

Clinical Trial Protocol Documents Manual

Division of AIDS (DAIDS)

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Clinical Trial Protocol Documents Manual.....	1
I. INTRODUCTION	7
II. DEFINITIONS.....	8
III. LIST OF ABBREVIATIONS.....	10
IV. PROTOCOL DOCUMENTS CONTENTS.....	12
Running Header and Footer	12
1. TITLE PAGE.....	12
2. SIGNATURE PAGE (Optional).....	13
3. TABLE OF CONTENTS	13
4. KEY ROLES.....	13
5. LIST OF ABBREVIATIONS	13
6. PROTOCOL SUMMARY.....	13
7. INTRODUCTION	14
7.1. Background Information.....	14
7.2. Rationale.....	15
7.3. Study Hypothesis/Hypotheses	15
8. OBJECTIVES.....	15
8.1. Primary Objective(s)	16
8.2. Secondary Objective(s).....	16
8.3. Exploratory Objective(s)	16
9. STUDY DESIGN	16
10. STUDY POPULATION	16
10.1. Inclusion/Exclusion Criteria	17
10.1.1. Participant Inclusion Criteria	17
10.1.2. Participant Exclusion Criteria.....	18
10.1.3. Co-enrollment Criteria.....	18
10.2. Recruitment Process.....	18
10.3. Participant Retention	19
11. INTERVENTIONS (including STUDY PRODUCT)	19
11.1. Biomedical Interventions.....	19
11.1.1. Regimen (dose, schedule, route, administration)	19

11.1.2. Study Product Formulation and Preparation	19
11.1.3. Device Studies	19
11.1.4. Study Product Supply and Accountability	20
11.1.5. Assessment of Participant Adherence with Study Product(s)/ Intervention(s)	21
11.1.6. Concomitant Medications and Procedures	21
11.1.7. Permitted Medications and Procedures.....	21
11.1.8. Prohibited Medications and Procedures	22
11.1.9. Precautionary Medications and Procedures	22
11.1.10. Required Medications	22
11.1.11. Rescue Medications.....	22
11.2. Behavioral Interventions:	22
12. STUDY PROCEDURES/EVALUATIONS.....	22
12.1. Clinical Evaluations and Procedures.....	23
12.2. Laboratory Evaluations.....	23
12.2.1. Specimen Preparation, Handling and Shipping	25
12.2.2. Biohazard Containment.....	25
12.2.3. Total Blood Volume	26
12.3. Schedule of Procedures/Evaluations: Timing and Definitions	27
12.3.1. Screening	27
12.3.2. Enrollment	27
12.3.3. HIV Counseling and Testing.....	28
12.3.4. Follow-Up	28
12.3.5. Early Termination Visit	28
12.3.6. Pregnancy Visit	28
12.3.7. Other Visits	28
12.3.8. Final Study Visit	29
13. ASSESSMENT OF SAFETY	29
13.1. Safety Assessment Overview.....	30
13.2. Adverse Event Procedures and Reporting Requirements	30
14. CLINICAL MANAGEMENT.....	34
14.1. Clinical Management of Adverse Events	34

14.2.	Other Disease Events.....	35
14.3.	Pregnancy	35
14.4.	Breastfeeding/Replacement Feeding (if applicable)	36
14.5.	Acquisition of HIV infection on study (if applicable)	37
14.6.	Treatment Failure (if applicable)	37
14.7.	Criteria for Discontinuation	37
14.7.1.	Criteria for Permanent Intervention Discontinuation for an Individual Participant	37
14.7.2.	Criteria for Premature Study Discontinuation for an Individual Participant	38
15.	STATISTICAL CONSIDERATIONS	39
15.1.	Overview and General Design Issues.....	39
15.2.	Study Endpoints.....	39
15.2.1.	Primary Endpoint(s).....	40
15.2.2.	Secondary Endpoint(s).....	40
15.2.3.	Exploratory Endpoint(s).....	40
15.3.	Study Objectives and Hypothesis/Hypothesis.....	40
15.4.	Sample Size Considerations.....	40
15.5.	Enrollment/Stratification/Randomization/Blinding Procedures/Unbinding Procedure	41
15.6.	Maintenance of Trial Treatment Randomization Codes (if applicable)	41
15.7.	Participant Enrollment and Follow-up	41
15.8.	Data and Safety Monitoring	41
15.8.1.	Planned Interim Analyses and Stopping Guidelines (if applicable)	42
15.8.1.1.	Interim Safety Review.....	42
15.8.1.2.	Interim Efficacy (or Immunogenicity) Review	43
15.8.2.	Analysis Plan	43
16.	DATA HANDLING AND RECORDKEEPING	43
16.1.	Data Management Responsibilities.....	43
16.2.	Essential/Source Documents and Access to Source Data/Documents	44
16.3.	Quality Control and Quality Assurance	44
17.	CLINICAL SITE MONITORING.....	45
18.	HUMAN SUBJECTS PROTECTIONS	45
18.1.	Institutional Review Board/Ethics Committee	45

18.2. Vulnerable Participants	46
18.2.1. Pregnant women and fetuses.....	47
18.2.2. Prisoners	47
18.2.3. Children	47
18.2.4. Illiterate participants	47
18.3. Informed Consent.....	48
18.3.1. Informed Consent Process.....	48
18.3.2. Assent Process (in Case of a Minor)	49
18.3.3. Documentation of Informed Consent	50
18.3.4. Waiver of Informed Consent	50
18.3.5. Waiver of Documentation of Informed Consent.....	51
18.3.6. Stored Samples and Associated Data Considerations	51
18.4. Risks	52
18.5. Social Impact Events.....	53
18.6. Benefits.....	53
18.7. Compensation.....	54
18.8. Participant Privacy and Confidentiality	54
18.9. Certificates of Confidentiality.....	54
18.10. Critical Event Reporting	55
18.11. Communicable Disease Reporting.....	55
18.12. Incidental Findings.....	55
18.13. New Findings	56
18.14. Study Discontinuation	57
18.15. Post-Trial Access	57
18.16. Ancillary Benefits	57
18.17. Community Advisory Board and Other Relevant Stakeholders	58
19. Administrative Procedures	58
19.1. Protocol Registration.....	58
19.2. Regulatory Oversight.....	58
19.3. Study Implementation.....	59
19.4. ClinicalTrials.gov	59

20.	PUBLICATION POLICY (OPTIONAL)	59
21.	REFERENCES.....	59
22.	APPENDICES.....	59
	APPENDIX A.....	60
V.	MANUAL REFERENCES.....	61

I. INTRODUCTION

The Division of AIDS (DAIDS) has established a protocol documents manual to ensure that all clinical trials that are supported and/or sponsored by National Institute of Allergy and Infectious Diseases (NIAID) (DAIDS) have protocol documents that are written in compliance with the U.S. Department of Health and Human Services (HHS) regulations; the International Conference on Harmonisation (ICH), Guidance for Industry, E6 Good Clinical Practice (GCP); DAIDS Clinical Research Policies; and when applicable, the U.S. Food and Drug Administration (FDA) regulations. DAIDS requires the inclusion of specific, detailed information in protocols for NIAID (DAIDS) - supported and/or -sponsored clinical trials. Although DAIDS does not require the use of a standard protocol format, a sample template has been developed to assist protocol teams and Protocol Chairs/Co-Chairs. The sample template is the preferred DAIDS protocol format. This manual identifies required content areas and provides guidance as to the level of detail required in a protocol. It references regulations, guidance documents, and DAIDS policies and standard procedures that should be consulted during the development of the protocol. All DAIDS policies, standard procedures, guidance documents, and manuals referenced in this document can be accessed at the NIAID website: [DAIDS Clinical Research Policies and Standard Procedures Documents](#).

Investigators are responsible for ensuring that the protocol documents adhere to all applicable in-country, local, and institutional laws, regulations, guidelines, and policies.

Instructions

Address each section from the manual in the protocol, as applicable.

II. DEFINITIONS

Adverse event: Any untoward medical occurrence in a patient or clinical investigation participant administered a study product(s)/intervention(s) 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) study product(s)/intervention(s), whether or not related to the medicinal (investigational) study product(s)/intervention(s). (DAIDS, modified from ICH E2A)

Alternative therapy: Nonstandard treatments in place of conventional treatments. (DAIDS)

Clinical Trial: A prospective study of human subjects designed to answer questions about biomedical or behavioral interventions, e.g., drugs, treatments, devices, or new ways of using known treatments to determine whether the intervention(s) are safe, efficacious, and effective. (NIAID)

DAIDS sponsored: NIAID (DAIDS) is responsible for the management (including submission of the Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) and the initiation of the study) and oversight for the clinical trial or study. (DAIDS)

DAIDS supported: Clinical research activities would be considered to be supported by NIAID (DAIDS) under one or more of the following circumstances:

1. NIAID (DAIDS) provides direct funding to an institution via a grant, contract or cooperative agreement for the clinical research activities; or (b) indirect funding via a subcontract executed under a NIAID (DAIDS)-supported award to another institution; and/or
2. NIAID (DAIDS) provides other tangible support for the clinical research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services; and/or
3. NIAID (DAIDS)-supported central laboratory or data management center receives from other organization specimens or data for processing or analysis and the results or analyses will be used to direct involvement of some or all subjects in the conduct of the clinical research activities. (DAIDS)

Expedited adverse event (EAE): An adverse event that meets the criteria for expedited reporting, as specified in the applicable DAIDS manual. (DAIDS)

Incidental finding: Results arising from a research-related evaluation or procedure that are beyond the purposes of the study. (DAIDS)

Interventions: Physical procedures by which data are gathered and manipulations of the participant or the participant's environment that are performed for research purposes. (DAIDS, modified from 45 CFR 46.102)

Investigational device exemption (IDE): An approved investigational device exemption permits a device that otherwise would be required to comply with a performance standard

or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. (FDA)

Medical device: Any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized. (FDA)

Study products: Any drug, biologic, vaccine, radiopharmaceutical, item or device that are either provided for the study or identified in the protocol as being a study product. (DAIDS)

Vulnerable participants: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. (ICH E6)

III. LIST OF ABBREVIATIONS

ACASI	Audio-Computer Administered Self Interview
AE	Adverse Event
ARV	Antiretroviral
CAB	Community Advisory Board
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control
CDRH	Center for Devices and Radiological Health
CE	Critical Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CQMP	Clinical Quality Management Plan
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
dbGaP	Database of Genotypes and Phenotypes
DPRS	DAIDS Protocol Registration System
DSMB	Data Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
EQA	External Quality Assurance
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FWA	Federalwide Assurance
GCP	Good Clinical Practices
GCLP	Good Clinical Laboratory Practices
GDS	Genomic Data Sharing
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	Good Participatory Practices
GWAS	Genome-Wide Association Studies
HHS	U.S. Department of Health and Human Services
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug Application
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IF	Incidental Finding

IoR	Investigator of Record
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVR	Intra-Vaginal Ring
LoA	Letter of Amendment
MO	Medical Officer
MOP	Manual of Operating Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
OHRP	U.S. Office for Human Research Protections
PI	Principal Investigator
PK	Pharmacokinetic
PRO	Protocol Registration Office
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SRC	Scientific Review Committee
STI	Sexually Transmitted Infection
SUSAR	Suspected, Unexpected Serious Adverse Reaction
WHO	World Health Organization

IV. PROTOCOL DOCUMENTS CONTENTS

RUNNING HEADER AND FOOTER

Include the protocol number, draft or final version, version number, date, and page number in header or footer.

1. TITLE PAGE

The title page of a protocol submitted to the DAIDS for review must contain, at a minimum, the following:

The full title of the protocol: Include type of study (e.g., dose-ranging, safety, efficacy, pharmacokinetic)

Title of the main protocol (if applicable): Include the main protocol title and protocol number

The clinical trial phase: 1, 1/2, 2, 2B, 2/3, 3, 4, when applicable

Local Protocol Number (if applicable): This is the protocol number the applicant (i.e., applicant institution) has given the protocol.

DAIDS-ES Document Number: Protocols approved for DAIDS also receive a DAIDS-ES protocol number assigned at DAIDS

NIAID Funding Mechanism and Principal Investigator (PI): (e.g., grant number and PI name)

Other Collaborators: List the other institutions (e.g., other National Institutes of Health (NIH) Institutes/Centers or entities) providing funding or other support.

