PREFACE

This document is the DMID protocol template, which is required for developing DMID-sponsored clinical research protocols. Note that instructions and explanatory text are indicated by italics and should be replaced in your protocol document with appropriate protocol-specific text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template. Text should be formatted using Body Text style. Bulleted lists should be formatted using Bullet (listing) style.

This template attempts to provide a general format applicable to all clinical trials evaluating an investigational product. Where specific examples are provided, they are often from the vaccine area.

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

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

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

TITLE

DMID Protocol Number:

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

Pharmaceutical Support Provided by: *(if applicable)*

Other Identifying Numbers:

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

Principal Investigator:

DMID Protocol Champion:

DMID Medical Monitor:

DMID Clinical Affairs Specialist:

DMID Regulatory Affairs Specialist: *(if applicable)*

Draft or Version Number: *(Refer to DMID SOP for assigning version numbers)*

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 Practice), Section 6.

STATEMENT OF COMPLIANCE

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://www.cancer.gov/clinicaltrials/learning/page3.

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.

Example text:

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)*:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (1997)
- NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

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

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
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
FWA	Federalwide 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 Committee of 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)
NCI	National Cancer Institute, NIH, DHHS
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
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
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

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

Title:	*Include type of trial (e.g., dose-ranging, observational, double-blind)*
Phase:	*I, II, III, IV*
Population:	*Include sample size, gender, age, general health status, geographic location*
Number of Sites:	*3 or fewer, list here; otherwise, list only in Section 1*
Study Duration:	*Provide time from when the study opens until the monitor completes the close out visit.*
Subject Participation Duration:	*Provide time it will take to conduct the study for each individual participant.*
Description of Agent or Intervention:	*Include dose and route of administration*
Objectives:	*Copy objectives and clinical/laboratory outcome measures from the appropriate sections of the protocol. Include primary/secondary outcome measures and method by which outcome will be determined.* Primary: Secondary:
Description of Study Design:	*This schematic should provide an overview of the study design, including study arms, sample size and schedule of interventions (e.g., vaccine administration), if applicable; a detailed schematic describing all visits and assessments (schedule of events) will be included in Appendix A.*
Estimated Time to Complete Enrollment:	

***Schematic of Study Design**:

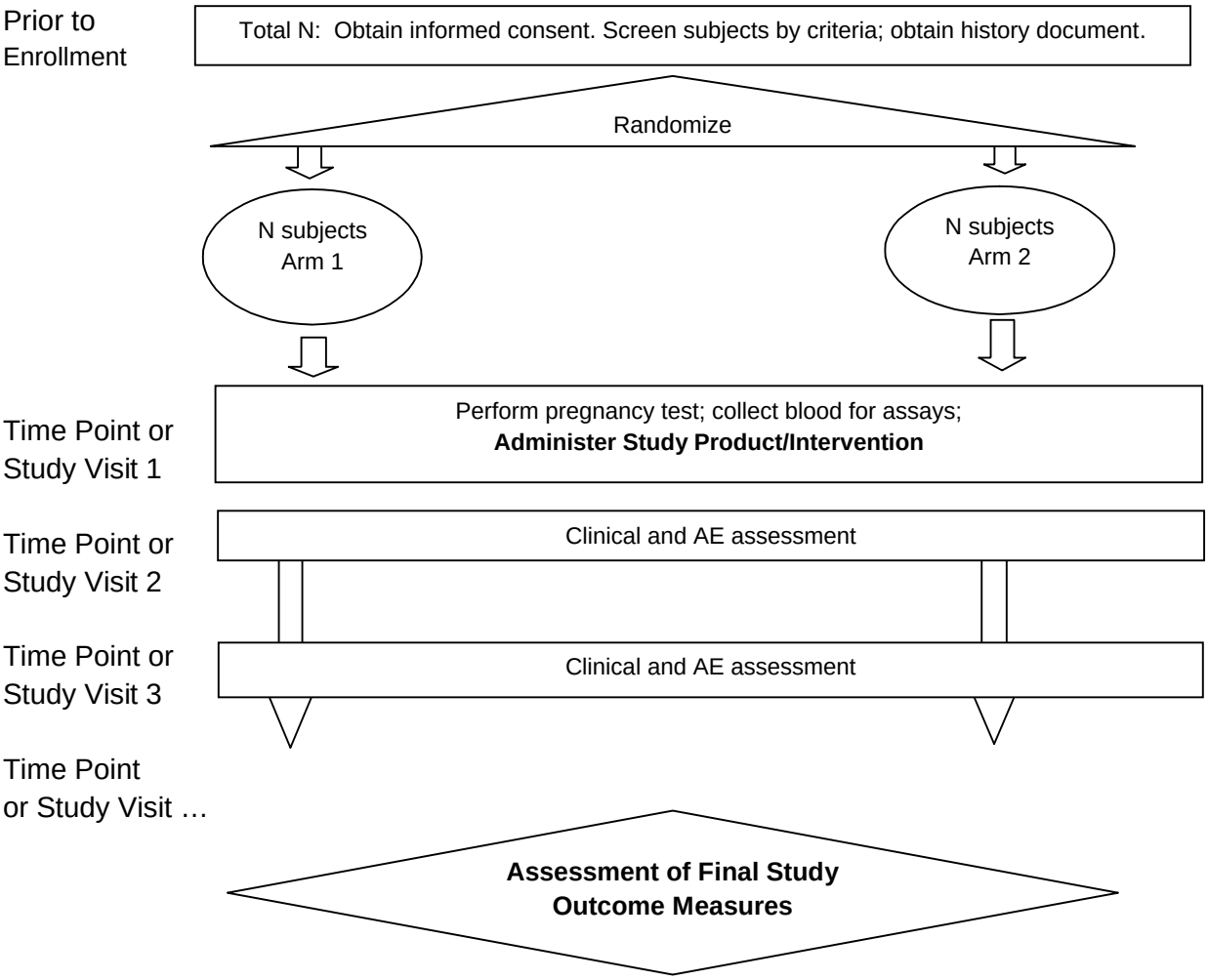
Example #1: Table format (e.g., dose escalation)

