

**Study Protocol Guide**

**Preface**

This document is the MRC protocol guide for developing protocols for clinical research projects supported, sponsored or conducted by MRC Unit, The Gambia. This guide refers to the protocol template provided. For preparing your protocol use the protocol template.

This guide and the template attempt to provide a general format applicable to all clinical studies. Throughout the protocol template, there may be subject headings that do not apply to your particular study. Delete this section. If in rare circumstances a main section does not apply, please write “not applicable”. Where information is duplicative, it is advised to reference another section rather than repeating the information.

Please insert the protocol number (and a brief title or identification code) on the left side into the header, incorporate the version and date on the left side of the footer, and the page number and number of pages on the right side of the footer.

Where applicable, reference is made in this guide to corresponding sections of the ICH GCP Guideline {6}.

For the consolidated guideline by ICH on Good Clinical Practice ICH (E6) please refer to:

<http://www.ich.org/LOB/media/MEDIA482.pdf>

The first page (or two pages) is the Title Page that contains general information on the trial, responsible persons or institutions and on the document itself.

**Study** **PROTOCOL**

(*Synonym*: Project Plan)

**Title** {6.1.1}

The title should be accurate and descriptive. It should include summary study design, investigational products, management or provisions, nature of the investigation (e.g. treatment, prophylaxis, or diagnosis), comparators and/or any placebos (if applicable), indication, patient population and setting (e.g. in-patient, out-patient)

**Protocol No:** {6.1.1}

The protocol number identifies the study protocol. In MRC sponsored trials this might be the SCC number.

**Brief Title** Include a brief title or identification code that can be used to identify single pages of the protocol and supporting documents.

**Other Number(s)** Other protocol number(s) may be the number or other review boards, and/or a public accessible registry number (eg the ClinicalTrials.gov Identifier) and/or other funding or registering number(s) provided by the sponsor.

**Protocol Version – Date** Refer to SOP-QUA-001 13 for assigning version numbers - write out the month and use international date format (e.g. 27 July 2007). {8.2.7}

**Sponsor** State name and address of the sponsor. {6.1.2} If the MRC Unit, the Gambia is the sponsor, it is:

**Medical Research Council Unit, The Gambia,   
PO Box 273 Banjul,   
The Gambia, West Africa**

**Principal Investigator** State name and title of the Principal Investigator(s) {6.1.5}

Protocol Amendment(s)

Amendment #:

* Number the amendment chronologically and date it. {6.1.1}
* Give a brief statement on the reason for amendment. {6.1.1}
* If there is no amendment (yet) please delete this section.

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| --- | --- | --- |
| **Principal Investigator:**    Name, Title | **Signature:** | **Date:** |

|  |  |  |
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| **Sponsor’s representative:**  *(if sponsor different from MRC)*    Name, Title | **Signature:** | **Date:** |

Signature page

* Provide a statement that the trial will be conducted in compliance with the protocol, the principles of good clinical practice or ICH Harmonised Tripartite Guideline for Good Clinical Practice, as appropriate, the MRC Guidelines for Good Clinical Practice in Clinical Trials, and the applicable regulatory requirements. {6.2.5}

***Example text:***

The study will be carried out in accordance with the protocol, the principles of good clinical practice as laid down in the ICH Harmonised Tripartite Guideline for Good Clinical Practice, the MRC Guidelines for Good Clinical Practice in Clinical Trials, <<*insert other regulations if applicable>>*, and in accordance with the legal and regulatory requirements.

* Insert applicable regulations as appropriate for study location and sponsor requirements.

**Note:** The following regulations usually do not apply to MRC sponsored trials. In external sponsored or funded studies please make sure which of these regulations are to be respected.

USA:

United States (US) Code of Federal Regulations (CFR) applicable to clinical research (45 CFR Part 46) or clinical investigations regulated by the FDA (21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312 and 812)   
<http://www.gpoaccess.gov/cfr/index.html>

NIH Clinical Terms of Award   
<http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf>

Form FDA 1572, Statement of Investigator  
<http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf>

Europe:

Directive 2001/20/EC on Clinical Trials on Medicinal Products for Human Use, 4 April 2001  
<http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf>

Directive 2005/28/EC on Principles and Detailed Guidelines for Good Clinical Practice, 8 April 2005  
<http://eur-lex.europa.eu/LexUriServ/site/en/oj/2005/l_091/l_09120050409en00130019.pdf>

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| **Principal Investigator:** { 4.5.1}    *Name, Title* | **Signature:** | **Date:** |

The protocol should be signed by the Principal Investigator, and by the investigator(s) who is/are responsible for the study implementation at his/her specific site, if different form the PI. In case of a multi-centre trial this page can be tailored to each site, otherwise it can get very long. If site specific signature pages are used a signed copy for each site must be held by the sponsor as essential document in addition to the site.