Pharmaceutical and other Study Product Support Provided by: List the names of any company(ies) providing support. Industry representative(s) should be indicated in the study team roster, when applicable.

IND Sponsor: The entity responsible for filing the Investigational New Drug Application (IND) with the FDA, if applicable. More specifically, the individual, company, institution, or organization as indicated in Box #1 of the Form FDA 1571 to be submitted to the FDA.

IND Number: If an IND study, provide the IND number or state pending. If a non-IND study, state non-IND.

Protocol Chair/Co-Chair: Individual(s) who is/are responsible for developing and conducting the study.

DAIDS Medical Officer/Medical Monitor: This person will generally be assigned by DAIDS after grant application review.

Version Number: Include "DRAFT Version 0.X" or "FINAL Version 1.0" on the first page and in the header or footer of the rest of the document.

Version Day Month Year: Use a date format that utilizes alphabet characters for the month and numeric characters for the date and year (e.g., 12 February 2013 or 12 FEB 13).

2. SIGNATURE PAGE (Optional)

See: International Conference on Harmonization ([ICH E6 Good Clinical Practice \(GCP\), Section 8.2](#))

DAIDS Policy [Protocol Registration](#)

DAIDS [Protocol Registration Manual](#)

DAIDS does not require the use of Signature Pages. A signature page may be included with the Essential Documents at the performance site.

3. TABLE OF CONTENTS

A detailed table of contents, clearly identifying the location of major sections and subsections is required in every protocol. The Table of Contents in the Protocol Documents Manual is an example that generally follows the format of this document.

4. KEY ROLES

See: ICH E6 GCP, Section 6.1

Include a list of persons/companies/groups serving in key roles (e.g., protocol chair/co-chair, protocol team members, DAIDS Program Officer and/or Medical Officer, if applicable, industry representative(s), sponsor(s)). Include contact information, such as institution name, mailing address, phone number, and email address.

5. LIST OF ABBREVIATIONS

Provide a glossary of acronyms and protocol-specific terms and spell out the acronym/term the first time mentioned in the protocol (with the acronym immediately following in parentheses).

6. PROTOCOL SUMMARY

A Protocol Summary should be included that is limited to 1-2 pages of the most pertinent protocol information. At a minimum, this will include:

Full Title

Include type of trial (e.g., dose-ranging, safety, efficacy, pharmacokinetic)

Title of Main Protocol (if applicable)

If protocol is a sub-study, include the title of the main protocol and protocol number

Short Title

An abbreviated title (either a few descriptive words or an acronym of the full title)

Sample Size

Include the total number of participants, participant pairs (e.g., mother-infant pairs, sero-discordant couples), or total number of evaluable participants, if applicable, as well as the number to be enrolled per arm.

Study Population

Include a brief description such as health status (healthy volunteers or human immunodeficiency virus (HIV) - positive), antiretroviral-naïve or treatment-experienced, adults or children, etc.

Participating Sites

List the participating sites in this section or reference where the complete list of sites can be viewed. State whether the sites are domestic or international and if any sites have restrictions.

Study Design

Provide an overview of the study design, including description of type (e.g., double-blinded, placebo-controlled, open label, dose-finding, parallel or crossover design, randomization scheme, and treatment), clinical phase, study arms, stratification, sample size, and intervention.

Study Schema

If the design or interventions are complex, provide a schematic representation of the study design including (if applicable): Stratification/arms, crossover, and the study timeline.

Schedule of Procedures/Evaluations

Reference where the Schedule of Procedures/Evaluations may be found.

Study Duration

State duration per participant, including the total length of time participants will be on study (intervention (e.g., 26 weeks) + follow-up (e.g., 12 weeks)). Indicate if duration per participant includes screening. Also include the total planned study duration (e.g., time from first participant enrollment until all participants are off study).

Study Regimen/Intervention

Provide a brief description of the study regimen (study product names, dosages, route of administration), including treatment duration. Differences in treatment arms, steps, or groups should be delineated. For a non-pharmaceutical study (device, procedure or behavioral intervention), provide a brief description.

Primary Objective(s)

List the primary objective(s).

Primary Endpoint(s)

Provide a brief description of the outcome measure(s).

7. INTRODUCTION**7.1. Background Information**

See: ICH E6 GCP, Section 6.2

Include:

A description of the disease/disorder the study is addressing

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

A summary of findings from pre-clinical studies that have potential clinical significance

A summary from relevant published and unpublished clinical trials, including studies with participants from the target population (e.g., pregnant women, adolescents, healthy volunteers), if available. Include references (e.g., publications, relevant websites) from which the information could be drawn

Discussion of important literature and data that are relevant to the trial and that provide background for the trial (list reference citations in [Section 21](#))

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

Discussion of relevant in-country policies and standard of care which may affect protocol implementation

List of study instruments (e.g., questionnaires), including validation information, that will be used during the conduct of the study, when the purpose of the instruments is to answer study endpoint(s)

7.2. Rationale

The rationale should justify the study and its design and support the primary objective(s). Justify any aspects of the study that are investigational or not approved by the FDA or regional health authorities (e.g., unapproved study product, unapproved formulation, dose or dosing schedule, route of administration, new combination of study products, or new study population for the study product(s)). Describe the importance of the study and any relevant treatment issues or controversies.

7.3. Study Hypothesis/Hypotheses

Include a statement of the hypothesis/hypotheses.

8. OBJECTIVES

See: ICH E6 GCP, Section 6.3

Study objectives are specific, succinctly worded statements that identify each of the major and minor scientific questions addressed in the study. Include endpoints and analyses in [Section 15](#) (Statistical Considerations) to support each objective. Each objective should have at least one corresponding endpoint.

Suggestions for study objectives include:

Statement of the 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, non-inferiority of intervention

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

Outcome measure or specified effect: i.e., the specific clinical, microbiologic, virologic, immunologic, etc. markers or tests that provide quantitative information or results

Specific study population

8.1. Primary Objective(s)

List the primary objective(s). Typically, this objective is/those objectives are used to power the study and is/are related to the primary endpoint(s) of the study, sample size, and analytic plan.

8.2. Secondary Objective(s)

List any secondary objectives.

8.3. Exploratory Objective(s)

List any exploratory objectives.

9. STUDY DESIGN

See: ICH E6 GCP, Section 6.4

A description should include:

Identification of major design elements (e.g., interventional, phase of trial, randomization scheme, placebo-controlled, open-label, double-blind, parallel design, dose escalation, dose-ranging, treatment)

Name of study product(s)/intervention(s)

Approximate time to complete study enrollment

Description and number of study groups or arms (e.g., control, case control, cohort) as well as elements such as dose escalations or stratifications

Size of each study group or arm and overall study sample size

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

The expected duration of participant involvement

Single-, limited-, or multi-center sites, etc.

10. STUDY POPULATION

See: 45 CFR 46, Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (45 CFR 46.201-46.207)

45 CFR 46, Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (45 CFR 46.301-46.306)

45 CFR 46, Subpart D – Additional Protections for Children Involved as Subjects in Research (45 CFR 46.401-46.409)

21 CFR 50, Subpart D – Additional Safeguards for Children in Clinical Investigations (21 CFR 50.50-50.56)

ICH E6 GCP, Sections 1.61, 6.5.1 and 6.5.2

The study population and inclusion/exclusion criteria must be clearly defined in this section of the protocol. The study population should be appropriate to meet the scientific objectives of the study. Describe the composition of the proposed study population in terms of sex/gender, racial/ethnic group(s), age group, and any special characteristics important to the study (e.g., human leukocyte antigen (HLA) type, high risk for HIV), and provide a rationale for the selection of such participants. If vulnerable participants (e.g., pregnant women, children, decisionally impaired) will be enrolled into the study, provide justification for the enrollment of these participants. For research on vulnerable populations, refer to NIH Grants and Funding [Research Involving Human Subjects](#). If women, minorities and children will not be recruited, explain why not. Refer to: NIH Grants and Funding [Inclusion of Women and Minorities as Participants in Research](#).

10.1. Inclusion/Exclusion Criteria

Define participant characteristics required for study entry in the inclusion criteria and exclusion criteria sections. The known risks of the study product(s)/intervention(s), strategy(ies), study population and scientific objectives 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 appropriately and judiciously (laboratory parameters selected should be related to the evaluation of safety, with ranges based on Adverse Event (AE) criteria).

10.1.1. Participant Inclusion Criteria

Provide a statement that the participant must meet all of the inclusion criteria to participate in this study and then list each criterion. Provide timeframes where applicable (e.g., within 14 days prior to study entry).

Examples include but are not limited to the following: informed consent obtained and signed, age, presence or absence of a medical condition/disease, required laboratory result(s), required concomitant medication(s), 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 potential will be enrolled, include

details of allowable or required contraception methods for study participants (e.g., use of both a barrier method and licensed hormonal methods), taking into account the potential effect of the study product(s) to cause teratogenicity and/or to impact spermatogenesis.

10.1.2. Participant Exclusion Criteria

Provide a statement that all participants meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. Provide timeframes where applicable (e.g., within 14 days prior to study entry).

Examples of reasons to exclude participants include but are not limited to the following: recent (specify time frame) acute illness that precludes or delays participation, pregnancy or breastfeeding, characteristics of household or close contacts (e.g., household contacts who are immunocompromised), known allergic reactions to components of the study product(s), use of excluded drugs, biologics, or vaccines within a specific time frame prior to study entry (e.g., systemic cancer chemotherapy, systemic investigational products), laboratory finding that precludes participation, history of drug/alcohol abuse, which in the opinion of the investigator, would interfere with adherence to study requirements, receipt of prohibited concomitant medications, any other condition or prior therapy, that in the opinion of the investigator, would preclude informed consent, make study participation unsafe, make the individual unsuitable for the study or unable to comply with the study requirements.

10.1.3. Co-enrollment Criteria

A study participant's involvement in more than one clinical trial at one time, or co-enrollment, may result in significant risk to the participant and also have a negative impact on the ability to evaluate the study results. Unless specified otherwise in the protocol document, co-enrollment into any clinical trial can only be approved by the Protocol Chair/Co-Chair (include entity that can approve co-enrollment) as the potential risks to the participant as well as the impact to the validity of the data must first be assessed.

For any study in which co-enrollment approval is predetermined (e.g., tissue repository study), the protocol number and title should be listed in the protocol and it should be specified that co-enrollment is acceptable. If it is known that participants will be prohibited from co-enrollment into specific types of studies (e.g., investigational HIV vaccine study, any investigational intervention etc.), those types of studies should also be listed in the protocol and designated as co-enrollment prohibited.

10.2. Recruitment Process

Describe the strategy/process by which participants will be recruited, screened, and enrolled in the study or reference where this information can be found. Include a description of the community from which the study population will be drawn as well as the recruitment locations (e.g., in-patient hospital setting, out-patient clinics, student health service).

10.3. Participant Retention

Describe the activity(ies) for retention of enrolled participants in the study and efforts to minimize possible loss to follow-up.

11. INTERVENTIONS (including STUDY PRODUCT)

See: 45 CFR 46.102

21 CFR 312, 21 CFR 600, and 21 CFR 812

ICH E6 GCP, Sections 6.4.4 and 6.6

For studies utilizing Recombinant DNA molecules, see:

[NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules](#)

DAIDS [Protocol Registration Manual](#)

Clinical trials can include both biomedical and behavioral interventions.

11.1. Biomedical Interventions

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

See: ICH E6 GCP, Section 6.6.1

Use the generic names for study product(s), and the convention Placebo for Generic Name for naming placebos.

11.1.2. Study Product Formulation and Preparation

See: ICH E6 GCP, Section 6.4.4

Include the formulation, manufacturer, strength, labeling information, and/or concentration. Also include excipient information if not in the Investigator's Brochure (IB) or the Product Package Insert, (e.g., brand and trade name). Exclude information about study formulation that could inadvertently unblind the study.

Include appropriate preparation information such as thawing, diluting, mixing, reconstitution, and preparation procedures, equipment and supplies needed for preparation. Include requirements for aseptic technique, or biosafety level containment requirements. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted. Include acceptable storage temperatures, storage conditions (humidity, protection from light, protection from carbon dioxide), security, and storage times for all study products and study supplies. As applicable, include acceptable storage temperature/conditions during transport to the clinic or in the participants' home if these differ from the pharmacy.