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

Instructions for progressing to next phase (if applicable):

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

Example #2: Flow diagram



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

1 KEY ROLES

Refer to ICH E6, 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:	**Protocol Champion:** *Division of Microbiology and Infectious Diseases (DMID) official authorized to sign the protocol and protocol amendments on behalf of the Protocol Team:* *Provide the following information for each individual:* *Name, degree, title* *Institution Name* *Address* *Phone Number* *Fax Number* *E-mail* **Principal Investigator:** *Site investigator responsible for conducting the study* **Medical Monitor:** *(if applicable)*
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 Name* *Address* *Contact Person/Local Investigator* *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 [MOP]) as appropriate

Institutional Review Board (IRB) contact information

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

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

Include:

The name and description of the study intervention/investigational products(s)

A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance

A summary from relevant clinical trials

Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations are listed in Section 17)

Applicable clinical, epidemiological, or public health background or context of the study

Importance of the study and any relevant treatment issues or controversies

2.2 Rationale

Include a description of and justification for the route of administration, dosage, dosing regimen, intervention periods, and selection of study population. Include a statement of the hypothesis.

2.3 Potential Risks and Benefits

Refer to 45 CFR Part 46.116 (a) (2) and (3)
(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116).

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

2.3.1 Potential Risks

Include a review of relevant literature, which should be referenced. Add relevant websites, etc from which the information could be drawn.

If a package insert 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.

Describe in detail any physical, psychological, social, legal, economic, or any other risks to subjects that the Principal Investigator (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, describe in detail any physical, psychological, social, legal, economic, or any other benefits to subjects that the PI foresees.

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

3 OBJECTIVES

3.1 Study Objectives

A detailed description of the primary and secondary 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

General purpose, e.g., efficacy, safety, immunogenicity, pharmacokinetics

Specific purpose, e.g., dose-response, superiority to placebo

Name(s) of intervention (e.g., vaccine, drug, biologic) being evaluated, specification of doses or dose ranges to be studied, dose regimens

3.2 Study Outcome Measures

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

This section should include the methods for assessing how the objectives are met, i.e., the study outcome measures.

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). Give succinct but precise definitions of the outcome measures used to measure the primary and key secondary outcomes stated in the study objectives, including the study visits at which the samples will be obtained and the specific laboratory tests to be used.

3.2.1 Primary Outcome Measures

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

3.2.2 Secondary Outcome Measures

Secondary outcome measures should be included, whether or not they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.

4 STUDY DESIGN

Refer to ICH E6, Section 6.4
(http://www.fda.gov/cder/guidance/959fnl.pdf).

