

Clinical Trial Protocol Documents Template

Division of AIDS (DAIDS)

For DAIDS Protocol Development Guidance, see the Clinical Trial Protocol Documents Manual v1.0

This document is a DAIDS sample protocol template, which is the preferred DAIDS protocol format. This policy does not apply to informed consent (IC) development or DAIDS IC templates. The IC Development Policy provides information on informed consent use and content. This protocol template was developed in conjunction with the Clinical Trials Protocol Document Manual and should be referenced when developing a protocol. Although DAIDS does not require the use of a standard protocol format, this sample template was developed to assist protocol teams and Principal investigators who are developing NIAID (DAIDS) -supported and/or -sponsored clinical trial protocols.

This template provides a general format applicable to all clinical trials that are evaluating study product(s)/intervention(s). Include each template section in the protocol, as applicable.

Note that instructions (including distinction between mandatory and sample templated language) are indicated by *italicized* font and should be replaced in the protocol document with appropriate protocol-specific text. See the applicable sections of the Clinical Trial Protocol Documents Manual for additional instructions and explanatory text to include in each section.

Mandatory templated language formatted in regular type must be included in the protocol document as provided in the template.

Sample templated language formatted in regular type can be included or modified as appropriate in the protocol document.

Refer questions regarding use of this protocol template to the appropriate DAIDS Program Officer or Medical Officer.

VERSION 1.0
SEPTEMBER 2014

1. TITLE PAGE

Full Title:

Title of Main Protocol and Protocol Number: *(if applicable)*

Clinical Trial Phase:

Local Protocol Number: *(if applicable)*

DAIDS-ES Document Number: *(protocol number provided by DAIDS)*

NIAID Funding Mechanism and Principal Investigator (PI):
(e.g., grant #, contract #)

Other Collaborators:

Pharmaceutical and other Study Product Support Provided by:
(if applicable)

IND Sponsor: *(if applicable)*

IND Number: *(if available)*

Protocol Chair/Co-Chair:

DAIDS Medical Officer/Medical Monitor:

Version Number:

Version Day Month Year:

2. SIGNATURE PAGE (OPTIONAL)

Sample Language:

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission of DAIDS, except when necessary to protect the safety, rights, or welfare of study participants.

I agree to personally conduct or supervise this study.

I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and approval (insert relevant terms of assurance here, e.g. 45 CFR 46, ICH/GCP, etc.) are met.

I agree to report to the sponsor adverse experiences as per _____ that occur during the course of this study.

I agree to maintain adequate and accurate study records and to make those records available for inspection by DAIDS, DAIDS' authorized representatives, and/or other applicable regulatory entities.

I will ensure that an EC or IRB that complies with the requirements of 45 CFR Part 46 will complete initial and continuing review and approval of the study. I also agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes to the study without DAIDS and EC/IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

Print/Type

Signed: _____ Date: _____

Name/Title

3. TABLE OF CONTENTS

List section and subsection titles with corresponding page numbers.

4. KEY ROLES

Include a list of persons/companies/groups serving in key roles. Include contact information, such as institution name, mailing address, phone number, and email address.

5. LIST OF ABBREVIATIONS

List all abbreviations included in the protocol.

6. PROTOCOL SUMMARY

Limit Protocol Summary to 2 pages. The summary may be presented in narrative or tabular format.

Full Title

Title of Main Protocol *(if applicable)*

Short Title

Sample Size

Study Population

Participating Sites

Study Design

Study Schema

Schedule of Procedures/Evaluations

Study Duration

Study Regimen/Intervention

Primary Objective(s)

Primary Endpoint(s)

7. INTRODUCTION

Include relevant background information, rationale supporting the importance of the study, and the study hypothesis.

- 7.1. Background Information**
- 7.2. Rationale**
- 7.3. Study Hypothesis/Hypotheses**

8. OBJECTIVES

Include the primary, secondary, and exploratory objective(s)

- 8.1. Primary Objective(s)**
- 8.2. Secondary Objective(s)**
- 8.3. Exploratory Objective(s)**

9. STUDY DESIGN

Include: identification of major design elements; name of study product/intervention(s); approximate time to complete study enrollment; description and number of study groups or arms including controls, as well as elements such as dose escalations or stratifications; size of each study group or arm and overall study sample size; description of the sequence and duration of all trial periods, including follow-up; expected duration of participant involvement; number of sites.

10. STUDY POPULATION

Clearly define study population and inclusion/exclusion criteria, including timeframes where applicable.