11.1.3. Device Studies

See: FDA device regulations, 21 CFR 800-892

[FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions about Medical Devices](#)

For further reference see also: FDA's Center for Devices and Radiological Health (CDRH) [Recent Medical Device Guidance Documents](#)

If intended use is for the investigation of basic physiology, there is no intent to develop the device for marketing, and the device is only being used to address the research question, then an IDE is not needed. Ethics Committee (EC)/Institutional Review Board (IRB) approval and informed consent should be obtained (21 CFR 812.2(a)). If an EC/IRB is uncertain whether a study is exempt, significant risk or non-significant risk, the FDA will make a determination. The sponsor submits a draft protocol and details about the device to be investigated in the form of a Pre-Submission. The FDA will issue a letter (usually within 60 days) with binding determination for both the sponsor and EC/IRB.

Consider all applicable ICH Good Laboratory Practice (GLP), GCP and Good Manufacturing Practice (GMP), World Health Organization (WHO), Organisation for Economic Co-operation and Development (OECD) and International Organization for Standardization (ISO) requirements.

When appropriate, include other relevant information about the device, such as care and maintenance of the device.

Device examples

Combination Products (drug + device, drug + biologic): consider if either product has received regulatory approval. In the U.S., the FDA Office of Combination Products assigns the major review to one agency branch based upon the primary action on the human body (e.g., antiretroviral (ARV)-containing Intra-Vaginal Ring (IVR) to be reviewed by CDRH; pre-filled vaccine syringe reviewed as a biological by FDA's Center for Biologics Evaluation and Research (CBER), and medicated catheter will be reviewed by CDRH). For the U.S., if neither product has existing regulatory approval, drugs and biological products must go through the series of clinical trials to show efficacy and safety. The device must meet the essential requirements and not add any deleterious effects (e.g., polymer leachables). If the drug or biologic is FDA approved for the intended application, then only the device must meet the above requirements. If the device is approved, the drug or biological have to follow the above evaluation for efficacy and safety.

Diagnostic Devices (e.g., diagnostic test kit development) will be reviewed by CDRH. Clinical trial data will be examined to determine whether the device is safe and effective. Investigators are responsible for ensuring that the protocol documents adhere to all applicable in-country, local, and institutional laws, regulations, guidelines, and policies.

11.1.4. Study Product Supply and Accountability

See: ICH E6 GCP, Section 6.4.7

Provide plans for how the study product(s)/intervention(s) will be distributed including information about the company or entity providing or supplying the study products, participation of a clinical research product distribution center, and details about how the pharmacist is to acquire the study product(s).

Include instructions for the receipt, handling, storage, dispensing, accountability, and retrieval of unused study products from participants. Provide directions regarding the disposition of study product returned by participants, as well as details on the return or destruction of unused study products both during and after the study is completed.

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

See: ICH E6 GCP, Section 6.6.3

Determine if and how participant adherence with study product(s)/intervention(s) will be assessed (e.g., pill counts, electronic monitoring devices, adherence questionnaires, direct observation, drug levels from laboratory tests), if applicable. If so, provide details on procedures for monitoring participant adherence. In the Analysis Plan in [Section 15.8.2](#), describe how this information will be incorporated into the analysis of the study results. If no such assessment is planned, state why it is not needed or cannot be incorporated into this protocol.

11.1.6. Concomitant Medications and Procedures

See: ICH E6 GCP, Section 6.6.2

Consider providing specific directions regarding the use of concomitant medications or procedures.

Sample language:

“Provide a list of selected concomitant medications or reference where the complete list can be viewed.”

“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 or 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

List types of medications (e.g. specific agents, including classes of investigational products, immunomodulators, prophylaxis or treatment for concurrent morbidities, complementary and alternative therapies) and procedures that are permitted on study.

11.1.8. Prohibited Medications and Procedures

List all medications and procedures that are NOT permitted while receiving study product(s) or while on study. Include drugs from the exclusion criteria if they are also prohibited while the participant is on study.

11.1.9. Precautionary Medications and Procedures

List all medications and procedures for which there are precautions for concomitant use with the study product(s)/intervention(s). Include instructions for dose modification, if appropriate.

11.1.10. Required Medications

List all medications that will be required on study. This may include medications used for prophylaxis. Indicate whether or not the medications will be provided as part of the study.

11.1.11. Rescue Medications

If applicable, list all medications that may be provided or required on study for “rescue therapy.” Rescue therapy is defined as the administration of medication in order to prevent or minimize significant side effects of the study product. For example, administering leucovorin or folate to minimize the effects of methotrexate toxicity.

11.2. Behavioral Interventions:

If applicable, provide the details of each behavioral intervention. Include the theoretical basis for the intervention, the target behavior, the hypothesized effect of the intervention, the plan for maintaining fidelity to the intervention, and how the intervention will be evaluated to determine if the intervention was successful. Also include relevant information on the person(s) conducting the intervention (e.g., background, training).

Examples of behavioral interventions:

Network-oriented peer education intervention for the prevention of HIV transmission

Enhanced nursing support by phone or text message to improve medication self-management and study adherence

Study of motivational interviewing for individuals with acute and early HIV-infection to improve linkage and retention in care

12. STUDY PROCEDURES/EVALUATIONS

Use of a Schedule of Procedures/Evaluations is strongly recommended. Information in this section should be consistent with [Appendix A](#) (Sample Schedule of Procedures/Evaluations) of this manual. 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. Either way, all information pertaining to study procedures and

evaluations that are required in accordance with the protocol should be described in this section and included under the appropriate title headings.

12.1. Clinical Evaluations and Procedures

List all clinical evaluations and procedures to be conducted during study visits, and provide details/timelines related to each action (and special instructions, if any). Include a description of the study instruments that will be used. When the study instruments are not included in the protocol appendices, reference where they can be found.

Examples include baseline assessment and follow-up clinical visits for:

Medical History: describe what is included as medical history, e.g., timeframe considerations, whether history will be obtained by interview or abstracted from medical records

Medication History: describe the information needed, e.g., complete medications history; current medications; prescription medications only; complementary and alternative medications; non-prescription medications. Assessment of eligibility should include a review of permitted and prohibited medications

Physical Exam: list the vital signs and organ systems to be assessed; if appropriate, discuss what constitutes a targeted physical exam and at what visit(s) it will occur

Reactogenicity assessments: e.g., pain, tenderness; describe rating scale

Adherence: describe procedures that will be used to assess adherence, such as pill count, electronic monitoring device, laboratory tests

Review of diary cards: e.g., food diary, signs/symptoms diary

Counseling procedures: e.g., HIV counseling and testing, post HIV acquisition¹, risk reduction)

Radiologic procedures: e.g., chest x-rays, dual-energy x-ray absorptiometry (DEXA) scans, computed tomography (CT) scans

Questionnaires and interviews: e.g., quality of life, behavior, audio-computer administered self interview (ACASI), food insecurity, assessment of understanding questionnaire, Behavioral and neuro-cognitive assessments: e.g., trail making test, digit symbol test

12.2. Laboratory Evaluations

See: DAIDS Policy [Requirements for Laboratories in Clinical Trials](#)

DAIDS Guidelines for [Good Clinical Laboratory Practice Standards](#)

¹ When applicable, post HIV acquisition counseling should provide details on the in-country standards that address when ARV therapy will be started (i.e., early versus late treatment) and availability of ARV therapy.

List all laboratory tests to be conducted during the study, and provide details at each visit of what is included and special instructions, if applicable. The choice of tests in the protocol pertains to:

1. The purpose of the study and the associated outcomes being assessed.
2. The study product(s) being evaluated and the expected safety and pharmacologic/immunogenicity profile.
3. The clinical and epidemiologic attributes of the population from which the participants are selected and for which they are considered representative.

Include specific test components (see examples below) and estimated volume and type of specimens needed for each test. Specify laboratory methods (e.g., plasma HIV-1 viral load by ribonucleic acid RNA polymerase chain reaction (PCR)); use consistent laboratory methods throughout the study to provide for appropriate longitudinal and cross-comparison.

If evaluations are used for diagnosis of infection (e.g., HIV, hepatitis B or C virus, tuberculosis), provide the diagnostic algorithm in the entry criteria, endpoints, or clinical management section of the protocol, as appropriate.

The protocol should mention that:

1. Laboratories in the United States that generate data used to make patient management decisions must be Clinical Laboratory Improvement Amendments (CLIA) certified, have a CLIA waiver, or be CLIA exempt.
2. All laboratories should be conducting operations in accordance with Good Clinical Laboratory Practices (GCLP). Links to these requirements and guidelines can be found at the beginning of this section.
3. Relevant information on the assays' validation, unique reagents, external quality assurance (EQA) enrollment for all DAIDS clinical trial analytes and laboratory data management plan should be included in the Manual of Operational Procedures (MOP) or accompanying documents. Links to these requirements and guidelines can be found at the beginning of this section.

Examples:

Clinical hematology: CBC with differential, platelet count

Clinical chemistry: alanine transaminase (ALT), aspartate aminotransferase (AST), BUN, creatinine, creatinine clearance (CrCl), Bilirubin (total and direct), glucose (fasting/non-fasting), lipid profile

Urinalysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required

Pregnancy test: specify the type of test (i.e., blood, urine) and timing of the test. State that result must be available prior to administration of study product

Biopsy (tissue) or other specimens (swabs, lavages, sputum, cerebrospinal fluid, blood) for microbiology culture, viral load determination, or other testing (resistance mutations)

Immunology: CD4+/CD8+ T-lymphocyte counts, lymphoproliferative assays, intracellular cytokine assays, immunohistochemistry assays, advanced multicolor flow cytometry

Infectious disease: HIV, viral hepatitis, tuberculosis, sexually transmitted infection (STI)

Pharmacokinetic studies

12.2.1. Specimen Preparation, Handling and Shipping

Basic information on specimen preparation, handling, storage and shipping (e.g., to where samples will be shipped) must be included in the protocol document. Detailed information must be included in a MOP, or in the protocol document, as an Appendix to the protocol, or other accompanying documents. Include information on required storage and shipping temperatures, where specimens will be stored, and how specimens will be labeled. State the frequency with which specimens are to be shipped and to what address as well as any necessary contact information and any labeling requirements for specimen shipping. Also, include any special instructions such as dry ice or the completion of a specimen-tracking log. When the details (e.g., storage temperatures, blood tube type, address where the specimens will be shipped) are not included in the protocol, reference where this information can be found. Refer to DAIDS Policy [Requirements for Laboratories in Clinical Trials](#), [Guidelines for Good Clinical Laboratory Practice Standards](#), [Manual of Operational Procedures](#), and [Required Site SOPs](#).

For information on long-term access and informed consent considerations, see [Section 18.3.6](#) (Stored Samples and Associated Data Considerations).

12.2.2. Biohazard Containment

The Principal Investigator is responsible for ensuring that procedures for biohazard containment are in accordance with local, national, and international regulations, as applicable.

Describe the procedures for biohazard containment that will be used in the study.

Sample language for United States (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

Document the total blood volume per study visit in the protocol-related documents or reference where this information can be found. For studies that involve children (usually persons under 18 years of age) and pregnant women, as well as other populations when indicated, include a running cumulative volume. This information can be included in the schedule of procedures/evaluations. Document the maximum amount of blood volume that will be collected over a given period of time (e.g., X mL over an 8-week period) in the protocol. The maximum amount of blood volume that will be collected under the protocol will adhere to currently accepted guidelines². Questions regarding allowable blood volume amounts should be discussed with the DAIDS Medical Officer (MO).

In clinical trials, as the number of blood draws or blood volumes increases, ethical issues often arise, especially in clinical trials with children. If there is a limited sample volume (e.g., child-participant, venous access is lost), the order of importance for blood tests should be listed, so that tests will be prioritized. To limit pediatric blood draws, a footnote may be inserted in the Schedule of Procedures/Evaluations.

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”

For studies that include an apheresis procedure, include the total whole blood volume per procedure, including the additional whole blood volume if venous access is lost.