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

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 description of the study population (e.g., healthy/sick, inpatient/outpatient)

The rationale for design features should be discussed

Phase of trial

Single or multicenter

The number of study groups/arms

Description of study groups/arms including sample size (including a table, if appropriate)

Approximate time to complete study enrollment

The expected duration of subject participation

Identification of the test agent and specifics of administration of other agents (e.g., placebo)

A description of the sequence and duration of all trial periods, including follow-up (specify individual subjects vs entire trial)

Changes in scheduling, such as dose escalation

Any stratifications

A specific statement of the primary and secondary outcomes to be measured during the trial (must be consistent with Study Objectives, as stated in Section 3)

Methods for collecting data for assessment of study objectives

Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)

Interim analysis plans

Identify structure for safety oversight per DMID guidelines (e.g., Data and Safety Monitoring Board (DSMB), Safety Monitoring Committee (SMC), and/or Independent Safety Monitor (ISM), and DMID medical monitor). Ensure consistency with Section 9.6. For DMID guidelines refer to: http://www.niaid.nih.gov/dmid/clinresearch/.

4.1 Substudies (if applicable)

Definition: A substudy asks a separate research question from the parent protocol and may or may not contribute to the parent protocol's objectives but uses all or a subset of study participants or specimens.

Note that substudies do not have full protocols but rather are incorporated into the main protocol.

A concept sheet for a proposed substudy must be approved by the DMID Project Officer/Program Officer. Once the concept for a substudy is approved by the Program Officer, a decision must be made by DMID, in conjunction with the investigator, whether the concept is appropriate as a substudy or should be a stand-alone study.

List with brief description:

Description of the substudy and its objectives

Impact on main study

Potential participating sites

Behavioral issues

If substudy is added to an ongoing study, a protocol amendment is required.

5 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 Subpart B – Additional Protections Pertaining to Research, Development and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization (45 CFR Part 46.201-46.211); Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (45 CFR Part 46.301-46.306); Subpart D – Additional Protections for Children Involved as Subjects in Research (45 CFR Part 46.401-409). 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. *Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46*; and *http://www.hhs.gov/ohrp/irb/irb_guidebook.htm.*

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, or 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, or general public). 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., review of medical records or laboratory tests), they must be performed under a separate screening consent form in addition to the consent form for study participation.

Eligibility Criteria:

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

The risks of the test agent/product should structure the development of the inclusion/exclusion criteria.

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 (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).

5.1 Subject Inclusion Criteria

Provide a statement that subjects must meet all of the inclusion criteria in order to be eligible to participate in the 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, 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 (April 1997)

5.2 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, etc.

5.3 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).

5.3.1 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.

5.3.2 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.

5.3.3 Reasons for Withdrawal

Provide a list of reasons subjects may be discontinued from the study. It may be appropriate to provide distinct discontinuation criteria for subjects and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. 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.

Example text:

A study subject will be discontinued from participation in the study if:

Any clinical adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

Development of any exclusion criteria may be cause for discontinuation.

Subjects are free to withdraw from participating in the study at any time upon request.

5.3.4 Handling of Withdrawals

Describe the efforts to follow subjects who withdrawal from the study. It is vital to collect safety data on any subject discontinued because of an AE or SAE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the subject should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable. Describe efforts to continue follow-up, especially for safety and efficacy (if applicable) outcome measures.

A discussion of replacement of participants who discontinue early, if allowed, should be included in this section.

5.3.5 Termination of Study

List possible reasons for discontinuation of the study in this section, e.g., development of laboratory toxicities, study closure due to DSMB review, discretion of DMID/or IND holder.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

Note: If multiple products are to be evaluated in the study, the following sections should be repeated for each product and the sections should be renumbered accordingly. Describe placebo or control product.

6.1 Study Product Description

Information in this section can usually be obtained from the IB or the package insert. Make IB or package insert available to all investigators as part of the study's MOP or distributed separately, as appropriate.

6.1.1 Acquisition

6.1.2 Formulation, Packaging, and Labeling

6.1.3 Product Storage and Stability

Describe product's storage needs. Include storage requirements and stability (temperature, humidity, security, and container).

Provide additional information regarding stability and expiration time for studies in which multidose vials are entered (i.e., the seal is broken).

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

List investigational agents, route, doses, and frequency of administration in this section. Include thawing, diluting, mixing, and reconstitution/preparation instructions, as appropriate. Include any specific instructions or safety precautions for 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.

6.3 Modification of Study Intervention/Investigational Product for a Participant

Clearly explain instructions for modification of dose due to toxicity or any other potential reason. Address dose modifications for specific abnormal laboratory values of concern or other AEs that

are known to be associated with the planned intervention regimen. Do not restate reasons for withdrawal of subjects. Cross-reference relevant sections, as appropriate.

