICH E6 GCP, Section 1.50
(*http://www.fda.gov/cder/guidance/959fnl.pdf*).

An SAE is any untoward medical occurrence that:

- *Results in death.*
- *Is life-threatening. Any adverse experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).*
- *Requires in-patient hospitalization or prolongation of existing hospitalization.*
- *Results in persistent or significant disability or incapacity.*
- *Is a congenital anomaly/birth defect.*
- *An event that required intervention to prevent permanent impairment or damage.*
- *Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they might jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed above.*
- *In addition, protocols may specify other events that require reporting as SAEs (e.g., HIV infection, pregnancy). Include time period of collection.*

9.3 Reporting Procedures

Note: All clinical studies greater than minimal risk 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), how decisions will be made regarding determining relatedness and grading severity, which forms should be completed, how reports will be distributed and what follow-up is required.

Include specific details of reporting procedures for:

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

(Refer to Appendix 8 of the Report of CIOMS Working Group entitled, Current Challenges in Pharmacovigilance: Pragmatic Approaches, for examples of narrative information for adverse event reports.)

Subsequent review of serious, unexpected and related adverse events by the Medical Monitor, Safety Monitoring Committee, ethics review committee or IRB, the sponsor(s), or the FDA or relevant local regulatory authorities may also result in suspension of the trial.

9.3.1 Serious Adverse Event Detection and Reporting

Example text:

"For those events meeting the previously described definition of Serious Adverse Events, the completion of a Serious Adverse Event report form is required. Specific information on where to send this form is included in the Manual of Procedures for this study.

All serious adverse events will be recorded on the appropriate serious adverse event case report form, followed through resolution by a study physician, and reviewed by a study physician. Any AE considered serious by the Principal Investigator or Subinvestigator or which meets the aforementioned criteria must be submitted on an SAE form to PPD Development, NIAID's pharmacovigilance contractor, at the following address:

Medical Affairs/Pharmacovigilance
PPD Development
929 North Front Street
Wilmington, NC 28401-3331
SAE Fax line: 888 488-9697
SAE Fax line Non North America: 011-910-772-7069

Questions about SAE reporting can be referred to the SAE Hotline (available 24 hours a day/7 days a week) at 800-201-8725
The study clinician will complete a Serious Adverse Event Form within the following timelines:

- *All deaths, whether associated or not associated, will be recorded on the Serious Event Form and sent by fax within 24 hours of site awareness of the death.*
- *Serious adverse events other than death, regardless of relationship, will be reported via fax by the site within 72 hours of becoming aware of the event.*

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible. All SAEs will be followed until satisfactory resolution or until the Principal Investigator or Subinvestigator deems the event to be chronic or the patient to be stable.

ICH GCP 6, Section 4.11 require that an investigator notifies the sponsor, regulatory authority(ies) and the local IRB immediately of any serious adverse event, deaths, or life-threatening problems that occur in the study. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported in accordance with reporting requirements specified in the protocol. "

9.3.2 Reporting of Pregnancy

State the study's pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures.

9.3.3 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, but should be stated specifically. Consider the context of the study and adjust reporting procedures appropriately for the study population. 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.

9.3.4 Type and Duration of the Follow-up of Subjects After Adverse Events

See ICH GCP 6, Section 6.8 (http://www.fda.gov/cder/guidance/959fnl.pdf).

Describe how adverse events will be followed until resolved or considered stable. Specify procedures for reporting and follow-up of AEs that are consistent with the Schedule of Procedures/Evaluations.

9.4 Halting Rules

Describe safety findings that would temporarily suspend enrollment and/or intervention until a safety review is convened (either routine or ad hoc), the objective of which is a decision as to whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed.

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.

Subsequent review of serious, unexpected and related AEs by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor(s), or the FDA or relevant local regulatory authorities may suspend further study procedures at a site.

10 CLINICAL MONITORING STRUCTURE

This section will describe the study monitoring to be conducted to ensure the safety and conduct of the study complies with 45 CFR 46, GCP and ICH Guidelines, DMID and other sponsor collaborator's guidelines, as appropriate.

See ICH E6 GCP, Section 5.18
(*http://www.fda.gov/cder/guidance/959fnl.pdf*).

Also refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.

10.1 Site Monitoring Plan

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

Preference is given to a separate monitoring plan, to be agreed upon with OCRA, which will describe protocol specific items to be monitored. The monitoring plan must include the number of subject charts to be reviewed, which/what proportion of data fields and what will be monitored, and who will be responsible for conducting the monitoring visits, and who will be responsible for ensuring that monitoring findings are addressed.

11 STATISTICAL CONSIDERATIONS

11.1 Study Outcome Measures

Discuss how the outcome measures will be measured and transformed, if relevant, before analysis (e.g., is the primary variable binary, categorical, or continuous?)