² Examples of blood volume guidance include WHO (<http://www.who.int/bulletin/volumes/89/1/BLT-10-080010-table-T2.html>) and OHRP (<http://www.hhs.gov/ohrp/policy/expedited98.html>)

12.3. Schedule of Procedures/Evaluations: Timing and Definitions

A table can be used to define the Schedule of Procedures/Evaluations at each study visit and should include all study procedures/evaluations. Define the procedures/evaluations in this section.

Throughout the protocol, refer to the Schedule of Procedures/Evaluations (e.g., as protocol Appendix A).

The schedule must include not only clinic visits but all contacts with the participants, e.g., telephone contacts.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the time point to study outcome measures (e.g., Pharmacokinetics (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).

Identify when screening and/or enrollment informed consent will be obtained.

Examples of typical visits that are required in protocols are included below. A protocol might not require the use of each visit type as listed below in sections 12.3.1-12.3.8:

12.3.1. Screening

Include only those evaluations necessary to assess whether a participant meets enrollment criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the timeframe prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment). Provide details, including if participants will be referred for medical care, due to a failed screening, such as a laboratory abnormality, STI, or positive HIV test.

12.3.2. Enrollment

Discuss evaluations/procedures necessary to assess or confirm whether a participant still meets the eligibility criteria and may be enrolled, and 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 that must be met (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).

12.3.3. HIV Counseling and Testing

When HIV counseling and testing will be part of the study interventions, state under what guidelines (e.g., WHO, Centers for Disease Control (CDC) and other National or local³ guidelines) HIV counseling will be performed, counseling method, and the information that will be reviewed. Include details on the assays used for HIV testing. Provide details on counseling and referral to care for participants who test HIV positive.

12.3.4. 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 adverse events, retention activities, etc.

12.3.5. Early Termination Visit

Specify which evaluations will be done at an early termination visit (intervention discontinuation and/or study discontinuation) if the participant terminates their participation in the study early and if the participant is willing. Participants may withdraw voluntarily from study participation at any time. Participants may also withdraw voluntarily from receiving the study intervention for any reason or may be withdrawn involuntarily from study product but may be willing to remain in study follow-up. Clearly differentiate between what evaluations are to be done in each of these circumstances, if necessary. See [Section 14.6](#) (Clinical Management) for discussion of criteria for discontinuation.

In some circumstances, it may be reasonable to ask the participant to continue scheduled evaluations, complete an end-of-study evaluation, or be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.

12.3.6. Pregnancy Visit

The protocol should address the procedures to be followed if a woman subsequently becomes pregnant or believes she may be pregnant while on study. Indicate whether the woman will be allowed to continue to receive the study product(s)/intervention(s). Provide any other guidance relevant to the study product/intervention and pregnancy and/or breastfeeding. (For example, the participant may be allowed to continue to receive study product during pregnancy but will not be allowed to have biopsies or certain imaging procedures.) See [Section 14.3](#) (Clinical Management, Pregnancy) for additional information on clinical management of women who subsequently become pregnant while on study.

12.3.7. Other Visits

Additional visits as well as specific evaluations might need to be performed at treatment failure, at premature discontinuation of study products, or for other special circumstances

³ Local guideline should be included if they are consistent with the standard of care (e.g., for implementation studies).

or events. For example, there might be alterations in the evaluations performed or schedule of evaluations for participants after permanent discontinuation of the study intervention. In complicated studies with multiple registration/randomization points, the investigator may wish to include the time of registration, randomization, and product dispensed.

12.3.8. Final Study Visit

Define when the final study visit should occur and any special procedures/evaluations or instructions to be given to the participant. Describe provisions for follow-up of ongoing adverse events/serious adverse events.

13. ASSESSMENT OF SAFETY

See: 21 CFR 312 (Investigational New Drug Application)

ICH E6 GCP, Sections 4.11 & 6.8

DAIDS Policy [Expedited Adverse Event \(EAE\) Reporting](#)

Information on expedited reporting of AEs, available on the Safety Office of the [DAIDS Regulatory Contractor](#) website, includes:

1. [Manual for Expedited Reporting of Adverse Events to DAIDS](#)
2. [DAIDS Expedited Reporting: DAIDS Adverse Experience Reporting System \(DAERS\)](#)
3. [DAIDS Protocol Template for Expedited Reporting](#)
4. [The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events](#)

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.](#)"

The U.S. Code of Federal Regulations (CFR) defines procedures and requirements governing the use of investigational new drugs and/or interventions and the monitoring of serious adverse events (21 CFR 312). Because the NIAID (DAIDS) sponsors an extensive program of research into investigational modalities for the treatment and prevention of AIDS, it is responsible for ensuring that the research is conducted in accordance with all applicable U.S. federal regulations.

One such U.S. federal regulation (21 CFR 312.32) requires that clinical trial study sponsors report all serious adverse events to the FDA for those studies being conducted under an IND. Similar requirements on the collection of serious adverse event data and reporting to the appropriate regulatory authorities are also described in the ICH E6 guidance. Another U.S. federal regulation (21 CFR 312.64(b)) describes investigator responsibilities that include prompt reporting of all serious adverse events to the sponsor. In addition, investigators are required (45 CFR 46.103) to inform, among others, clinical trial study sponsors of unanticipated problems involving risks to participants or others.

13.1. Safety Assessment Overview

DAIDS uses DAERS to fulfill its serious adverse event reporting requirements to the FDA. All protocols requiring expedited reporting of adverse events to DAIDS should follow the guidance in the document DAIDS Protocol Template (Section 13.0 Assessment of Safety). In the event that DAIDS is not the study sponsor and does not receive expedited adverse event reports through DAERS, the template language can be used as a guide to fully describe the components of an expedited reporting system.

The safety assessment overview section provides relevant information on the development of an adverse events expedited reporting section in a protocol.

13.2. Adverse Event Procedures and Reporting Requirements

The protocol must define its AEs, and follow DAIDS or local (EC/IRB or safety review committee) guidelines for reporting AEs in an expedited fashion. For definitions of SAE and SUSARs, refer to the DAIDS Policy [Expedited Adverse Event \(EAE\) Reporting](#) and [Manual for Expedited Reporting of Adverse Events to DAIDS](#).

General Considerations

In any protocol, a section detailing the assessment of safety should include precise definitions of AEs (e.g., as defined in [ICH E2A](#)), as well as, procedures for collecting, recording, and assessing adverse events. For example, the time period within which AEs will be collected, how they will be collected (i.e., solicited versus unsolicited AEs) and in what format they will be collected (e.g., in a diary card or as a structured questionnaire) should be stated. This section should also describe the circumstances in which other clinical findings and/or abnormal laboratory values will be recorded as AEs on the Case Report Forms (CRFs), and a timeframe within which the AE must be submitted. Finally, it should include specific criteria and procedures for determining which AEs require expedited reporting to the sponsor.

Of note, any medical condition that is present before the administration of a study product(s) and/or intervention(s) should be recorded during the baseline assessment. If the AE worsens while the participant is participating in the study, the condition should be recorded as an AE and reported under the protocol parameters.

Complete descriptions of all AEs must be available in source documents (e.g., medical records). An AE description should include all of the following:

1. AE term (i.e., the one term that best describes what occurred)
2. AE start and stop dates
3. Severity grade of the AE (see grading table information below)
4. Study product(s) and/or intervention(s) administered
5. Relationship of the AE to the study product(s) and/or intervention(s)
6. Action taken regarding the study product(s) and/or intervention(s)⁴
7. AE outcome (e.g., recovered or resolved, not recovered or not resolved, recovered or resolved with sequelae, or unknown)

8. What seriousness criteria, if any, were met (for SAE definition, refer to the [DAIDS Policy Expedited Adverse Events Reporting](#))

In order to maintain consistency among clinical trials and clinical research sites for evaluating the severity of an AE, DAIDS developed a table of common clinical and laboratory AEs. The Division of AIDS [Table for Grading the Severity of Adult and Pediatric Adverse Events](#) lists criteria used to assess the severity and intensity of specific AEs. It also contains instructions on how to assess severity for an event that is not included in the table. However, a protocol-defined grading system may also be provided if AEs of interest are not specified or if a greater degree of detail than what is listed in the grading table is required. A decision concerning the use of a protocol-defined grading system is usually made during the protocol development stage, and the alternate grading system must be included in the final version of the protocol.

While all AE information must be submitted to the clinical trial sponsor (see below), DAIDS also requires that site investigators submit all AE information in accordance with the local EC/IRB, local regulatory entity and/or other local authority requirements. Reporting procedures for each local regulatory entity and/or other local authorities should be specified in the expedited reporting section of the protocol, or reference where this information can be found.

Finally, if a particular study does not warrant expedited reporting to a sponsor, a justification as to why adverse events will not be reported in an expedited manner must be incorporated into the protocol.

Expedited Reporting of Adverse Events Using the DAIDS Adverse Experience Reporting System (DAERS)

For those protocols reporting EAEs to DAIDS, all information must be submitted through DAERS. If a clinical research site experiences technical difficulty accessing DAERS, the Division of AIDS Safety Office Expedited Adverse Event (EAE) Reporting Form must be used. All information requested on the DAIDS EAE Form must be provided and the form faxed or e-mailed as an attachment to the Safety Office at the DAIDS Regulatory Contractor. Fax numbers and the email address are listed on the form.

To fully define the expedited reporting requirements, the protocol must specify the following:

1. The reporting category to be used (i.e., either serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR)) and any additional protocol-specific reporting requirements,
2. The study product(s) and/or intervention(s) for which expedited reporting to DAIDS is required,
3. The duration of the protocol-defined expedited reporting period (typically from study enrollment to study completion or discontinuation). If an extended follow-up period after study completion or discontinuation is warranted, this must be specified in the protocol.
4. The version number of the DAIDS grading table and any additional or modified protocol-specific grading tables that will be used in the study.

Expedited Reporting of Adverse Events Using Other Systems

For those protocols that will not use DAERS to report AEs (e.g., some studies under non-DAIDS-held IND), an AE reporting system must be adequately described. The following provides a sample outline of an AE Reporting Section in a protocol:

1. Definitions – all AE-related terms must be defined and may include:
 - a) AEs or adverse reactions
 - b) Suspected adverse reactions
 - c) SAEs
 - d) Suspected, serious adverse reactions
 - e) Unexpected AEs
 - f) Other AEs (e.g., SUSARs, non-treatment emergent adverse events, or other events that do not warrant expedited reporting to the sponsor, such as pre-existing conditions)
2. Unanticipated problems (these are related to, but distinct from, AE reporting and have a separate reporting mechanism, because while all unexpected AEs are unanticipated problems, not all unanticipated problems are AEs). See Section 18.10 (Critical Events Reporting) for additional information.
3. Documentation of AEs – information on how AEs will be recorded and documented in the study must be included:
 - a) Define the AE collection period (typically from the time of participant enrollment through study completion or discontinuation).
 - b) Describe what information will be collected on the AE (e.g., the AE term, AE start and stop dates, AE severity grade, study product(s) and/or intervention(s), relationship of the AE to the study product(s) and/or intervention(s), action taken regarding the study product(s) and/or intervention(s), AE outcomes such as recovered or not resolved, and what seriousness criteria, if any, were met (see SAE definition above)).
 - c) Explain how participants will be assessed for AEs (e.g., active solicitation of events from the participant, review of the participant’s diary) and the frequency of the assessment (e.g., only at specified study visits, periodic calls to participant). Assessments will include unsolicited AEs and re-assessments of previously reported AEs. If no AEs are documented during an AE solicitation period, the protocol should specify whether this information will be captured.
 - d) Specify where the AE data will be recorded (e.g., AE CRF) and stored (e.g., at a data management center) along with the timeframes for doing so.
4. Reporting Procedures – list the steps involved in expedited reporting to the sponsor, namely:
 - a) Describe the type of AEs that will be submitted in an expedited timeframe, including any assessment categories that will be used to determine reportability