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

Provide plans for how the study intervention/investigational product(s) will be distributed including participation of a drug repository, frequency of product distribution, amount of product shipped, and plans for return of unused product.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

Include this section, if applicable.

Include plans for compliance assessment (e.g., questionnaires, direct observation, pill counts) in this section.

6.6 Concomitant Medications/Treatments

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.

7 STUDY SCHEDULE

Information outlined in this section should refer to and be consistent with the information in the Schedule of Events in Appendix A and in Section 8.

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).

7.1 Screening

Include only those evaluations necessary to assess whether a subject meets eligibility criteria. Discuss the sequence of events that should occur during screening 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).

This section must include instructions for obtaining signed informed consent. State if a separate screening consent will be used. If a separate screening consent will not be used, the study consent must be signed prior to screening.

If an individual's medical chart or results diagnostic tests performed as part of an individual's medical care are going to be used for screening, written informed consent must be obtained prior to review of that information.

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

7.2 Enrollment/Baseline

Discuss evaluations/procedures necessary to assess or confirm whether a subject still meets the eligibility criteria and may be enrolled, and discuss those assessments that are required at baseline for later outcome measure comparison after study intervention (e.g., baseline signs and symptoms prior to vaccination). Discuss the sequence of events that should occur during enrollment and/or initial administration of study product. List any special conditions (e.g., results of the pregnancy test must be negative and available prior to administration of study product). List the procedures for administering the study product or intervention and follow-up procedures after administration (e.g., assessment of vital signs, reactogenicity).

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

7.3 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.

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

7.4 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).

7.5 Early Termination Visit

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. Clearly differentiate between what evaluations are to be done in each of these circumstances.

7.6 Unscheduled Visit

Specify how unscheduled visits(s) will be handled and documented.

8 STUDY PROCEDURES/EVALUATIONS

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

8.1 Clinical Evaluations

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

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).

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.

Counseling procedures.

Criteria for dose adjustment.

Rescue therapy.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

List all laboratory evaluations. Differentiate screening laboratories from those taken after vaccination, 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.

Examples:

Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.

Biochemistry: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).

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.

8.2.2 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 1 laboratory will be used, specify which assays will be done by each laboratory.

8.2.3 Specimen Preparation, Handling, and Shipping

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

Special instructions for the preparation, handling, and storage of specimens should be explained clearly in this section (or refer to the study's MOP), including required temperatures, aliquots of specimens, if samples are frozen, where they will be stored, and how they will be labeled. Include a discussion of long-term access and consent for future use of specimens (Section 14.7).

8.2.3.2 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, include any special instructions such as dry ice or wet ice or the completion of a specimen-tracking log (or refer to the study's MOP).

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Reference safety parameters that are outcome measures (Section 3.2). Include other parameters if not primary study outcome measures.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Refer to ICH E6, Section 1.2
(http://www.fda.gov/cder/guidance/959fnl.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.

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 decisions will be made regarding determining relatedness and grading severity.

Describe how unsolicited events will be captured.

Include time period of collection (e.g., Days 0 -28) and note how long SAEs are collected – usually collected through entire study.

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.

Example text:

Adverse Event:

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. 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 local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

All AEs must be graded for severity and relationship to study product.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Severity of Event: All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, than the following guidelines will be used to quantify intensity.

Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.

Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Life threatening: any adverse drug experience that places the patient or 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 severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article (vaccine or study drug) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.2 Reactogenicity (for Vaccine Studies and Some Therapeutic Trials)

Reactogenicity events are AEs that are common and known to occur for the intervention/investigational product being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Provide a definition of expected vs unexpected AEs and local vs systemic events, based on the risk profile of the intervention/investigational product. This information is found on the IB or package insert. Typically, reactogenicity AEs are solicited and collected on memory cards and documented on a reactogenicity CRF. This information comes from the participant who may also have a memory aid to help recollect their symptoms.

The following is an example of a functional scale for assessing reactogenicity or other parameters not specifically listed in the toxicity table:

0 = Absence of the indicated symptom

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)

4 = Life threatening

9.2.3 Serious Adverse Events

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

Refer to ICH E6, Section 1.50
(http://www.fda.gov/cder/guidance/959fnl.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.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

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

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected" as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or

as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

21 CFR 312.64 Investigator reports

(b) Safety reports: An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record non serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

Some protocols may list events specific to the protocol that they want reported as serious with expedited reporting. An example might be for a maternal immunization protocol before eclampsia or preterm delivery.

