PREFACE

This document is the DMID protocol template, which is required for DMID-sponsored clinical studies that pose only minimal risk to study subjects. 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

Categories of research that are minimal risk are defined by OHRP guidelines. Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm

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.

The Principal Investigator (PI) must attach all explanatory and appended materials (including, but not limited to, surveys, consent forms, interview scripts, and recruitment flyers/brochures) referred to in the protocol.

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:

Principal Investigator:

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

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 clinical study will be conducted in compliance with the protocol, 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

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
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.

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.

Primary:

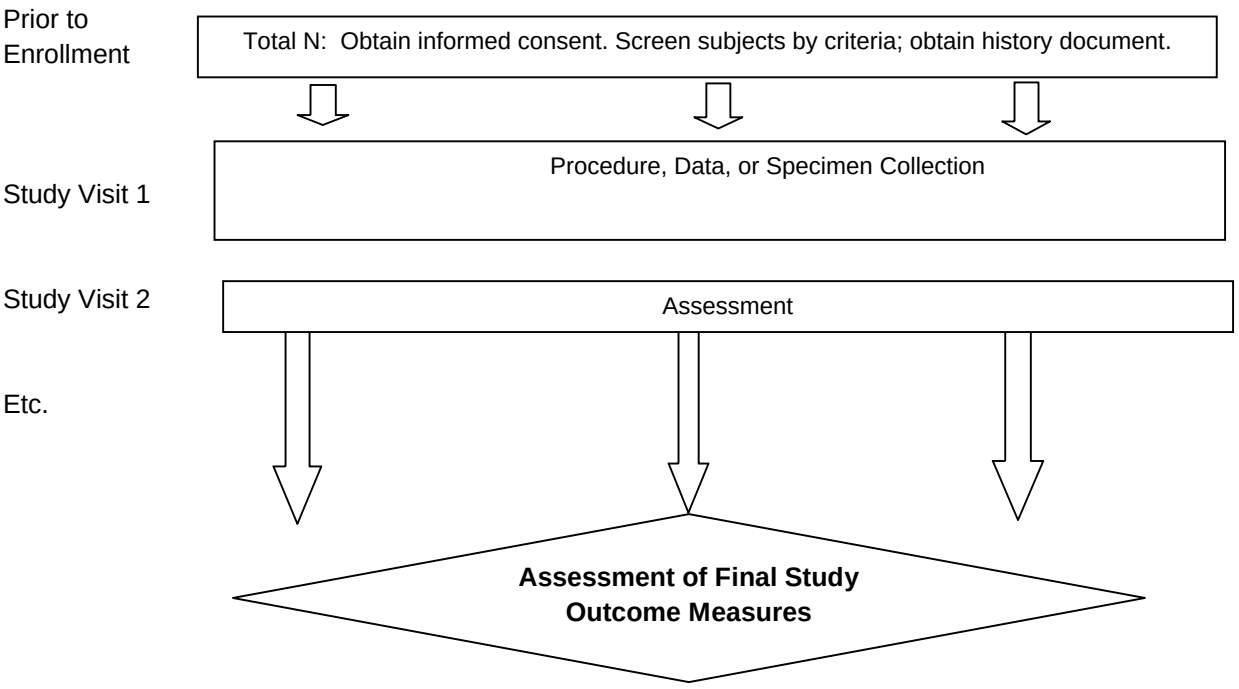
-

Secondary:

-

Schematic of Study Design: *Optional*

Example: Flow diagram



1 KEY ROLES

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

Individuals: **DMID Representative**

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

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:*
Protocol Data Manager, Epidemiologist, Statistician
DMID Clinical Affairs Specialist

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.*
- *A discussion of important literature and data that are relevant to the study and that provide background for the study. List the full citations for the references (reference citations are listed in Section 10). Discuss deficiencies in the literature and, in general, how they will be addressed. Write concisely.*
- *Applicable clinical, epidemiological or public health background or context of the study*

2.2 Scientific Rationale

- *Include a description of and justification for selection of study population. Briefly assess the need to acquire data from humans. The desired data may already exist.*
- *Address the applicability of animal subjects and computer simulations in place of human subjects.*

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.*

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 design of the study 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)*

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 selection of the study population and inclusion/exclusion criteria.