11.2 Sample Size Considerations

Provide information needed to validate your calculations, and also to judge the feasibility of enrolling subjects and obtaining the necessary number of specimens.

In particular, specify all of the following:

- *Approach to handling withdrawals and protocol violations*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Discuss any measures to decrease bias or increase precision in ascertainment of study endpoints (e.g., blinding of laboratory staff, use of a central laboratory to perform assays).*

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.

In some circumstances, exploratory or pilot studies may be planned for convenience of obtaining samples.

11.3 Participant Enrollment and Follow-Up

Summarize the total number of enrollees and the total duration of accrual and retention capabilities.

11.4 Analysis Plan

This section can be used to elaborate on primary analyses that underlie the sample size calculation in Section 11.2 above and to describe secondary analyses for the primary or

secondary objectives. Details must be provided in a separate statistical analysis plan written later, but prior to interim or ad hoc analyses.

Plans must clearly identify the analyses cohorts, if applicable, and methods to account for missing, unused or spurious data. If specialized statistical techniques (e.g., methods for sequencing or microarray analysis) will be used, please discuss and indicate who will be performing the analysis.

12 ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of ICH E6 GCP, 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.

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

Refer to: http://www.fda.gov/cder/guidance/959fnl.pdf.

13 QUALITY CONTROL AND QUALITY ASSURANCE

This section will briefly indicate the plans for local quality control (QC). Each site should have standard operating procedures (SOPs) for quality management. Data will be evaluated for compliance with protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol. The types of materials to be reviewed, who is responsible, and the schedule for reviews may be specified or referenced in other documents. Types and mechanisms of training of staff for the study should be specified.

SOPs must be used at all clinical and laboratory sites. Regular monitoring and an independent audit must be performed according to GCP/ICH (e.g., data monitoring).

Briefly describe methods (e.g., internal auditing) for assuring protocol compliance, ethical standards, regulatory compliance, data quality and proper storage and handling of samples. (Refer to ICH GCP E6, Section 5.1 http://www.fda.gov/cder/guidance/959fnl.pdf).

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

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

14.1 Declaration of Helsinki

Include this section if applicable.

If the study is conducted at international sites, include a statement about compliance with the Declaration of Helsinki.

Example text:

> *"The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonisation Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject."*

14.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics review committee (IEC) or Institutional Review Board (IRB) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In both the United States and in other countries, only institutions holding a current U. S. Federal-Wide Assurance issued by OHRP may participate. Refer to: http://ohrp.osophs.dhhs.gov.

14.3 Informed Consent Process

Refer to ICH GCP E6, Section 4.8 (http://www.fda.gov/cder/guidance/959fnl.pdf).

Refer to FDA Regulations on Informed Consent 21 CFR Part 50 - Subpart B (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=50).

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

See also Tips on Informed Consents (http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm).

See also Informed Consent Checklist (http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm)

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

Informed consent is required for all subjects participating in a DMID-sponsored study, unless the requirement of informed consent is specifically waived by the IRB/IEC. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. 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.

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

Example text:

> *"Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the subjects and their families. Consent forms describing in detail the study procedures and risks are given to the subject and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to being enrolled in the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study."*

Provide each institution with a sample consent form for subject participation. The consent form should be separate from the protocol document.

14.3.1 Informed Consent/Assent Process (in Case of a Minor or others unable to consent for themselves)

Refer to ICH E6, Section 4.8.12

(http://www.fda.gov/cder/guidance/959fnl.pdf).

When a study includes subjects who may be enrolled in the study only with the consent of the subject's legally authorized representative (e.g., minors or subjects unable to consent for themselves), the subject should be informed about the study to the extent compatible with the subject's understanding. If capable, the subject should assent and sign and personally date the written consent form. A separate IRB-approved assent form, describing (in simplified terms) the details of the study, study procedures and risks may be used. Assent forms do not substitute for the consent form signed by the subject's legally acceptable representative. Consult with the institutions policies regarding enrolling participants who are unable to provide informed consent for themselves.

Subjects who are unable to give consent for themselves should not be enrolled in non-therapeutic research unless the objectives of the research cannot be met by enrolling only persons who are able to give consent for their participation. The reviewing IRB/IEC must give approval or a favorable opinion on their inclusion.

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

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

14.5 Subject Confidentiality

Include procedures for maintaining subject confidentiality, any special data security requirements, and record retention per the sponsor's requirements.

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

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor 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.

14.6 Future Use of Stored Specimens

If residual specimens will be maintained after the study is complete, 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, if the site's IRB will review future studies, and protections of confidentiality for any future studies with the stored specimens, e.g., specimens will be coded, bar-coded, de-linked. Include a statement that genetic testing will not be performed if required by the IRB.

Refer to Human Research Regulation Chart 2 at:

http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm.