Example text:

Serious Adverse Event (SAE):

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.

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

All SAEs will be:

- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

9.2.4 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.

9.3 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 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.

9.3.1 Serious Adverse Events

Example text:
AEs 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 20814, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Phone Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

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

The DMID medical monitor and clinical protocol 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 investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to the DMID Pharmacovigilance Group.

9.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Example text:

Following notification from the investigator, DMID, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of 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. 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 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 serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

9.3.3 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.

9.3.4 Other Adverse Events (if applicable)

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

9.3.5 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 (e.g., discontinuation of vaccination while continuing safety follow-up, following pregnant women to pregnancy outcome).

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

Refer to ICH E6, Section 6.8
(http://www.fda.gov/cder/guidance/959fnl.pdf).

Describe how AEs will be followed until resolved or considered stable. 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).

9.5 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 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.

9.6 Safety Oversight (ISM plus SMC or DSMB)

DMID requires safety oversight in one of 3 forms: ISM, SMC, or DSMB. 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. State who is responsible for safety oversight, i.e., ISM, SMC, or

DSMB. Will they meet at prearranged time points (enrollment milestones, prior to next stage in protocol) in the study? Will meetings be dependent on the halting rules? State which safety outcome measures will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

Example text:

Safety oversight will be under the direction of a DSMB composed of a pediatrician, an intensivist, a statistician, and a cardiologist. The DSMB will meet semiannually to assess safety and efficacy data on each arm of the study. The DSMB will review aggregate safety data for increased rate of occurrence of serious suspected adverse reactions. If halting rules are initiated, more frequent meetings may be held. The DMSB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will advise DMID of its findings.

10 CLINICAL MONITORING

Refer to ICH E6, Section 5.18
(http://www.fda.gov/cder/guidance/959fnl.pdf).

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

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.

10.1 Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protection, 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. This section will give a general description of how site monitoring will be conducted. A separate monitoring plan document should be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. Most DMID-sponsored studies are monitored by TRI/ICON Clinical Research Operations and Management Support (CROMS), and the clinical monitoring plan is written jointly by DMID and TRI/ICON.

Preference is given to a separate monitoring plan to be agreed upon with the Office of Clinical Research Affairs (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, who will be responsible for conducting the monitoring visits, and who will be responsible for ensuring that monitoring findings are addressed.

11 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.*

11.1 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).

11.2 Sample Size Considerations

Provide all information needed to validate your calculations, and also to judge the feasibility of enrolling and following the necessary numbers of subjects.

In particular, specify all of the following:

Outcome measure used for calculations (almost always the primary variable)

Test statistic

Null and alternate hypotheses

Type I error rate

Type II error rate

Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible

Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc also justified

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 it and for any software utilize, and

Method for adjusting calculations for planned interim analyses, if any (see Section 11.3).

Further, 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.

11.3 Planned Interim Analyses (if applicable)

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.

Describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing.

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

11.3.1 Safety Review

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.

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

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

11.3.2 Immunogenicity or Efficacy Review

Provide the same information as in Section 11.3.1, but for immunogenicity or efficacy outcome measures. Also discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

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

11.4 Final Analysis Plan

This section can be used to elaborate on primary analyses that underlie the sample size calculation in Section 11.2 and to describe secondary analyses for the primary or secondary objectives. Even more details can be provided in a separate statistical analysis plan written later but prior to performing any analyses.

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

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?).

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Describe who will have access to records. 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 clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

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

13 QUALITY CONTROL AND QUALITY ASSURANCE

This section will address the plans for local quality assurance and quality control. (http://www.fda.gov/cder/guidance/959fnl.pdf).

All sites conducting research under the sponsorship of the DMID 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.

See Section 10.1 for detail on Site Monitoring.

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

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

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

14.1 Ethical Standard

Include in this section the guiding ethical principles being followed by the study.

Example text:

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

If the study is conducted at international sites, the statement could be as above and/or reference compliance with the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the most protection to human subjects.

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 committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federalwide Assurance issued by OHRP may participate. Refer to: http://www.hhs.gov/ohrp/assurances/.

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).

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

Refer also to 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, children, illiterate or non-writing individuals, vulnerable populations.
(Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/ic-non-e.htm).