10.1. Inclusion/Exclusion Criteria

10.1.1. Participant Inclusion Criteria

10.1.2. Participant Exclusion Criteria

10.1.3. Co-enrollment Criteria

10.2. Recruitment Process

10.3. Participant Retention

11. INTERVENTIONS (INCLUDING STUDY PRODUCT)

Include information on biomedical and behavioral interventions as applicable

11.1. Biomedical Interventions

11.1.1. Regimen (dose, schedule, route, administration)

11.1.2. Study Product Formulation and Preparation

11.1.3. Device Studies

11.1.4. Study Product Supply and Accountability

11.1.5. Assessment of Participant Adherence with Study Product(s)/Intervention(s)

11.1.6. Concomitant Medications and Procedures

Sample language:

1. Provide a list of selected concomitant medications or reference where the complete list can be viewed.
2. Whenever a concomitant medication or study product is initiated or the dose changed, investigators must review the concomitant medications' and study products' most recent package inserts, investigator's brochure, as well as updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

11.1.7. Permitted Medications and Procedures

11.1.8. Prohibited Medications and Procedures

11.1.9. Precautionary Medications and Procedures

11.1.10. Required Medications

11.1.11. Rescue Medications

11.2. Behavioral Intervention(s)

12. STUDY PROCEDURES/EVALUATIONS

Include information pertaining to study procedures and evaluations under the appropriate title headings in this section.

12.1. Clinical Evaluations and Procedures

12.2. Laboratory Evaluations

12.2.1. Specimen Preparation, Handling and Shipping

12.2.2. Biohazard Containment

Sample language for U.S. sites:

Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory pathogens such Mycobacterium tuberculosis (MTB) are transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the Centers for Disease Control and Prevention in the United States, the WHO internationally and the National Institutes of Health.

Mandatory language for protocols requiring the transfer of specimens or infectious substances (U.S. and international sites):

All protocol specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

12.2.3. Total Blood Volume

Sample language, pediatric blood draw limit:

NOTE: Infant blood draw amounts are expected to be limited; therefore, priorities for laboratory assays will be as follows. If venipuncture is not successful, collect Dried Blood Spot (DBS) for storage via heel stick method per the Manual of Operating Procedures (MOP).

1. Safety laboratory assessments (Chemistries and complete blood count (CBC))
2. HIV Nucleic Acid Testing (NAT)/ enzyme immunoassay (EIA)
3. Stored DBS
4. Stored plasma

12.3. Schedule of Procedures/Evaluations: Timing and Definitions

- 12.3.1. Screening**
- 12.3.2. Enrollment**
- 12.3.3. HIV Counseling and Testing**
- 12.3.4. Follow-Up**
- 12.3.5. Early Termination Visit**
- 12.3.6. Pregnancy Visit**
- 12.3.7. Other Visits**
- 12.3.8. Final Study Visit**

13. ASSESSMENT OF SAFETY

Provide information on procedures for collecting, recording, evaluating severity, determining expectedness, and assessing the relationship to study product/intervention(s). This information should also include specific criteria and procedures for determining the reporting of adverse events and procedures for those adverse events that require expedited reporting.

13.1. Safety Assessment Overview

13.2. Adverse Event Procedures and Reporting Requirements

All protocols requiring expedited reporting of adverse events to DAIDS must include the current version of the "[Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-Sponsored Protocols](#)."

14. CLINICAL MANAGEMENT

Provide information on plans for managing adverse events, other clinical events, pregnancy, breastfeeding/ replacement feeding, acquisition of HIV infection while on study, and criteria for discontinuing study participation, as applicable.

14.1. Clinical Management of Adverse Events

Sample language for the toxicity management section:

Unanticipated and anticipated toxicities will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (latest) Version _____.

Sample language:

AEs assessed as related to non-study drugs (concomitant medications) should be handled according to the relevant package inserts and the best medical judgment of the site investigator.

14.2. Other Disease Events

14.3. Pregnancy

Sample language for pregnant women:

For pregnant women, additional clinical evaluations may be required to rule out gestational diabetes, preeclampsia, or treatable causes of anemia.

Sample language for protocols that include voluntary or required pregnancy registries (such as ART registry):

In addition, if the participant continues her pregnancy, the site or patient are encouraged to prospectively register her pregnancy in the "[Antiretroviral Pregnancy Registry](#)" (In US and Canada: 1-800-258-4263, international: 910-256-0238).