- (e.g., DAIDS uses seriousness, severity, causality, and expectedness as assessment criteria).
- b) Identify any additional protocol-specific reporting requirements (e.g., all \geq Grade 3 hepatic laboratory values; all cancers).
 - c) List the study product(s) and/or intervention(s) that require expedited reporting to the sponsor.
 - d) State the expedited reporting timeframe (e.g., within 24 hours of occurrence; within three business days after site awareness) and specify if there are different timeframes for reporting different events (e.g., 24 hours for death or life-threatening events).
 - e) Specify whom sites should contact to submit their AEs (e.g., the study sponsor). If there are additional parties that should be copied on the submission (e.g., the local EC/IRB), ensure they are listed as well.
 - f) Define the method of expedited reporting of events to the sponsor (e.g., by telephone, fax, electronic reporting).
 - g) Specify the reporting period (typically from the time of participant enrollment through study completion or discontinuation). If there is an additional follow-up period after study completion (e.g., long-term surveillance), state the duration of the follow-up period and if assessment and reporting of AEs are required during this time period.
 - h) DAIDS-specific requirement: If the protocol is planning to use any of the DAIDS expedited reporting materials (e.g., the DAIDS EAE manual or the DAIDS grading table), those materials should be cited in the protocol.
 - i) DAIDS-specific requirement: Specify the provisions (if any) for informing DAIDS of any events that meet expedited reporting requirements, including those subsequently submitted as safety reports (e.g., MedWatch) to regulatory authorities.
5. Pause and Stopping Rules – list the criteria involved in determining whether or not administration of a study product(s) and/or intervention will be withheld or discontinued for the study:
- a) State the criteria for temporarily withholding a study product(s) and/or intervention(s) from participants and include provisions for the resumption of study product(s) and/or intervention(s) administration. (i.e., tests which must be evaluated for participant safety prior to re-initiation of the intervention).
 - b) State the criteria for stopping enrollment and administration of a study product(s) and/or intervention(s) and include the provisions (if any) for resuming enrollment in the study and continued administration of the study product(s) and/or intervention(s).
6. Unblinding Procedures, if applicable – describe the steps for unblinding study product(s) and/or intervention(s):
- a) State reason(s) why the participant(s) or study may be unblinded

- b) State how the unblinding will be documented (e.g., noted in the participant's source documentation)
 - c) Define who will be notified of the unblinding and the timeframe for notification
7. Safety Monitoring See [Section 15.8](#) (Statistical Considerations) for information on data and safety monitoring, to be included in the protocol.

14. CLINICAL MANAGEMENT

14.1. Clinical Management of Adverse Events

The AE clinical management section, which includes management of toxicities, describes management of commonly occurring, serious, or important adverse events, or clinical or laboratory findings associated with the use of the study product(s)/intervention(s).

Criteria used for participant management should be very clear and include:

1. A standardized AE management scheme for commonly occurring, serious, or important events associated with the use of the study product(s)/intervention(s) or that reasonably could be expected to occur to the participants during the course of the study due to the underlying disease process and mechanism of action of the study intervention(s).
2. Guidelines for when study product(s)/intervention(s) are to be held, stopped, and restarted and what procedures should be followed if study product(s) are restarted. Instructions for dose modifications, and changes in additional evaluations (e.g., change in dose or need for additional follow-up visits) should be included. Consider the use of dose modification tables or flow charts to describe various AE management scenarios. This information should be described as comprehensively as necessary on the basis of the study product(s)/intervention(s) or population.
3. A description of the management for each intervention, if the study is investigating multiple study interventions. Specify how to manage the study intervention(s) for various anticipated clinical or laboratory AEs, including the sequence of reintroducing or substituting study products and/or other study interventions, and the use of rescue medications, if there are any. Note that when an AE occurs in a study with combination therapy, it might be difficult to determine which agent is responsible and how to manage the AE.

Sample language:

“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 _____.”

See [Section 15.8](#) (Statistical Considerations) for information on AE data and safety monitoring activities.

Site investigators will manage AEs based on the criteria in the protocol (e.g., severity grade in the DAIDS toxicity table) and, in some cases, relationship to study product. Clinical management of AEs might best be described by adverse event or clinical or laboratory findings and presented in table format.

Examples of Commonly Managed AEs that may be listed in a separate table:

Anemia and neutropenia

Elevated ALT or AST

Decreased creatinine clearance

Rash

Elevated serum triglycerides or cholesterol

Consider including information on the management of AEs that occur as a result of a study procedure.

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

Describe the management of other relevant infections or clinical events and other treatment complications in this section (e.g., development of hepatitis C and how diagnosis will be defined).

Define particular events or reference where this information can be found. The investigator or team may wish to standardize the definition of some clinical events, to standardize a definition between sites or for the entire duration of the study. For example, define the criteria for confirmed and probable diagnoses of cryptococcal meningitis or progression of a clinical event such as myocardial infarction.

14.3. Pregnancy

The protocol should describe the procedures to be followed if a female participant believes she may be pregnant or in the event a woman subsequently becomes pregnant, including if there is an additional study-specific pregnancy consent form for continuation on the

study. Provide appropriate modifications to study procedures (e.g., discontinuation of study product(s)/intervention(s), conditions under which continuation of the intervention may occur, or alterations in study evaluations such as limiting radiation exposure or blood volumes). In most instances, some form of follow-up of the woman will be needed until the pregnancy outcome is known. The protocol should describe what pregnancy-related information will be collected (e.g., medical complications, obstetrical complications, pregnancy outcome including births and fetal loss/abnormalities, and maternal and infant follow-up). Include appropriate mechanisms for reporting to sponsor, study leadership (as appropriate), EC/IRB, and regulatory agencies. The protocol should also describe whether there is a rollover protocol for the woman and/or the infant/child.

Sample language:

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

If the participant is receiving antiretrovirals or other products for which voluntary or required pregnancy registries exist, consider inclusion of a statement about this registry in the protocol. Include details about how information is reported to the registry.

Sample language:

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

14.4. Breastfeeding/Replacement Feeding (if applicable)

The protocol should follow the current [WHO](#) or applicable in-country infant feeding guidelines. The protocol should state whether or not study participants (applicable to both mothers and infants) will be allowed to breastfeed or formula feed.

Breastfeeding

If breastfeeding is permitted during study participation, the protocol should provide guidance on how to manage HIV-positive study women who plan to breastfeed their infants.

Replacement Feeding

When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-infected mothers is currently recommended. When deciding if formula feeding will be allowed, also consider whether safe water to reconstitute formula is readily available.

14.5. Acquisition of HIV infection on study (if applicable)

The protocol should include a testing algorithm for confirmation of HIV infection. This algorithm should be followed for any participant for whom the acquisition of HIV infection is suspected. For participants that subsequently become HIV infected, describe how often participants will be followed after HIV infection is confirmed, what assessments will be performed, and to what extent study participation and study product(s)/ intervention(s) will continue. Also include other information such as counseling and referral for medical care, including management of HIV infection.

14.6. Treatment Failure (if applicable)

When managing treatment failure (e.g., HIV, Tuberculosis, or Hepatitis C treatment) is part of the objectives of the protocol, address how treatment failure will be monitored and managed.

When applicable, for HIV ARV regimen treatment failure, the protocol should describe the criteria to define virologic or immunologic treatment failure and provide details on how treatment failure will be monitored (e.g., specific laboratory tests that will be performed, documentation of drug resistance) and managed. For participants that subsequently fail the protocol's ARV regimen, provide information on managing the treatment failure (e.g., stop study product administration, list available alternate ARV regimens).

14.7. Criteria for Discontinuation

See: ICH E6 GCP, Sections 6.4.6 and 6.5.3

There may be situations where the study product(s)/intervention(s) will be discontinued but the participant will continue to be followed under certain parameters, as specified in the protocol.

The reasons for permanently discontinuing the study product(s)/intervention(s) for a participant and reasons for prematurely discontinuing the study for a participant may differ and will require separate clearly defined criteria.

See [Section 15.8.1](#) (Statistical Considerations) for criteria for stopping rules for participant subgroups or the entire study.

14.7.1. Criteria for Permanent Intervention Discontinuation for an Individual Participant

The protocol must provide:

Criteria for permanent discontinuation of study product(s)/ intervention(s) to an individual; and

Plans for continued follow-up of the participant and, as applicable, resulting modifications to the schedule and duration of follow-up

Sample language:

1. “The criteria for permanent discontinuation of further study product(s)/ intervention(s) for an individual participant are:
 - a) Study product/intervention-related adverse event (see [Section 14](#), Clinical Management)
 - b) Requirement for prohibited concomitant medications
 - c) Pregnancy or breastfeeding (if applicable)
 - d) Reaching a defined clinical endpoint (if applicable)
 - e) Completion of study product(s)/intervention(s) as defined in the protocol
 - f) Request by participant to terminate study product(s)/intervention(s)
 - g) 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
 - h) Recommended by the EC/IRB, DSMB, OHRP, in-country national health or regulatory entity
2. 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 Participant⁵

Safety or other considerations may make it appropriate to have a participant prematurely discontinue the study. The reasons for premature study discontinuation are likely to vary based on the purpose or phase of the study. The protocol must provide explicit criteria for premature study discontinuation for an individual participant.

Sample language:

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

- a) Lost to follow up as evidenced by failure by the participant to attend (XX) consecutive clinic visits, at the discretion of the site investigator
- b) Participant repeatedly non-compliant (define) with study product(s)/ intervention(s) as prescribed
- c) Pregnancy or breastfeeding (if applicable)

⁵ At the discretion of the EC/IRB, Food and Drug Administration, NIAID, investigator, or pharmaceutical supporter. (If a non-IND study, remove “Food and Drug Administration”; if no pharmaceutical support, remove “pharmaceutical supporter”.)

- d) Request by participant to withdraw
- e) Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant
- f) 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
- g) A defined study endpoint is reached (if applicable)”

15. STATISTICAL CONSIDERATIONS

See: [ICH E9 Statistical Principles for Clinical Trials](#)

Consolidated Standards of Reporting Trials ([CONSORT statement](#)) and relevant extensions

[NIH Policy on Data and Safety Monitoring](#)

[NIH Data Sharing Policy and Implementation Guidance](#)

[NIAID Policy on Data and Safety Monitoring Board \(DSMB\) Operations](#)

For trials outside of DAIDS’s trials networks, see:

DAIDS Policy [Data Management and Statistics, Appendix 3](#)

DAIDS Policy [Study Progress and Safety Monitoring](#)

This section should show how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many of the elements touched on below (and others) are addressed in detail in ICH guidance document E9 (Statistical Principles for Clinical Trials) and/or the CONSORT statement with extensions, which describes standards for improving the quality of reporting randomized controlled trials.

15.1. Overview and General Design Issues

Succinctly restate the scientific rationale for the study, and the primary and most important secondary objectives from Section I, that motivate choice of design, study population, endpoints, hypotheses and factors for determining sample size. Give a very concise restatement of the eligibility criteria (e.g., vaccine-naïve healthy volunteers between the ages of 18 and 65). Describe any control groups (i.e., active or placebo control groups, concurrent or historical controls, etc.) and provide a synopsis of the rationale for choosing them (i.e., including scientific rationale, risk versus benefit balance for the participant and other applicable ethical considerations). State the proposed formal design (e.g., two-period crossover, two-by-three factorial parallel group, or case-control).

15.2. Study Endpoints

Each endpoint should have at least one corresponding objective.

15.2.1. Primary Endpoint(s)

List the primary endpoint(s) and provide or refer to its precise definition(s) in the protocol.

15.2.2. Secondary Endpoint(s)

List key secondary endpoints and provide or refer to their definitions.

15.2.3. Exploratory Endpoint(s)

List exploratory endpoints and provide or refer to their definitions.

15.3. Study Objectives and Hypothesis/Hypothesis

State precisely the primary and key secondary objectives and the associated statistical approach (e.g., estimation or hypothesis testing). If relevant, 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).

15.4. Sample Size Considerations

Provide all information needed to validate the calculations and to judge the feasibility of enrolling and following the proposed numbers of participants (for individual sites as well as overall) needed to meet the key objectives of the study. Note that pilot studies are generally not powered for estimation or hypothesis testing.

The approach should reflect whether the goal is limited to estimation or entails statistical testing of hypotheses.