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| **Sponsor’s representative:** { 4.5.1}  (if sponsor different from MRC)    *Name, Title* | **Signature:** | **Date:** |

If appropriate, other responsible persons such as the statistician, local safety monitor, etc. could sign the protocol as well.

Key roles

(*Synonym:* Team Roster)

* Give contact information as follows. Outline further contact persons to communicate particular issues as appropriate.

***Example text:***

For questions regarding this protocol, contact <<*insert name of appropriate MRC staff>>* at MRC << *insert address, email, phone(s), fax, >>*.

* Please complete the list below as appropriate. Provide the following information for each individual and/or institution, as appropriate.

Name, degree, title,   
Institution Name, Address  
Phone / Fax / E-mail

* If a person fulfills several functions, only the name needs to be repeated.

|  |  |
| --- | --- |
| **Author:**  *also:*  - Protocol Champion,  - Protocol Expert |  |
| **Sponsor’s representative:** {6.1.3} | Officially authorised to sign the protocol and protocol amendments on behalf of the sponsor (if not MRC) |
| **Principal Investigator(s):** *also:* - Chief Investigator,  - Lead Investigator,  - Coordinating Investigator {6.1.5} | Investigator(s) who is/are responsible for conducting the trial |
| **Investigator(s):** *also:* - Sub-Investigator (s) - Co-Investigator(s) | Investigator(s) who is/are responsible for conducting the trial at site (s), if different from Principal Investigator |
| **Trial Physician:** {6.1.6}*also:* - Trial/Study Clinician  - Research Clinician | In MRC sponsored trials he/she acts as the Sponsor’s Medical Expert |
| **Sponsor’s Medical Expert:** {6.1.4} | If applicable |
| **Trial Monitor(s):** {6.1.2} *also*: - Clinical Research Associate |  |
| **Local Safety Monitor Chair of DMC/DMSB:** |  |
| **Statistician:** |  |
| **Data Manager:** |  |

* Insert in the following clinical laboratories and other medical or technical departments and/or individuals or institutions, as applicable. {6.1.7}

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| --- | --- |
| **External Adviser:** | If applicable |
| **Clinical Laboratory/ies:** | All laboratories involved should be listed here |
| **Other institutions:** | e.g. major collaborators, epidemiologist, industry representative(s), etc |
| **Ethics Committee** | Contact Information of the independent ethics committee(s) and/or institutional review board(s) (e.g. Gambia Government/MRC Joint Ethics Committee, c/o MRC Laboratories (UK), PO Box 273, Banjul, The Gambia, West Africa) |

* List other individuals of the study team roster in a separate document (e.g. the trial specific SOP) as appropriate.

List of abbreviations

* Please modify list to include your protocol-specific terms or to delete terms from the list that are not used.
* List all abbreviations used and define them, if appropriate.
* Use accepted international medical abbreviations.
* Standardise trial specific abbreviations within your trial.

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| --- | --- |
| AE | Adverse event/adverse experience |
| AR | Adverse reaction |
| CIOMS | Council for International Organizations of Medical Sciences |
| CFR | Code of Federal Regulations |
| CRF | Case report form |
| DMC | Data monitoring committee |
| FDA | Food and Drug Administration |
| FWA | Federalwide Assurance |
| GCP | Good clinical practice |
| IB | Investigator’s Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent or institutional ethics committee |
| IMP | Investigational medicinal product |
| IND | Investigational new drug application |
| INN | International nonproprietary name |
| IRB | Institutional review board |
| MRC | Medical Research Council; represents MRC Unit, The Gambia |
| PI | Principal Investigator |
| SAE | Serious adverse event |
| SAR | Serious adverse reaction |
| SCC | Scientific Coordinating Committee |
| SIS | Subject information sheet |
| SmPC | Summary of Product Characteristics |
| SOP | Standard operating procedure |
| TMF | Trial (site) master file (regulatory file) |
| TSC | Trial steering committee |
| US | United States |
| WHO | World Health Organization |