14.4. Breastfeeding/Replacement Feeding (if applicable)

14.5. Acquisition of HIV Infection while on Study (if applicable)

14.6. Treatment Failure (if applicable)

14.7. Criteria for Discontinuation

14.7.1. Criteria for Permanent Intervention Discontinuation for an Individual Participant

Sample language:

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

Study product/intervention-related adverse event

Requirement for prohibited concomitant medications

Pregnancy or breastfeeding (if applicable)

Reaching a defined clinical endpoint (if applicable)

Completion of study product(s)/intervention(s) as defined in the protocol

Request by participant to terminate study product(s)/intervention(s)

Clinical conditions, which in the best judgment of the investigator are believed to be harmful or potentially life-threatening to the participant, even if not addressed in the AE Management section of the protocol

Recommended by the EC/IRB, DSMB, OHRP, in-country national health or regulatory entity

The participant will continue to be followed with his/her or a guardian's permission if study product(s)/intervention(s) is/are discontinued. No subsequent modifications to the visit schedule and duration of continued follow-up will be made, except for discontinuation of the study product.

14.7.2. Criteria for Premature Study Discontinuation for an Individual Participant

Sample language:

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

Lost to follow up as evidenced by failure by the participant to attend [XX] consecutive clinic visits, at the discretion of the site investigator

Participant repeatedly non-compliant [define] with study product/intervention as prescribed

Pregnancy or breastfeeding (if applicable)

Request by participant to withdraw

Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant

Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of study results

A defined study endpoint is reached (if applicable)

15. STATISTICAL CONSIDERATIONS

Provide information on how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible.

15.1. Overview and General Design Issues

15.2. Study Endpoints

15.2.1. Primary Endpoint

15.2.2. Secondary Endpoint(s)

15.2.3. Exploratory Endpoint(s)

15.3. Study Objectives and Hypothesis/Hypotheses

15.4. Sample Size Considerations

- 15.5. Enrollment/Stratification/Randomization/Blinding Procedures/Unblinding Procedures**
- 15.6. Maintenance of Trial Treatment Randomization Codes (if applicable)**
- 15.7. Participant Enrollment and Follow-up**
- 15.8. Data and Safety Monitoring**
 - 15.8.1. Planned Interim Analyses and Stopping Guidelines (if applicable)**
 - 15.8.1.1. Interim Safety Review**
 - 15.8.1.2. Interim Efficacy (or Immunogenicity) Review**
 - 15.8.2. Analysis Plan**

16. DATA HANDLING AND RECORDKEEPING

Provide a brief description on steps that will be taken to ensure that the data collected are accurate, complete, reliable, legible, and timely. Describe the role of relevant parties in collecting, transferring, and interpreting the data.

- 16.1. Data Management Responsibilities**
- 16.2. Essential/Source Documents and Access to Source Data/Documents**
- 16.3. Quality Control and Quality Assurance**

17. CLINICAL SITE MONITORING

Provide a general description of how site monitoring will be conducted and specify the entity responsible for the monitoring.

Sample language if DAIDS is responsible for the clinical site monitoring:

Site monitors under contract to the National Institute of Allergy and Infectious Diseases (NIAID) will visit participating clinical research sites to review participants records, including consent forms, CRFs, medical records (e.g., physicians' progress notes, nurses' notes, individuals' hospital charts), and laboratory records to ensure protection of study participants, compliance with the EC/IRB approved protocol/amendments, and accuracy and completeness of records. The monitors will inspect sites' regulatory files to ensure that local regulatory requirements, in addition to U.S. Federal regulations, are being followed. They will also inspect sites' pharmacies to review product storage and management.

18. HUMAN SUBJECTS PROTECTIONS

Provide information that addresses protection of participants, including the informed consent process, risks and benefits, and confidentiality.

18.1. Institutional Review Board/Ethics Committee

18.2. Vulnerable Participants

18.2.1. Pregnant women and fetuses

18.2.2. Prisoners

18.2.3. Children

18.2.4. Illiterate participants

18.3. Informed Consent

18.3.1. Informed Consent Process

18.3.2. Assent Process (in Case of a Minor)

18.3.3. Documentation of Informed Consent

18.3.4. Waiver of Informed Consent

18.3.5. Waiver of Documentation of Informed Consent

18.3.6. Stored Samples and Associated Data Considerations

18.4. Risks

18.5. Social Impact Events

Sample language:

Individuals enrolled in this study may experience personal problems resulting from the study participation. Such problems are termed social impact events. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that participants may experience stigmatization or discrimination as a result of being perceived as being HIV-infected or at risk for HIV infection. For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Problems may also occur in circumstances in which study participation is not disclosed, such as impact on employment related to time taken for study visits.