Specify the following as relevant:

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

Statistics (for estimation or for testing)

Desired level of precision and its rationale (for estimation)

For testing:

Null and alternate hypotheses

Type I error rate

Type II error rate

For either estimation or hypothesis testing:

Assumed event rate for dichotomous outcome (or assumed mean and variance for continuous outcome) for each study arm, justified and referenced by representative historical data to the extent possible

Assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc., similarly justified

Approach to handling withdrawals and protocol violations and whether an “intent to treat” or “per protocol” analysis will serve as the primary one

Statistical method used to calculate the sample size, with a reference, and details for any software utilized

Adjustments to account for multiple comparisons (of multiple outcomes, multiple test or control groups, multiple times of measurement, etc.), where applicable

Method for adjusting calculations for planned interim analyses, if any

Present calculations from a suitable range of potential assumptions to gauge the robustness of the proposed sample size

As applicable, discuss whether the sample size also provides sufficient power for addressing key secondary objectives or secondary analyses of the primary outcome, e.g., in subgroups of special interest.

15.5. Enrollment/Stratification/Randomization/Blinding Procedures/Unbinding Procedure

Describe enrollment procedures, stratification procedures, and randomization (if applicable to the study design), including a description or a table that describes how study participants will be assigned to study groups. Allow for the necessary flexibility for masking or randomization (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not). If applicable, describe plans to replace participants who discontinue early or whose collected data are insufficient to be included in the evaluation of the study objectives (e.g., not evaluable).

Provide details on any particular strategies to avoid bias or to decrease variability, such as centralized laboratory assessments, blinding of laboratory staff, etc.

15.6. Maintenance of Trial Treatment Randomization Codes (if applicable)

Include a discussion plan for the maintenance of trial randomization codes and maintaining appropriate blinding for the study. Include the timing and procedures for planned and unplanned breaking of randomization codes. Include a statement regarding anticipated circumstances for which unblinding may occur and who may unblind.

15.7. Participant Enrollment and Follow-up

Summarize the total number of enrollees and the total duration of accrual and of final follow-up, being specific about the number of clinical research sites and their enrollment and retention capabilities. Also be explicit about distinct stages in enrollment, if applicable.

15.8. Data and Safety Monitoring

NIH policy states that data and safety monitoring is required for all intervention studies, in order to ensure the safety of participants and the validity and integrity of the data. The

policy further elaborates that the form of monitoring should be commensurate with risks and with the size and complexity of the trial. NIAID/DAIDS must ensure that this monitoring is appropriately planned, executed, and the results communicated to the Sponsor.

Refer to the DAIDS Policy [Study Progress and Safety Monitoring](#) for a description of the type(s) of monitoring that may be required (e.g., Data and Safety Monitoring Board, Study Monitoring Committee, Independent Safety Monitor, and Study Team Review (also called Protocol Safety Review Team)), approval of reviewers by DAIDS, study progress and safety monitoring plan specifications, and types of study monitoring reports.

Indicate whether any of the above types of monitoring bodies will oversee the study. For any such body that has not been established directly by NIAID, reference where information on the monitoring body can be obtained, including number of members, types of expertise, and members' affiliations. If applicable, indicate also if other monitoring body(ies) (e.g., Clinical Monitoring Committee, Toxicity Review Group, Endpoint Verification Committee) will be utilized.

While the detailed study progress and safety monitoring plan must be provided as a separate document and approved in writing by DAIDS before study initiation, the protocol must include a basic study monitoring plan that describes the frequency of monitoring, key parameters for assessment of study progress, feasibility, safety, and efficacy, and pause rules as appropriate. If safety or efficacy monitoring criteria are apt to change during the study (e.g., due to the monitoring body recommendation), provide only a general description of the plan in the protocol, with details described in the [Study Progress and Safety Monitoring Plan](#). Components to address are described below.

15.8.1. Planned Interim Analyses and Stopping Guidelines (if applicable)

Describe the types of statistical interim analyses and permanent stopping guidelines (if any) that are proposed, including their timing. The criteria that will be used to guide decisions stemming from interim reviews of safety and efficacy (or immunogenicity) should be pre-specified to the extent possible.

15.8.1.1. Interim Safety Review

Describe any proposed statistical analysis rules for pausing study enrollment or study product(s)/intervention(s) administration for safety, including whether they pertain to the entire study, specific study arms, participant subgroups, or other components of the study. See [Section 13](#) (Assessment of Safety) for information to include in the protocol on pause and stopping rules.

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

Describe any statistical rules that will be used to pause enrollment into all or a portion of the study, the specific 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.

15.8.1.2. Interim Efficacy (or Immunogenicity) Review

Describe how efficacy or immunogenicity outcome measures will be monitored, if relevant. Discuss the impact of the interim monitoring plan on final efficacy analyses, particularly on Type I error. If formal interim analyses will be performed, provide (in the protocol or monitoring plan) complete instructions so that an independent statistician could perform the analyses. Consider including criteria for stopping guidelines that address futility.

15.8.2. Analysis Plan

This section should be used to elaborate on primary analyses and to describe secondary analyses for the primary and secondary objectives. It should specifically describe all primary and key secondary analyses of safety as well as of efficacy and/or immunogenicity. Further details may be provided in a separate statistical analysis plan written later, although (except for exploratory trials) that plan must be finalized prior to performing any analyses. If exploratory objectives are of particular interest, include information on the statistical analyses for those measures as well.

Plans must clearly identify the analyses cohorts to be analyzed (e.g., “Per Protocol” or “Intent to Treat” and also subsets of interest) and methods to account for missing, unused or spurious data.

16. DATA HANDLING AND RECORDKEEPING

16.1. Data Management Responsibilities

See: ICH E6 GCP, Section 4.9

DAIDS Policy [Requirements for Data Management and Statistics](#)

Data collection is the responsibility of the clinical research site staff under the supervision of the Investigator of Record (IoR). During the study, the IoR must maintain complete and accurate documentation for the study.

If data are to be generated by a party in one location and transferred to a party in a different location, 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.

Briefly describe steps that will be taken to ensure that the data collected are accurate, complete, reliable, legible, timely and in accordance with ICH E6 GCP, Section 4.9. Details on these steps must be provided in a MOP or other separate documents.

16.2. Essential/Source Documents and Access to Source Data/Documents

See: 21 CFR Parts 11, 50, 54, 56, and 312

ICH E6 GCP

DAIDS Policy [Essential Documents](#)

DAIDS Policy [Storage and Retention of Clinical Research Records](#)

Each clinical research site is responsible for maintaining accurate clinical research records and documentation in compliance with DAIDS policies, ICH E6 GCP, and all other applicable regulatory and institutional requirements. Essential documents are clinical research records, source documents, or files that permit the evaluation of both the conduct of a clinical trial and the quality of the data produced. Source data are all information, original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. All source documents and source data are considered essential documents.

As part of participating in a NIAID (DAIDS)-supported and/or -sponsored clinical trial, protocols must include language indicating that they will permit authorized representatives of the sponsor(s), DAIDS, and regulatory agencies to examine (and when required by applicable law, to copy) clinical research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Essential documents should be readily accessible and must be stored in a manner that ensures confidentiality and security. Protocols must include a description of who will have access to these records. Each clinical research site must have Standard Operating Procedures (SOPs) for management of essential documents, i.e., data management and record retention. It is acceptable to use CRFs as source documents. Any data from procedures/evaluations that will be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data must be identified as such.

16.3. Quality Control and Quality Assurance

See: ICH E6 GCP, Section 5.1

DAIDS Policy [Clinical Quality Management Plans](#)

All clinical research sites conducting or participating in NIAID (DAIDS)-supported and/or -sponsored clinical research are required to have a Clinical Quality Management Plan (CQMP). Since extensive external monitoring by DAIDS is not feasible, DAIDS has instituted a requirement for each clinical research site to develop, implement and evaluate a CQMP. Quality management activities will allow planning for effective protocol implementation, assure compliance with sponsor and applicable regulatory requirements, identify areas in need of corrective action, verify data accuracy, and assure a constant state of readiness for an external audit or monitoring visit. Each clinical

research site must have SOPs for quality management. These SOPs may be provided in a MOP or as accompanying documents.

17. CLINICAL SITE MONITORING

See: DAIDS Policy [Requirements for On-Site 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.”

If an entity other than DAIDS or its designee is responsible for clinical site monitoring (e.g., pharmaceutical company, other NIH Institute or its designee), provide a general description of how site monitoring will be conducted and specify the entity responsible for the monitoring.

A separate monitoring plan document should be developed to describe who will conduct the monitoring, the detailed scope of the monitoring to be performed, and the frequency of monitoring visits.

18. HUMAN SUBJECTS PROTECTIONS

18.1. Institutional Review Board/Ethics Committee

Institutions located in the United States (U.S.) or in other countries must have a current U.S. Federalwide Assurance (FWA) issued by the U.S Office for Human Research Protections (OHRP) to participate in human subjects research supported and/or sponsored by NIAID (DAIDS).

Information on FWAs is available on the [OHRP website](#).

Each participating institution is responsible for assuring that this protocol, informed consent document(s) and associated study-related documents, are reviewed by an EC/IRB that is registered with OHRP, prior to protocol implementation, as well as any applicable regulatory entity approvals (e.g. national ethics committee).

Information on EC/IRB registration is on the [OHRP website](#).

All DAIDS-approved changes to the protocol, informed consent(s), or other study-related documents (e.g., full version amendments and Letters of Amendment (LoA)) must first be approved by the site’s EC/IRB prior to implementation. For studies that will be utilizing

the DAIDS protocol registration system, the protocol must include the applicable DAIDS-approved template protocol registration language for full version amendments and LoA registrations. The requirements for protocol registration can be found in the [DAIDS Protocol Registration Manual](#). Under circumstances when the IoR or designee notes an apparent immediate danger to enrolled participants, the IoR or designee may immediately implement changes to the research to protect the safety of research participants and eliminate the danger before EC/IRB approval is obtained. Such instances must be documented in writing in the site's regulatory file. However, EC/IRB approval must still be obtained. The study team must send all protocol amendments and consent changes for the DAIDS Medical Officer to review prior to submitting the protocol amendments and consent changes to the EC/IRB.

EC/IRB continuing review and approval will be obtained from the reviewing EC/IRB at least once per year. If EC/IRB approval expires (e.g., lapse in continuing review), all ongoing research activities will stop, unless the investigator determines that it is in the best interested of already-enrolled participants to continue their study-related activities. New participants will not be enrolled on the study until EC/IRB approval to continue the research is obtained.

18.2. Vulnerable Participants

See: 45 CFR 46.111(3) and .111(b), Subparts B, C and D

21 CFR 50, Subpart D

21 CFR 56.111(a)(3) and .111(b)

ICH E6 GCP, Section 1.61

NIH Grants and Funding [Research Involving Vulnerable Populations](#)

Examples of vulnerable participants include children, prisoners, pregnant women, refugees, cognitively impaired, illiterate, terminally ill, unemployed or impoverished persons, ethnic minority groups, homeless persons, nomads, elderly, soldiers, or students.

[Section 10](#) (Study Population) discusses providing justification in the protocol for the inclusion of vulnerable populations. In addition, the protocol needs to identify additional protections that will ensure the participant's rights and welfare. Additional protections may include but are not limited to limited access to identifiable data, obtaining a Certificate of Confidentiality ([see section 18.9](#)), modified informed consent processes, if hospital based research involving minors, the pediatric ombudsman for additional information regarding the child's rights as a research participant, and the addition of supplemental EC/IRB-approved informed consent materials, such as tapes, videos and audiobooks.

18.2.1. Pregnant women and fetuses

Protocols involving women who are currently pregnant, or who become pregnant during the course of the study, or fetuses must satisfy the conditions listed in 45 CFR 46.204. The conditions to be addressed in the protocol include:

1. Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, with data for assessing potential risks to pregnant women and fetuses.
2. Assurance that investigators will not offer inducements to terminate the pregnancy.
3. Assurance that investigators will have no part in determining the viability of a neonate.

The protocol should state whether there is expected direct benefit to the pregnant participants and/or the fetus.

If the study product is labeled with an FDA pregnancy category (i.e., A, B, C, D, X), include this information in the protocol and other related documents.

18.2.2. Prisoners

See: OHRP Guidance on the [Involvement of Prisoners in Research](#)

OHRP [Prisoner Research Frequently Asked Questions \(FAQs\)](#)

Studies involving participants who are currently prisoners or who become prisoners during the course of the study must address the additional protections outlined in 45 CFR 46, Subpart C. The protocol must show that the research meets one or more of the four permissible categories of research as listed under 45 CFR 46.306(2)(i-iv).