Protocol summary

(*Synonyms*: Outline, Synopsis)

* Please provide a protocol summary limited to one to two pages.
* Give the reader sufficient information to understand the rationale for the trial, its objectives and the methods that will be used to achieve these objectives, completed by a schematic of trial design.

|  |  |
| --- | --- |
| **Title:** | Insert title from title page |
| **Brief title** | Insert brief title from title page |
| **Phase** (if applicable) | State I, II, III, IV |
| **Population:** | Include sample size, gender, age, general health status, geographic location, etc |
| **Number of Sites:** | List here also field sites of MRC and Health Centers. If there are more than 5 sites refer to Section 1. |
| **Study Duration:**  **- Clinical Phase**  **- Whole study** | Clinical Phase: Provide time from when the trial starts (usually first participant’s first consent) until the end (usually last participant’s last visit or close of data base).  Whole study: Provide time from Ethics Committee approval until results for the primary objective(s) are available |
| **Subject Participation Duration:** | Provide time it will take to conduct the study for each individual participant. |
| **Description of Products or Intervention:** | Include names, dose, route/mode of administration, etc, as applicable. |
| **Objectives:** | State objectives and clinical and/or laboratory outcome measures in accordance with section 2. Include primary/secondary endpoints (outcome parameters) and method by which outcome will be determined. |
| **Description of Study Design:** | Provide an overview of the study design, including study arms, sample size and schedule of interventions. Include a detailed schematic describing all visits and assessments (schedule of events) in an appendix. |

# Background information and rationale

Before any clinical study is carried out, the reason for its execution and the essentials of the problem itself should be given.

For the consolidated guideline by ICH on general considerations for clinical trials ICH (E8) please refer to: <http://www.ich.org/LOB/media/MEDIA484.pdf>

## Background information

{6.2}

The background that is relevant to the design and conduct of the study should be described.

* Consider the magnitude of the problem, its frequency, the affected geographical areas, ethnic groups, and gender.
* Introduce the investigational products or intervention by name, if any, and give a brief description. {6.2.1} In case of medicinal products (IMP) give the generic name (INN) and/or composition, if appropriate, and for licensed products the proprietary name (*synonym*: brand name, trademark). If there is an Investigator’s Brochure (IB), it should be referred to, but it is still useful to include a summary here. Details are to be given in the section on investigational products or intervention.
* Include a summary of findings from previous in-vitro investigations and/or non-clinical studies that have potential clinical significance. {6.2.2} Include epidemiological or public health background.

For the consolidated guideline by ICH on non-clinical safety studies ICH (M3) please refer to: <http://www.ich.org/LOB/media/MEDIA506.pdf>

* Summarise relevant clinical trials. {6.2.2}
* In the case of a new intervention or product set the scene with a brief description of the indication, its incidence, current treatment(s) and their limitations. Indicate a worthwhile improvement in clinical outcome(s), and any background information or justification to suggest that the intervention may achieve this improvement and the relevance to health care practice.
* Discuss important literature and data that are relevant to the study and that provide background for the trial. Discuss the importance of the study and any relevant issues or controversies. {6.2.7}
* Describe the population to be studied or cross-refer to the corresponding section. {6.2.6}

References of literature and data are listed in Section 14.

## Rationale

* Give a description of and justification for the intervention, route or mode of administration, dosage, dosing regimen, intervention periods, and selection of study population. {6.2.4}
* Include a statement of the hypothesis.
* Discuss the importance of the study and any relevant issues or controversies.

## Potential risks and benefits

{6.2.2}

For practical reasons the potential risks and benefits should be discussed under ethical considerations. Provide corresponding information here.

***Example text:***

The potential risks to human subjects and known benefits, if any, are summarised in section ‘Ethical considerations’.

# Study objectives

{6.2.3}

* Please give a clear and detailed description of the primary and, if applicable secondary objectives of the study. This must be consistent with objectives as stated in the summary.

Include:

* Statement of purpose {6.2.2}  
  (e.g. to assess, to determine, to compare, to evaluate)
* General purpose,   
  (e.g. efficacy, safety, immunogenicity, effectiveness, pharmacokinetics)
* Specific purpose,   
  (e.g. dose-response, superiority to placebo, non-inferiority to comparator).
* Be completely objective and do not suggest any prejudge of the outcome.
* Include the exploratory or confirmatory characterisation of the outcome measures.