In the event that a participant reports a social impact event, every effort will be made by study staff to provide appropriate assistance, and/or referrals to appropriate resources. Social impact events are documented and reviewed

on a scheduled basis by the protocol team leadership with the goal of reducing their incidence and enhancing the ability of study staff to mitigate them when possible.

Social impact events that are judged by the IoR/designee to be serious, unexpected, or more severe or frequent than anticipated, will be reported to the responsible site's EC/IRB promptly, or otherwise in accordance with the EC/IRB's requirements.

18.6. Benefits

18.7. Compensation

18.8. Participant Privacy and Confidentiality

Sample language:

All participant-related information including case report forms, laboratory specimens, evaluation forms, reports, etc., will be kept strictly confidential. All records will be kept in a secure, double locked location and only research staff will have access to the records. Participants will be identified only by means of a coded number specific to each participant. All computerized databases will identify participants by numeric codes only, and will be password-protected. Upon request, participant records will be made available to the study sponsor, the sponsor's monitoring representative, representatives of a participating pharmaceutical sponsor and applicable regulatory entities.

18.9. Certificates of Confidentiality

18.10. Critical Event Reporting

18.11. Communicable Disease Reporting

18.12. Incidental Findings

18.13. New Findings

18.14. Study Discontinuation

Sample language:

The study may be discontinued at any time by the EC/IRB, NIAID, the pharmaceutical supporter(s) or designee, the FDA, or other government entities as part of their duties to ensure that research participants are protected. (If a non-IND study, remove “FDA”; if no pharmaceutical support, remove “pharmaceutical supporter or designee.”)

18.15. Post-Trial Access

18.16. Ancillary Benefits

18.17. Community Advisory Board and Other Relevant Stakeholders

19. ADMINISTRATIVE PROCEDURES

When applicable, provide information on protocol registration with the DAIDS Protocol Registration Office, study IND and sponsorship arrangements, and registration in ClinicalTrials.gov.

19.1. Protocol Registration

19.2. Regulatory Oversight

19.3. Study Implementation

19.4. ClinicalTrials.gov

Mandatory language, when applicable:

This protocol is subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA) and will be registered in ClinicalTrials.gov.

20. PUBLICATION POLICY (OPTIONAL)

Provide plans for publication and authorship rules, unless included in a separate document.

21. REFERENCES

Provide citations for publications and presentations referenced in the text of the protocol.

22. APPENDICES

APPENDIX A

SAMPLE SCHEDULE OF PROCEDURES/EVALUATIONS

Procedures	Follow-Up Schedule							Study Completion	Premature Discontinuation of Study or Study Intervention
	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.			
Informed Consent	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	X
Study Intervention		X							
Physical Exam	Complete	X						X	X
	Symptom-Directed		X	(X)	(X)	(X)	(X)		
	Reactogenicity		X	X					
	Vital Signs		(X)	(X)	(X)	(X)	(X)		
Assessment of Adverse Events			(X)	(X)	(X)	(X)	X	X	

HIV Counseling and Testing	X	X	(X)	(X)	(X)	(X)	X	X
Chemistry	X	X	(X)	(X)	(X)	(X)	X	X
Hematology	X	X	(X)	(X)	(X)	(X)	X	X
Urinalysis	X	X	(X)	(X)	(X)	(X)	X	X
Immunology		X		(X)		(X)	X	X
Virology	X	X		X		X	X	X
Other procedures		(X)		(X)		(X)	(X)	(X)

(X) – As indicated/appropriate. Provide a list of tests to be performed, e.g.,

Hematology – CBC with differential, platelet count

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

Urinalysis – Protein and glucose, as appropriate for the study, with/without urine sediment microscopy

Immunology – Specify specimen types for non-standard laboratory assays

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

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

Specify time points for follow-up in days, weeks, or months, as appropriate for the protocol. At baseline, all procedures should be done before study intervention.

Indicate volume of blood over specified intervals (e.g., 2-month) and cumulative totals per same interval, if frequent or large phlebotomies are part of the study.

Information outlined in the Schedule of Procedures/Evaluations: Timing and Definitions, Section 12.3, should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix A. The description of the procedures/evaluations and the sequence of procedures/evaluations can either be written as separate sections or combined into one section, as appropriate or as preferred. Investigators must decide on the best presentation of study evaluations.