18.2.3. Children

See: OHRP [Research with Children Frequently Asked Questions](#)

Protocols involving children must provide sufficient details to support a risk/benefit analysis and assessment of the need for child assent, as discussed in 45 CFR 46, Subpart D and, when applicable, 21 CFR 50, subpart D. See the DAIDS policy, [Enrolling Children \(including Adolescents\) in Clinical Research: Protocol Document Requirements](#), for additional information that must be included in the protocol.

18.2.4. Illiterate participants

See: 45 CFR 46.116 and 46.117

21 CFR 50.25 and 50.27

21 CFR 56.111(b)

ICH E6 GCP, Sections 4.8.6 and 4.8.9

FDA Guidance [A Guide to Informed Consent - Information Sheet](#)

FDA Guidance [Institutional Review Boards Frequently Asked Questions - Information Sheet, question's 40 and 41](#)

The informed consent form and discussion must be in a language understandable to the prospective participant and, in most situations, documented in writing. A participant who speaks and understands the language used during the consent discussion and in the informed consent form but who is unable to read or write (illiterate) can be enrolled in a study by "making a mark" on the informed consent form, as long as this practice is consistent with applicable local law. Similarly, a participant who is unable to verbally communicate and physically unable to write so he/she cannot make a mark, but who understands the spoken language used during the verbal consent process and who also understands the study's concepts, risks and benefits, can be enrolled. In this instance, the participant would have to be able to indicate his/her approval or disapproval to enroll in the study by other means, as long as this procedure is consistent with local law. In both of these cases, there should be an impartial witness of the entire consent process who signs the informed consent form. Furthermore, the EC/IRB should consider if additional safeguards are needed when enrolling such participants.

When some or all participants are anticipated to be illiterate, include information in the protocol or a protocol-related document on how the consent process for illiterate participants will be conducted.

18.3. Informed Consent

18.3.1. Informed Consent Process

See: 45 CFR 46

21 CFR 50

ICH E6 GCP

OHRP Guidance [Tips on Informed Consents](#)

OHRP Guidance [Informed Consent Checklist](#)

OHRP memo [Obtaining and Documenting Informed Consent of Non-English Speakers](#) (OPRR Memo, 1995)

OHRP [Informed Consent FAQs](#)

FDA Guidance [A Guide to Informed Consent - Information Sheet Guidance for Institutional Review Boards and Clinical Investigators](#)

DAIDS Policy [Requirements for Informed Consent Development](#)

Informed consent (IC) is a process, not just a form, and is continuous throughout an individual's study participation. The procedures used in obtaining IC should be designed to educate the participant population in terms they can understand. The informed

consent form (ICF) must be written and conveyed in "lay language" (e.g., reading level of the ICF is written such that persons being asked to participate in the study will understand). See [Section 18.3.3](#) for information when potential participants are not fluent in the language of the ICF. Investigators should identify the consent form(s) that are needed for the study (e.g., screening, study participation, future use of specimens) as applicable. ICF (s) and any documentation that will be distributed to study participants must have prior EC/IRB approval, as well as any applicable regulatory entity approvals (e.g. national ethics committee).

Investigators should review the ICF with participants and discuss the study's purpose, duration, procedures, alternatives, risks, and benefits, etc. Investigators should be available to answer any questions that might arise. It is the investigators responsibility to ensure that participants are informed about the research, and are aware that their enrollment is voluntary, that they can withdraw their consent at any time, and that the quality of their medical care will not be affected if they decline to participate.

IC must be obtained before any study procedures are conducted on a participant. A copy of the ICF will be given to the participant for their records. Protocols must include a description of procedures for obtaining and documenting IC.

18.3.2. Assent Process (in Case of a Minor)

See: 45 CFR 46, Subpart D

ICH E6, Section 4.8.12

DAIDS Policy [Enrolling Children \(including Adolescents\) in Clinical Research: Protocol Document Requirements](#)

When a study includes participants who may be enrolled in the trial only with the consent of their parent or legal guardian (e.g., minors or participants with severe dementia), participants should be informed about the trial to the extent compatible with the participant's understanding. If capable, the participant should provide their assent, and sign and personally date the written assent form. The protocol should include recommendations whether eligible children may be capable of providing assent, so the EC/IRB can determine that adequate provisions are made for soliciting the assent of these children.

Although the assent process varies from institution to institution and will be approved by the EC/IRB, certain elements remain constant. Before the process can begin, parents or legal guardians must give permission for their child/children to participate. The participant may be provided with a form that explains, in concrete and age-appropriate terms, the purpose of the research, what they will be asked to do, what procedures they will undergo as well as any discomforts and inconveniences the participant may experience if he or she agrees to participate.

The research team may use other approaches in addition to written forms, conversations, and question-and-answer sessions. These might include EC/IRB-approved

videotapes, diagrams, pictures, or drawings. Researchers also may provide a chance for the young person to speak with other children or teens that have been in similar trials and are willing to talk about their experiences. Similar to the informed consent process, the assent process is intended to be an ongoing, interactive conversation between the research team and the participant.

Note, assent forms do not substitute for the consent form signed by the parents or legal guardians.

18.3.3. Documentation of Informed Consent

See: 45 CFR 46.116 and 117

21 CFR 50.25 and 27

ICH E6 GCP, Section 4.8.10

OHRP Guidance [Obtaining and documenting informed consent of subjects who do not speak English](#)

U.S. regulations and international guidance require that informed consent, in most cases, be documented by the use of a written informed consent form that was approved by the EC/IRB, as well as any applicable regulatory entity (e.g. national ethics committee). The participant should be presented with an ICF that incorporates the required elements of informed consent. Alternatively, a short consent form written in a language spoken by the participant could be used. This short form should state that the elements of consent have been presented orally to the participant using a written summary. This summary could be the EC/IRB-approved informed consent form developed for the study.

When the short form is used, there must be a witness who is fluent in both the language of the summary, and the language of the short consent form. The participant must be given copies of the short form and the summary. The form should be signed or marked by the participant or his/her legally authorized representative, and the witness. The summary must be signed by the study staff obtaining consent and the witness. If the study staff obtaining consent is assisted by a translator, the translator may serve as the witness.

18.3.4. Waiver of Informed Consent

See: 45 CFR 46.116(c) and (d)

OHRP [Informed consent FAQs](#)

The HHS regulations allow an EC/IRB to waive the requirement for obtaining informed consent or parental permission, or to approve a consent procedure that leaves out or alters some or all of the elements of informed consent otherwise required under 45 CFR 46.116(a) and (b).

Waiving the requirement for obtaining informed consent or parental permission means that the EC/IRB has determined that investigators do not need to obtain the participant's

informed consent to participate in research. For example, some behavioral research in a clinic setting may require that participants be unaware that the research is taking place.

When applicable, provide sufficient detail in the protocol to justify the waiver. Specifically, address each criterion for waiving informed consent under the applicable regulation (45 CFR 46.116(c) or (d)).

18.3.5. Waiver of Documentation of Informed Consent

See: 45 CFR 46.117

OHRP [Informed consent FAQs](#)

A waiver of documentation of informed consent is a request whereby a signed informed consent form is not required. Examples include implied and verbal consent. Consent will still be obtained from participants; however, they will not be required to sign the informed consent form. There are only two circumstances when the EC/IRB may waive the requirement to obtain a signed informed consent form.

An EC/IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all participants if it finds either:

1. That the only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality, or
2. That the research presents no more than minimal risk of harm to the participant and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the EC/IRB may require the investigator to provide participants with a written statement regarding the research.

Examples where a waiver of documentation of informed consent may be appropriate:

A web-based survey

A telephone survey that presents no more than minimal risk

A paper-and-pencil survey that is anonymous

When applicable, provide sufficient detail in the protocol to justify the waiver for documentation of informed consent, under the applicable regulation (45 CFR 46.117(c) (1) or (2)), to support the EC/IRB's determinations on waiving the requirement to obtain a signed consent form.

18.3.6. Stored Samples and Associated Data Considerations

See: OHRP Guidance [Issues to Consider in the Research Use of Stored Data or Tissues](#)

OHRP Guidance on [Research Involving Coded Private Information or Biological Specimens](#)

NIH [Genomic Data Sharing Policy](#)

NIH Website for the [database of Genotypes and Phenotypes \(dbGaP\)](#)

DAIDS Sample Informed Consent Template for Stored Samples for Future Use

Human samples and associated data are an invaluable resource for current and future research on human health and disease. Protocol teams need to consider the technical aspects as well as the ethical, social, and regulatory issues surrounding the collection, storage, and use of samples and associated data. The following information should be considered for inclusion in a protocol and informed consent form:

Type of sample(s) to be collected (e.g., vaginal secretions, blood, etc.)

How samples and associated data will be used in the current study

Disposition of samples at the study's completion (destroyed vs. stored for future use)

Mandatory vs. voluntary storage of leftover samples after the study's completion

Collection of additional samples to be stored for future use, if applicable

Location of where samples may be stored, or whether samples will be shipped and/or stored outside of the country where they were collected

Length of time of storage (i.e., indefinite vs. a finite specified length of time)

Types of future research that may be done and any associated risks (e.g., limited vs. broad genetic testing, development of cell lines, research on HIV and related diseases, etc.)

Possibility of being re-contacted for the use of samples for future research not described in the informed consent form, if applicable

Use of a separate informed consent form for those studies planning to store samples and associated data for future use

Discussion of GWAS and dbGAP issues for those protocols that meet the [NIH Policy for Genome-Wide Association Studies \(GWAS\)](#)

18.4. Risks

Describe in detail any physical, psychological, social, legal, economic, or any other reasonably foreseeable risks, discomforts, or inconveniences to study participants, including those associated with the study intervention(s), study procedures (e.g., phlebotomy, pelvic exams, DEXA scans), and study participation (e.g., developing drug resistance with sub-optimal treatment and consequential limitation of future treatment options, development of vaccine-induced seropositive test result, pregnancy outcomes). When applicable, include any known risks to a fetus and/or breastfeeding infant.

The physical risks should be based on the risk profile of the study product(s) and/or intervention(s) or the trial strategy. When available, use a package insert or Investigator's Brochure (IB) as the primary source of physical risk information. If a

package insert or IB is not available, the physical risk information discussion will be based on information obtained from a literature search and relevant unpublished data.

Include any relevant information as to how risks may be mitigated.

The risks described in the protocol must correspond with the risks statement in the sample informed consent form.

18.5. Social Impact Events

Social impact events (i.e., “social harms”) may occur in NIAID (DAIDS) -supported clinical trials. Examples of social impact events include inadvertent disclosure of study participation, resulting in stigmatization or discrimination, and physical or psychological harm from disclosure of study participation. Describe the reasonably foreseeable social impact events in the protocol. State the actions that the study staff will take (e.g., provide participant with appropriate assistance, refer participant to appropriate resources, report social impact event to the study team) and when the social impact event will be reported to the local EC/IRB. In some instances, it may be beneficial to include background information related to social impact issues relevant to where the study will be conducted in the protocol.

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

Describe any reasonably foreseeable benefits, if any, to the study participant, and to “society”. If there are no anticipated benefits, the protocol will include a statement that the research will not provide any direct benefit to participants.

The benefits described in the protocol must correspond with the benefits statement in the sample informed consent form.

Note: Participant compensation is not considered a “benefit”.

18.7. Compensation

When applicable, include plans to provide participants compensation, such as compensating participants for their time and effort, as well as any plans to reimburse participants for travel to/from study visits, pending local EC/IRB approval. Site-specific amounts should be specified in the study site-specific informed consent forms.

18.8. Participant Privacy and Confidentiality

See: 45 CFR 46

ICH E6

Include procedures for maintaining participant privacy and confidentiality of participant’s study data, any special data security requirements, and record retention requirements. Include the names of persons or entities that might have access to records.

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

See NIAID [Certificate of Confidentiality SOP](#)

For some studies, it may be necessary to obtain a Certificate of Confidentiality. These certificates are issued to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

If the study is covered under a Certificate of Confidentiality, inform participants in the informed consent form of the use and limits of the certificate... Note: Certificates of

Confidentiality are only effective in the U.S. However, if data from a trial are collected in a country outside of the U.S. but these data are maintained in the U.S., the certificate would be in effect.