## Study endpoints

{6.4.1}

Trial endpoints (outcome parameters) are the response variables that are chosen to assess effects of the intervention that are related to pharmacologic parameters, efficacy, safety, immunogenicity and/or effectiveness. This means to record an observation variable at one or more time points after enrolment for the purpose of assessing the effects of the study intervention.

A primary endpoint should reflect clinically relevant effects and is typically selected based on the primary (principal) objective of the trial. This is usually used for the statistical power calculations to decide targeted number of participants.

For the consolidated guideline by ICH on statistical principles for clinical trials ICH (E9) please refer to: <http://www.ich.org/LOB/media/MEDIA485.pdf>

If there is more than one primary endpoint the outcome measures should be prioritized.

Secondary endpoints assess other effects of the intervention that may add information about the primary objective or may not be related to it. Their importance and role in the analysis and interpretation of study results should be discussed.

* Give succinct but precise definitions of the end points used to measure the primary and key secondary outcomes stated in the trial objectives.
* Describe the methods for assessing, how the objectives are met, including the study visits at which the samples will be obtained and the specific laboratory tests to be used.

# Study design

{6.4}

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. This will contain information to show that the trial has been designed to meet the objectives, protect the study participants from injury or inappropriate risk, and ensure the scientific validity of the data generated. The rationale for design features should be discussed.

For the choice of control group and related issues in clinical trials ICH (E10) please refer to  
<http://www.ich.org/LOB/media/MEDIA486.pdf>

## Type of study and design

* Specify the type (e.g. double-blind, placebo-controlled, dose-escalation) and, if applicable phase of the trial. {6.4.2}
* Describe the trial design (e.g. parallel groups, cross-over design, single or multi-centre). {6.4.2}
* State the number of trial groups/arms, and describe the study groups/arms including sample size (including a table, if appropriate), stratifications, if any.
* Describe the expected duration of subject participation and approximate time to complete study enrolment. {6.4.5}
* Describe the sequence and duration of all clinical study periods (e.g. screening, treatment, follow-up), specify individual participants versus entire trial. {6.4.5}
* Describe other protocol-specific details, such as centralisation of evaluations (e.g. central laboratory or central reading centre for clinical scans).
* Describe the “stopping rules” or “discontinuation criteria” for individual participants, parts of the trial and entire trial, and/or cross-refer to the corresponding section. {6.4.6}

## Randomisation and blinding procedures

The measures taken to minimise or avoid bias as randomisation and blinding (*synonym*: masking), including procedures and practical arrangements, should be described. It should be avoided to being so specific that blinding or randomisation might be compromised (e.g. the ratio between intervention and placebo groups may be stated but the randomization block sizes should not).

### Randomisation

{6.4.3}

A clear summary statement should be included concerning the randomisation schedule (e.g. block, stratified) and whether numbers assigned to each intervention arm will be equal or maybe fewer in one arm, and supporting justification.

* State if the trial will be randomised or not. If not give a justification.
* Describe (or list in a table) the randomization schedule and how study participants will be assigned to study groups.
* Justify the randomization schedule and assignment.
* Include plans for the maintenance of trial randomisation codes.
* Describe the circumstances under which the randomisation codes may need to be broken and/or cross-refer to the corresponding section.
* Provide timing and procedures for planned and unplanned breaking of randomisation codes. {6.4.8} It is essential that the procedures for breaking the randomisation code are simple, straightforward and can be carried out outside working hours because they may need to be implemented at a moment’s notice.

### Blinding

{6.4.3}

* State whether the trial arms will be blinded (if more than one intervention), and justify if not or only parts of the study.
* Describe the blinding (e.g. single blind, double-blind, analyst, administrator, etc).
* Explain why the method of blinding has been selected.
* Discuss plans for maintaining appropriate blinding for the trial.
* Describe the circumstances under which the blinding may need to be broken and/or cross-refer to the corresponding section.
* Provide timing and procedures for planned and unplanned breaking of blinding. {6.4.8} It is essential that the procedures for breaking the blinding are simple, straightforward and can be carried out outside working hours because they may need to be implemented at a moment’s notice.