Additional guidance can be provided by OCRA/ORA staff.

15 DATA HANDLING AND RECORD KEEPING

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 GCP guidelines and 21 CFR Part 11. The description should include reference to source documentation, case report forms, instructions for completing forms, data handling procedures, and procedures for data monitoring. Details may be provided in a Manual of Procedures, User's Guide or other citable reference document.

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

15.1 Data Management Responsibilities

Describe responsibilities for data handling and record keeping as they specifically relate to the sponsor, clinical site, laboratory, and data coordinating center. Information should include the role in data collection, review of data, study 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. Describe who will send a copy of all datasets to DMID electronically.

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse Events must be graded, assessed for severity and causality and reviewed by the site Principal Investigator or designee.

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

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

Indicate the roles of each party with regard to interpretation of data, plans for analysis, review of tables and listings, and plans for reporting.

15.2 Data Capture Methods

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

15.3 Types of Data

Indicate the types of data that will be collected.

15.4 Timing/Reports

Indicate the schedule for data review and reports. Specify whether reviews or reports are ongoing, interim, or periodic. Identify plans for data analysis and submission of reports, steps for freezing the data prior to analysis, and precautions related to blinded data. Indicate whether and when coding is to occur.

15.5 Study Records Retention

Specify the length of time for the investigator to maintain all records pertaining to this study. Indicate whether permission is required prior to destruction of records.

15.6 Protocol Deviations

Plans for detecting, reviewing and reporting deviations from the protocol should be described. A statement may be included to indicate that exemptions for specific inclusion/exclusion deviations are not allowed (if not handled separately in an investigator agreement) and/or provisions for approval of inclusion/exclusion deviations can be described.

16 PUBLICATION POLICY

If appropriate, the publication policy may be described in the study Manual of Procedures (MOP).

The publication and authorship policies should be determined and clearly outlined in this section. Refer to contract or clinical trials agreements. Policies regarding substudies should be outlined in this section.

The following language may used in the protocol:

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered either on or before the onset of patient enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005 before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (eg, Phase 1 trials), would be exempt from this policy.

17 LITERATURE REFERENCES

Include a list of relevant literature references in this section. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., NEJM, JAMA). The preferred format is the Vancouver format, used in the American Medical Association Manual of Style.

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):257-259.

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, eds. *The Principles and Practice of Nephrology*. Philadelphia, PA: BC Decker Inc.; 1991:396-403.

A full listing of Vancouver style guidelines can be found at:
International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *JAMA*. 1997;277:927-934.

You may also refer to:
http://www.library.uwa.edu.au/guides/citingsources/vancouver.html

SUPPLEMENTS/APPENDICES

Required Documents:

Provide with protocol:

- *Consent Form*
- *Assent Form, if applicable*
- *Future Use Consent, if applicable*
- *Schedule of Events*

Can be provided at a later time:

- *CVs*
- *Conflict of Interest Statement (COI)*
- *Confidentiality Agreement (CDA)*
- *Manual of Procedures*
- *Safety Monitoring Plan*
- *Site Monitoring Plan*
- *Copies of Case Report Form(s)*

Additional/optional supplements:

- *Biosafety Precautions*
- *Repository Instructions*
- *Laboratory Handling*
- *Site Roster*

Appendix A: Study Schedule

Procedures		Screening	Baseline	Follow-Up Schedule: Time Point 1	Time Point 2	Time Point 3	Time Point 4, etc.	Study Completion	Premature Discontinuation
Signed Consent Form		X	X						
Assessment of Eligibility Criteria		X	X						
Review of Medical History		X	X						
Review of Concomitant Medications		X	X	X	X	X	X	X	X
Study Procedures			X						
Physical Exam	Complete	X						X	X
	Symptom-Directed		X	(X)	(X)	(X)	(X)		
	Vital Signs		(X)	(X)	(X)	(X)	(X)		
Assessment of Adverse Events				(X)	(X)	(X)	(X)	X	X
Clinical Laboratory	Chemistry	X	X	(X)	(X)	(X)	(X)	X	X
	Hematology	X	X	(X)	(X)	(X)	(X)	X	X
	Urinalysis	X	X	(X)	(X)	(X)	(X)	X	X
Research Laboratory	Immunology __mL whole blood		X		(X)		(X)	X	X
Other Procedures			(X)		(X)		(X)	(X)	(X)

(X) – As indicated/appropriate.

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

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

Biochemistry – Sodium, potassium, chloride, urea, creatinine, glucose, uric acid, bicarbonate, amylase, lipase, albumin, total bilirubin, cholesterol, triglycerides, and CPK, as appropriate for the study. These are examples, specify list of tests.

Urinalysis – Protein and glucose, as appropriate for the study

Immunology – Specify specimen types for non-standard laboratory assays

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

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 intervention.

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