18.10. Critical Event Reporting

See: 45 CFR 46

21 CFR 56

DAIDS [Critical Events Policy](#) and [Critical Events Manual](#)

Include a section that addresses reporting critical events (CEs) to DAIDS and other entities in the protocol. Critical events include the following classes of events: unanticipated problems involving risks to participants or others, serious noncompliance, continuing noncompliance, suspension or termination of EC/IRB approval, and suspected research misconduct.

State the time period for reporting CEs to DAIDS. Identify other applicable entities that will receive the CE report and the time period for reporting to these entities. Include the time period for reporting CEs to the local EC/IRB in the site MOP.

18.11. Communicable Disease Reporting

When applicable, include an explanation of requirements and plans for study staff to comply with applicable local requirements for reporting communicable diseases identified among study participants to local health authorities. This information must also be included in the informed consent document.

18.12. Incidental Findings

See: NIH [Frequently Asked Question from Applicants-- Incidental Findings](#)

DAIDS Sample Informed Consent Template for Stored Samples for Future Use and Instructions Page

DAIDS Protocol Specific Informed Consent Template—General Use and Instructions Page

NIH [Genomic Data Sharing \(GDS\)](#)

Planning for what constitutes an incidental finding (IF) in clinical research and whether or not it should be disclosed to the participant is an important consideration to be addressed by all protocol teams developing NIAID (DAIDS)-sponsored and/or -supported studies. An IF is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. Implementing a comprehensive approach to address both the responsibility of researchers to disclose these findings and the expectation of participants to receive this information, may be logistically challenging. Thus, protocol teams should consider and plan for better management of incidental

findings discovered during HIV research participation that are important for the health of participants and are actionable at the level of the study participant. As laboratory assays and many other research results used in HIV research are becoming validated and more standardized, research participants are increasingly expecting to learn about these results.

Furthermore, IFs should be considered in both primary and secondary research. The easier IFs to discern are those found during the conduct of primary research, e.g., an X-ray finding beyond the study aims; but there are still issues with this type of IF, such as the need for experts to interpret this finding. IFs found during secondary research are more challenging. They are discovered by other researchers not directly involved in the primary research, e.g., a biobank or repository or by a researcher obtaining and analyzing biobank data or samples.

The main questions to be answered when considering IFs are:

What information to offer back to individuals?

Whose data and samples are stored in biobanks and archived data sets? (More specific to secondary research)

Who has the responsibility to disclose IFs? (More specific to secondary research)

What should protocol teams and sites have in place to address these IFs?

There are several approaches as to what constitutes an IF and when it should be returned to the research participant. These approaches can be summarized as follows:

Sharing all incidental findings with research participants regardless of their importance

Sharing only those findings that are important and actionable

Not sharing any findings

Both DAIDS IC templates (Protocol Specific Informed Consent Form, Future Research Use of Stored Samples and Associated Health Information) ask HIV research participants for their permission to be re-contacted for IFs that are both important for their health and actionable at the participant level, a variation of the second approach above.

18.13. New Findings

When applicable, indicate in the protocol how already enrolled and potential participants will be informed about any study-relevant new findings reported during the course of the study that may impact their willingness to continue on study and/or willingness to join the study (e.g. “Dear Participant” letter, revised informed consent form, discussion of new findings with study staff that is documented in the participant’s research chart). This section of the protocol should also address how the local EC/IRB will be kept informed of such new findings, as well as address the requirement of re-

consenting participants already enrolled onto the study. Similarly, the informed consent form should address the issue of new findings.

18.14. Study Discontinuation

Indicate in the protocol which entities have the authority to discontinue the study.

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

The NIH recognizes the importance of research participants having access to beneficial interventions in relevant circumstances at the conclusion of a clinical trial, for example, at the conclusion of efficacy trials when one or more products are proven effective. The Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) guidelines emphasize the importance of post-trial access. However, the NIH’s ability to directly fund access to effective interventions, or any treatment, at the completion of a trial is limited by our Congressional mandate to “encourage and support research” (42 USC 284(b)(1)(A)). Furthermore, predicting and managing product availability depends on multiple factors such as regulatory approvals, manufacturing scale-up and infrastructure. During study planning, it is appropriate for investigators to discuss post-trial access by engaging with host countries’ authorities, pharmaceutical partners and other relevant stakeholders with the aim of facilitating post-trial access where appropriate. When relevant, address plans for post-trial access in both the protocol and the ICF.

When applicable for post-trial ARV access, see the [NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries.](#)

18.16. Ancillary Benefits

The NIH recognizes the importance of providing various forms of ancillary care and other benefits during clinical trials. However, there is no consensus on the extent of researcher ethical obligations to provide ancillary care in clinical trials, though the CIOMS guidelines (see guideline 21) and the Declaration of Helsinki do offer some limited guidance. In addition, the NIH’s ability to directly fund ancillary care, or any intervention, during a clinical trial is limited by our Congressional mandate to “encourage and support research” (42 USC 284(b)(1)(A)). Therefore, if possible, investigators should manage ancillary care by engaging with host countries’ authorities, pharmaceutical partners and other relevant stakeholders in order to find mechanisms

to provide ancillary care or to refer research participants to local available care. When relevant, address plans for ancillary care in both the protocol and the ICF.

18.17. Community Advisory Board and Other Relevant Stakeholders

When applicable, consider including a description of the contribution of the Community Advisory Board (CAB) and other relevant stakeholders during the protocol development process, conduct, and follow-up. DAIDS requires CAB input, which is in accordance with [Good Participatory Practices](#) (GPP) and all local and national guidelines. Obtaining CAB and other relevant stakeholder input will help ensure that locally appropriate cultural and linguistic needs of study populations are met. This includes, but is not limited to: protocol review, articulating community concerns, feedback regarding acceptability and feasibility of the study, cultural competencies, participant recruitment, etc.

19. Administrative Procedures

19.1. Protocol Registration

See: DAIDS Policy [Protocol Registration](#)

DAIDS [Protocol Registration Manual](#)

It is DAIDS policy that each participating institution must complete the protocol registration process for all clinical research supported and/or sponsored by NIAID (DAIDS) that undergoes review⁶ and approval by a DAIDS Scientific Review Committee (SRC). Sites cannot begin the protocol registration process until the protocol has completed the DAIDS protocol development requirements.

All sites are required to submit protocol registration materials to the DAIDS Protocol Registration Office (PRO) through the DAIDS Protocol Registration System (DPRS). Information on mandatory DPRS training is available on the [DAIDS Regulatory Support Center \(RSC\) website](#).

Protocol registration must occur before the clinical research site can enroll any participants into the study. Additional information on the protocol registration process is available on the [DAIDS Regulatory Support Center \(RSC\) website](#).

19.2. Regulatory Oversight

When applicable, include a paragraph regarding which entity is responsible for regulatory oversight including sponsorship arrangements and if an IND will be submitted to the U.S. FDA.

⁶ Protocols that have a courtesy review by a DAIDS SRC are not subject to the DAIDS protocol registration process

19.3. Study Implementation

When applicable, include references to other documents that provide additional details on protocol implementation, such as the Site MOP.

19.4. ClinicalTrials.gov

Indicate if the protocol is subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA) and will be registered in 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)

Include plans for publication and authorship rules in the protocol unless this information is included in a separate document such as a Clinical Trial Agreement, contract or study MOP.

21. REFERENCES

List all references cited within the protocol. Each reference must include the title, names of all authors, book or journal, volume number, page numbers, and year of publication. For information not publicly available (e.g., manuscript drafts or local government/regulatory treatment guidelines not available on the Internet), include copies as accompanying documents.

22. APPENDICES

Appendices may include:

Informed Consent Form or Sample Informed Consent Form

Schedule of Procedures/Evaluations (see Appendix A)

Biosafety Precautions

Repository Instructions

DAIDS AE Grading Table

Specimen Handling

Protocol team roster contact information

Study instruments, including questionnaires, interview questions

APPENDIX A

SAMPLE SCHEDULE OF PROCEDURES/EVALUATIONS

(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.

V. MANUAL REFERENCES

[HHS regulations for the Protection of Human Subjects at 45 CFR 46](#)

[FDA regulations for the Protection of Human Subjects at 21 CFR 50](#)

[FDA regulations on Institutional Review Boards at 21 CFR 56](#)

[FDA regulations on Investigational New Drug Application at 21 CFR 312](#)

[FDA regulations on Biological Products at 21 CFR 600](#)

[FDA regulations on Devices at 21 CFR 800-892](#)

[ICH Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A](#)

[International Conference on Harmonization \(ICH\) E6 Good Clinical Practice \(GCP\)](#)

[ICH Guideline Statistical Principles for Clinical Trials E9](#)

[World Medical Association Declaration of Helsinki](#)

[Council for International Organizations of Medical Sciences \(CIOMS\) International Ethical Guidelines for Biomedical Research Involving Human Subjects](#)

[OHRP Federalwide Assurances \(FWAs\)](#)

[OHRP Guidance: Informed Consent Checklist](#)

[OHRP Guidance on the Involvement of Prisoners in Research](#)

[OHRP Guidance: Issues to Consider in the Research Use of Stored Data or Tissues](#)

[OHRP: Guidance on Research Involving Coded Private Information or Biological Specimens](#)

[OHRP Guidance Tips on Informed Consent](#)

[OHRP Informed Consent FAQs](#)

[OHRP Institutional Review Boards](#)

[OHRP Memo Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English](#)

[OHRP Prisoner Research Frequently Asked Questions](#)

[OHRP Research with Children Frequently Asked Questions](#)

[FDA Guide to Informed Consent- Information Sheet](#)

[FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions about Medical Devices](#)

[FDA Institutional Review Boards Frequently Asked Questions- Information Sheet](#)

[FDA CDRH Recent Medical Device Guidance Documents](#)

[WHO/UNAIDS/UNICEF infant feeding guidelines](#)

[Consolidated Standards of Reporting Trials \(CONSORT\) statement](#)

[NIH Database of Genotypes and Phenotypes \(dbGaP\)](#)

[NIH Genomic Data Sharing \(GDS\)](#)

[NIH Genomic Data Sharing Policy](#)

[NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries](#)

[NIH Policy for Data and Safety Monitoring](#)

[NIH Data Sharing Policy and Implementation Guidance](#)

[NIH Frequently Asked Questions from Applicants, Human Subjects Research-Incidental Findings](#)

[NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules](#)

[NIH Inclusion of Women and Minorities as Participants in Research Involving Human Subjects- Policy Implementation Page](#)

[NIH Policy for Genome-Wide Association Studies \(GWAS\)](#)

[NIH Research Involving Human Subjects](#)

[NIH Research Involving Vulnerable Populations](#)

[NIAID Certificate of Confidentiality](#)

[NIAID Policy on Data and Safety Monitoring Board \(DSMB\) Operations](#)

[DAIDS Clinical Research Policies and Standard Procedures Documents](#)

[DAIDS Critical Events Manual](#)

[DAIDS Expedited Adverse Event Reporting Policy](#)

[DAIDS Guidelines for Good Clinical Laboratory \(GCLP\) Standards](#)

[DAIDS Manual for Expedited Reporting](#)

[DAIDS Policy Clinical Quality Management Plans](#)

[DAIDS Policy Data Management and Statistics](#)

[DAIDS Policy Enrolling Children \(Including Adolescents\) in Clinical Research: Protocol Document Requirements](#)

[DAIDS Policy Essential Documents](#)

[DAIDS Policy Identification and Classification of Critical Events: Site Responsibilities](#)

[DAIDS Policy Requirements for Informed Consent Development](#)

[DAIDS Policy Requirements for Laboratories in Clinical Trials](#)

[DAIDS Policy Manual of Operational Procedures](#)

[DAIDS Policy Requirements for On-site Monitoring](#)

[DAIDS Policy Storage and Retention of Clinical Research Records](#)

[DAIDS Policy Study Progress and Safety Monitoring](#)

[DAIDS Protocol Registration Manual](#)

[DAIDS Protocol Registration Policy](#)

[DAIDS Required Site SOPs](#)

[Protocol Registration Training](#)

[DAIDS Regulatory Support Center \(RSC\) Protocol Registration](#)

[DAIDS Regulatory Support Center \(RSC\) Safety and Pharmacovigilance](#)

[The Antiretroviral Pregnancy Registry](#)

[Good Participatory Practice, Guidelines for Biomedical HIV Prevention Trials 2011](#)