Informed consent is required for all subjects participating in a DMID-sponsored study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to 45 CFR Part 46 and/or ICH, GCP. 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, screening for human immunodeficiency virus, 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 this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. 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 any procedures being done specifically for 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 trial. 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 model inform consent form for subject participation. The consent form should be separate from the protocol document. Each institution should place the informed consent document in its own template. Each institution may add but not remove anything from the model consent form.

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

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 trial only with the consent of the subject's legally authorized representative (e.g., minors or subjects whose cognitive impairment is such that they are unable to give informed consent), the subject should be informed about the trial 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 intervention/product, study procedures, and risks may be used. Assent forms do not substitute for the consent form signed by the subject's legally authorized representative.

Note that additional considerations exist for enrollment of minors. Refer to 45 CFR Part 46.

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. Possible persons that might have access to records, in addition to the clinical monitor, would be funding institutions, IND sponsor, representatives of DMID, representative from the IRB/IEC, and representatives of the pharmaceutical company supplying product to be tested.

Example text:

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 Study Discontinuation

In the event that the study is discontinued, provide a plan for the following:

Describe procedures for subjects to continue therapy, if appropriate

Describe crossover to study drug for placebo recipients at the completion of the study.

14.7 Future Use of Stored Specimens

Refer to Human Research Regulation Chart 2
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm.

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, delinked. Include a statement that genetic testing will not be performed, if required by the IRB.

Additional guidance can be provided by OCRA or the Office of Regulatory Affairs (ORA) staff.

15 DATA HANDLING AND RECORD KEEPING

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 an MOP, User's Guide or other citable reference document.

Example text:

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 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 documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained

DMID and/or it designee will provide guidance to investigators on making corrections to the source documents and eCRF.

15.1 Data Management 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.

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

Example text:

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 PI or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

The EMMES Corporation will serve as the Statistical and Data Coordinating Center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

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.

Example text:

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by The EMMES Corporation. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

15.3 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.

Example text:

Data for this study will include safety, laboratory (immunologic and virologic), and outcome measures (e.g., reactogenicity, immunogenicity, virology).

15.4 Timing/Reports

Indicate the schedule for data review and reports, how outcome measure data are collected and monitored, data for stopping rules, and reports for DSMB. Specify whether reviews or reports are ongoing, interim, or periodic. Identify plans for data analysis and interim and final study reports, steps for freezing the data prior to analysis, and precautions related to masked 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 (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.

Investigational product records may be addressed here if not addressed elsewhere in the protocol.

Example text:

Study documents should be retained for a minimum of 2 years after 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. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

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 deviations are not allowed, unless a statement is included in investigator agreement. Provisions for approval of deviations can be described.

Example text:

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures 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 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 to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via The EMMES Corporation's IDES or via the TRI/ICON DMID-Clinical Research Operations and Management Support (CROMS) email (protocoldeviations@dmidcroms.com), web-(www.dmidctm.com) or fax-based system (1-215-699-6288).

Note: Those sites participating in trials with a designated 'central unit' will follow the reporting requirements specified in their protocols and MOPs. The 'central unit' will be responsible for submission of the protocol deviation information to TRI/ICON DMID-CROMS.

All deviations from the protocol must be addressed in study subject source documents. A completed copy of the DMID Protocol Deviation Form (TRI/ICON DMID-CROMS or IDES form) must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

16 PUBLICATION POLICY

If appropriate, the publication policy may be described in the study's 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.

The following language may be used in the protocol:

Following completion of the study, the investigator is expected to 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 on or before 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 (e.g., Phase I trials), would be exempt from this policy.

*Journal Citation:

De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351:1250-1.

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., N Engl J Med, JAMA, etc). The preferred format is 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.

SUPPLEMENTS/APPENDICES

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH E3: Structure and Content of Clinical Study Reports. These materials should not be included as part of the protocol.)

Supplements and Protocol Appendices

Substudies

Schedule of Events

Toxicity Grading Scales

Sample Consent Form(s)

Related Documents

Site Roster

Manual of Procedures

Repository instructions

Biosafety Precautions

Laboratory Handling

Other Documents

CRF copies

Quality Management Plan

Data Management Plan

Clinical Monitoring Plan

APPENDIX A: SCHEDULE OF EVENTS

				Follow-Up Schedule					
Procedures		Screening	Baseline	Time Point or Study Visit 1	Time Point or Study Visit 2	Time Point or Study Visit 3	Time Point or Study Visit 4, etc.	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 Intervention			X						
Physical Examination	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.
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.