## Sub-studies

(if applicable)

A sub-study asks a separate research question from the parent protocol and may or may not contribute to the parent protocol’s objectives but uses all or a subset of study participants or specimens. Sub-studies do not have full protocols but rather are incorporated into the main protocol.

* Describe briefly the sub-study and its objectives;
* State briefly the impact on main study.
* Indicate the potential participating sites.

## Investigational products or interventions

{6.4.4}

The investigational products or interventions administered to the participants should be described in detail. In case of medicinal products (*synonyms*: medicines, drugs) the information could usually be obtained from the Investigator’s Brochure (IB) or in case of licensed medicinal products from the Summary of Product Characteristics (SmPC) or package insert leaflet or other sources on product information, and should be in accordance with the available product information.

If other treatments are administered apart from the investigational products or interventions they should also be described here. It should be well distinguished which products or interventions are investigational and which are not.

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

### Description of product or intervention

* Describe the investigational product or intervention in detail including the name.
* Describe placebo or control product or measure.

### Formulation, packaging and labelling

(where applicable)

{6.4.4}

* Describe the formulation, packaging, and labeling of the investigational product, placebo or other control product. Include the source of manufacture and a mock-up of the label. It should be stated that trial medication(s) are only for use of trial participants.

### Product storage and stability

(where applicable)

* Describe the product’s storage and stability (e.g. temperature, humidity, security, and container). Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc. or expiration time for trials in which multidose vials (e.g. the seal is broken).

## Dosage, preparation and administration of investigational product or intervention

* Describe the dosage and dosing regimen as well as changes in scheduling such as dose escalation. Include the total dose or dose per kg body weight, the strength of the unit dose, dose in each phase of the trial, frequency and timing of dose in each phase and group or arm of the trial, methods for individualised doses, etc. {6.4.4}
* Explain instructions for modification of dose or due to toxicity or any other potential reason and/or cross-refer to corresponding section, as appropriate.
* Include thawing, diluting, mixing, and reconstitution/preparation instructions, as appropriate.
* Describe the techniques for administration, if appropriate (e.g. double dummy).
* Describe the routes or modes of administration.
* Describe the intervention period(s), including the follow-up period(s) for participants for each investigational product or measure and group/arm of the trial and/or cross-refer to the corresponding section. {6.6.1}
* Include any specific instructions or safety precautions for administration of investigational product or blinding of the product or the administrator or refer to appropriate study specific SOP.
* Provide plans for how the study products will be distributed (dispensing records), shipped, and returned if unused (accountability). {6.4.7}
* Include plans for compliance assessment (e.g., questionnaires, direct observation, ‘pill’ counts). {6.6.3}
* Include plans for appropriate medical treatment in case of emergencies (e.g., for anaphylactic reactions).

## Concomitant medications/treatments

* List all medications and/or treatments that are permitted, including rescue medications, before and/or during the study. {6.6.2}
* Describe continuation on study medication or other medication after completion of the trial, if this has been decided. Include the prescribing and dispensing arrangements as appropriate.

**Note**: This section should be consistent with the medications restrictions in the inclusion/exclusion criteria.

# Selection and withdrawal of participants

{6.5}

## Selection of participants

The trial population and eligibility criteria should be clearly defined and the recruitment strategies discussed.

* Provide the target sample size, including actual numbers to be enrolled.
* Describe the study population (e.g. healthy/sick, age, sex) including ethnic group, prognostic factors, etc, where relevant
* Include numbers of women, minorities, and children expected to be recruited or not be recruited and explain and justify the exclusion, if appropriate.
* Indicate from where the study population will be drawn (e.g. inpatients, outpatient clinics, previous trial cohort, general public, etc). Include names of hospitals, clinics, etc.
* Identify strategies for participant recruitment and retention and/or cross refer to the corresponding section.
* State whether participants require sensitization and/or screening. Distinguish between screening participants (e.g. discussing the study with them) and enrolling participants (e.g. obtaining informed consent and obtaining samples). The screening laboratory tests should be carefully selected, if they will be used.

## Eligibility of participants

A definition of participant characteristics required for study entry should be provided. The risks of the intervention or investigational products should structure the development of the inclusion and exclusion criteria.