5.1 Selection of the Study Population

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

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.*
- *Describe the gender, race, age and ethnicity of the subjects. Provide justification for Exclusion in Ethics/Protection of Human Subjects, Section 16.4. Refer to: http://grants2.nih.gov/grants/funding/women_min/women_min.htm*
- *Provide a rationale for any restrictions in subject selection. For instance, if subjects are drawn from an organization that provides services only to women, that fact should be stated. Or, if the equipment to provide certain measurements requires persons with certain physical characteristics, it is better to describe the limitations of your subject recruitment based on the requirements of the equipment (e.g., require arm length of X inches) rather than saying only men will be recruited.*
- *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.*

- *State the PI's relationship to any organization or institution allowing the PI access to its members or clients, e.g., the PI is an employee of the institution, a member or volunteer of the organization.*
- *Describe the general state of health (mental and physical) required of the subjects. If it is a requirement of the research that the subjects are in good mental or physical health, indicate who will determine their mental/physical health and how they will determine the subjects' good mental/physical health, or upon what basis the subjects' fitness will be judged.*
- *If the subjects are minors, mentally incompetent, or members of any other legally restricted group, provide an explanation as to the necessity for using these participants.*
- *If the subjects are minors, and their parents/guardians will not be allowed to see the results of the child's participation, the PI must state those conditions in the protocol and in the consent form. Parents/guardians should be notified of the limitation on their access to collected or recorded data before they give informed consent.*
- *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.*

5.2 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria should provide a definition of subject characteristics required for study entry.

- *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >32 years old as an inclusion criterion and also age ≤32 years old as an exclusion criterion).*
- *Specify if pregnant and/or breastfeeding women will be enrolled*
- *If men and women of reproductive capability will be enrolled, include details of allowable contraception methods for trial (e.g., licensed hormonal methods).*

6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures

- *Specify the type of information the PI will gather, along with the means for collecting and recording it. Include where the data will be stored during the study and how long the PI intends to keep the data. 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.*

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

- *State the overall duration of the project. If more than one visit will be required, indicate the amount of time required for each visit. Indicate the total amount of time required of each subject to participate in the project.*

- *Describe the process for using anonymized samples, if applicable.*

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 description of assays to be performed.

6.2.2 Specimen Collection, Preparation, Handling and Shipping

6.2.2.1 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. Describe the process for using anonymized samples, if applicable. There may need to be additional considerations for biological specimens, especially biohazardous specimens that require special containment.

6.2.2.2 Specimen Shipment

State the frequency with which specimens are to be shipped and to what address, if applicable. 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 should be included. Place specific details in a Manual of Procedures and reference within the protocol.

7 STATISTICAL CONSIDERATIONS

7.1 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?).

7.2 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.

7.3 Participant Enrollment and Follow-Up

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

7.4 Analysis Plan

This section can be used to elaborate on primary analyses that underlie the sample size calculation in Section 7.2 above and to describe secondary analyses for the primary or secondary objectives. 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, 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.

8 SUBJECT CONFIDENTIALITY

Include procedures for maintaining subject confidentiality, any special data security requirements, and record retention per the sponsor's requirements. State whether human subjects will be identifiable directly or through identifying information. State how the data will be linked to the subjects during the study. State how and where the data will be stored, and how it will be protected.

Subject confidentiality is held strictly 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 clinical study site will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study.

State what the PI will do with the information obtained from the subjects. Describe which elements of the project might be openly accessible to other agencies or appear in publications.

Describe the immediate use of data by the PI and others. Describe the long-range use of data by the PI and others. Explain what will happen to the data upon completion of the study. If the data will be retained specify for how long and by whom. If the data will be destroyed, specify the time.

8.1 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.

9 INFORMED CONSENT PROCESS

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

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 clinical study, 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.

When seeking informed consent, be sure to give the subject a sufficient amount of time to consider whether or not to participate. This will minimize the possibility of coercion or undue influence. The informed consent document is the only evidence that the subject was informed of the risks and benefits of the study. It also provides evidence that the subject gave consent, at that time, to participate.

The subject may revoke consent orally or in writing at any time and for any reason. Therefore, the PI must continually monitor the subject's consent. All informed consent documents must be written in language understandable by each member of the subject population, usually at the sixth to eighth grade reading level.

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.

9.1 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 acceptable 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 enrollment of participants who are unable to provide informed consent for themselves.

10 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*