The criteria should be described and a justification included, if necessary. The same criterion should not be listed as both an inclusion and exclusion criterion (e.g. it should not be stated age >32 years old as an inclusion criterion and also age ≤32 years old as an exclusion criterion). If males and females of reproductive potential will be enrolled, specific contraception requirements should be provided, if appropriate.

{6.5.1}, {6.5.2}

It should be a statement provided that participants must meet all of the inclusion criteria in order to be eligible to participate in the trial before listing of each criterion, and that participants meeting any of the exclusion criteria at baseline will be excluded from the trial before listing of each criterion.

***Example text:***

Participants must meet all of the inclusion and none of the exclusion criteria in order to be eligible to participate in the trial.

### Inclusion criteria

* List each inclusion criterion.   
  Examples for inclusion criteria are informed consent obtained and signed, age, presence or absence of a medical condition/disease, required laboratory result, ability to comply with study procedures for the entire length of the study, etc.

### Exclusion criteria

* List each exclusion criterion.   
  Examples for exclusion criteria are medical condition or laboratory finding that precludes participation, recent (with time frame) febrile illness that precludes or delays participation, pregnancy or lactation, characteristics of household or close contacts (e.g. household contacts who are immunocompromised), known allergic reactions to components of the study product(s), treatment with another investigational medicinal product (with time frame), history of drug/alcohol abuse, disallowed concomitant medications, etc.

## Withdrawal of participants

{6.5.2}

* Specify withdrawal criteria for participants (e.g. development of laboratory toxicities, exclusion criteria).
* Provide a list of reasons participants may be discontinued from the study.
* Note that subjects may withdraw voluntarily from participation in the study at any time for any reason. Participants may also withdraw voluntarily from receiving the study intervention for any reason.

***Example text:***

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

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

For further details on participant’s premature termination see corresponding section below.

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

# Study procedures and evaluations

The methods and timing for assessing, recording, and analysing of efficacy {6.7.2} and/or safety {6.8.2} and/or immunogenicity and/or effectiveness and/or other parameters should be defined in detail and/or cross-referred to the corresponding section.

* Include all visits at the site as well as all visits done at home and all planned contacts (e.g. telephone contacts) into the schedule.
* Specify the purpose of the visits as appropriate (screening, enrolment, follow-up, final visit, etc).
* State allowable windows for all visits. Consider feasibility and relevance of the time point to study outcome measures (e.g. pharmacokinetic (PK) studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).
* Specify how unscheduled visits(s) will be handled and documented.
* If a sensitisation procedure will be used, describe this in a separate section before screening.

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

## Study schedule

The evaluations to be done may be listed individually in this section or, alternatively referred to the Schedule of Events.

### Screening

* Include only those evaluations necessary to assess whether a participant meets eligibility criteria.
* Discuss the sequence of events that should occur during screening and the decision points regarding eligibility.
* List the time frame prior to enrolment within which screening tests and evaluations must be done (e.g. within 28 days prior to enrolment).

If screening procedures are required for eligibility (e.g. review of medical records or laboratory tests), they must be performed under a separate screening consent form in addition to the consent form for study participation*.* If a separate screening consent will not be used, the study consent must be signed prior to screening.

* Describe procedure for obtaining signed informed consent or cross-refer to the corresponding section.
* State if a separate screening consent will be used that must be signed prior to screening.

### Enrollment (Baseline)

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

### Follow-up

* Describe 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 counseling, review of reactogenicity, medications, assessment of AEs, etc, as applicable.

### Final study visit

* Define when the final trial visit should occur.
* Describe any special procedures/evaluations or instructions to the participant.
* Describe provisions for follow-up of ongoing AEs/SAEs and/or cross-refer to appropriate sections.

### Early termination visit

* If an early termination occurs, specify which of the evaluations required for the final study visit should be done on an early termination visit - given that the participant is willing - and/or cross-refer to appropriate sections.

## Study evaluations

* Specify the efficacy and/or safety and/or immunogenicity and/or effectiveness and/or other parameters to be used and/or cross-refer to appropriate sections. {efficacy 6.7.1; safety 6.8.1}
* Define the circumstances in which abnormal laboratory values will be reported as adverse events.
* For further safety considerations cross-refer to the corresponding section.

### Clinical evaluations

* List all clinical evaluations to be done during the study and/or cross-refer to appropriate sections.
* Provide details of what are included and special instructions, if any.

If appropriate, cross-refer to corresponding documents such as clinical standard operating procedures.

***Examples:***

*Medical history (describe what is included for history, e.g. time-frame considerations, whether history will be obtained by interview or from medical records).*

*Medications history (e.g. describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter and/or traditional medicine). Assessment of eligibility should include a review of permitted and prohibited medication.*

*Physical examination (list the vital signs [including height and weight]* *and organ systems to be assessed; address whether it is an actual measurement or participant's self report); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur. If an adverse event occurs, describe if a full physical examination should be done.*

* Describe review of diary cards, if used.
* Describe the counseling procedures.
* List the criteria for dose adjustment or cross-refer to the corresponding section.
* List the rescue therapy or cross-refer to the corresponding section.

If appropriate, cross-refer to corresponding documents such as clinical standard operating procedures.

### Laboratory evaluations

* List all laboratory evaluations including special assays or procedures required to assess the investigational product or measure (e.g. immunology assays, PK studies, photographs).
* Specify which evaluations will be done by each laboratory. Differentiate screening laboratories from those taken after administration of the investigational product or investigational measure, as appropriate.
* Include specific test components and estimated volume and type of specimens needed for each test.
* Specify laboratory methods.
* Provide special instructions or precautions for procedures.
* Provide special instructions for the preparation, handling, and storage of specimens including required temperatures, aliquots of specimens, if samples are frozen, where they will be stored, and how they will be labeled.
* State the frequency with which specimens are to be shipped and where to. Include contact information for laboratory personnel. Include days and times shipments are allowed, and any labeling requirements for specimen shipping. Also, include any special instructions such as dry ice or wet ice or the completion of a specimen-tracking log.
* Include a discussion of long-term access and consent for future use of specimens.

If appropriate, cross-refer to corresponding documents such as laboratory standard operating procedures.

***Examples:***

*Haematology: hemoglobin, haematocrit, white blood cells (WBC) with differential count, platelet count.*

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

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

*Pregnancy test, results must be available prior to administration of investigational product, where applicable.*

# Safety considerations

The context of the trial should be considered and reporting procedures appropriately adjusted for the trial population and investigational product or measure being studied. Appropriate toxicity tables will define what values or findings are considered abnormal.

For the consolidated guideline by ICH on safety issues for clinical trials ICH (E2A) please refer to: <http://www.ich.org/LOB/media/MEDIA436.pdf>

* Include safety parameters others than outcome measures.
* Include definitions in the following sections as appropriate

**Definitions**

Although an international harmonisation was achieved to great extend, some slight differences still exist in terminology. Since this might be especially important where safety issues are concerned, all relevant definitions are provided in the following. In the study protocol the appropriate definition should be chosen.

**Adverse Event (or Adverse Experience)**

**ICH:** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.   
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

**Adverse (Drug) Reaction**

**ICH:** All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

**Serious Adverse Event or Serious Adverse (Drug) Reaction**

**ICH**: A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

results in death,

is life-threatening,

requires inpatient hospitalisation or prolongation of existing hospitalisation,

results in persistent or significant disability/incapacity, or

is a congenital anomaly/birth defect.

**Note**: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**FDA:** Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

**Important Medical Event**

**ICH:** Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

**Note:** The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

**Unexpected Adverse Event/Drug Reaction/Experience:**

**ICH-GCP:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) {1.60}

**FDA:** Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

**Note:** Adverse events may also be defined as unexpected if not described in published medical literature or if not reasonably expected due to the natural history and progression of the underlying disease or condition of the study population.

## Methods and timing for assessing, recording, and analysing safety parameters

### Adverse events

* Describe how adverse events will be captured.
* State clearly when to start collection and recording of AEs and which will be considered as solicited AEs.
* Plan the data collection and documentation system to avoid double capture. Include time period of collection and note how long AEs are collected. {6.8.2}
* Describe how AEs will be followed until resolved or considered stable. Include duration of collection and recording for appearance of AEs and/or cross-refer to the corresponding section. {6.8.3}
* Describe how decisions will be made regarding relatedness and grading severity of adverse events.
* Provide a definition of expected versus unexpected AEs, based on the risk profile of the investigational product or measure or population.

For further details refer to the MRC SOP on ‘Recording, Management and Reporting of Adverse Events’, Blue B 09.

### Reactogenicity

(if applicable)

In vaccine trials the reactogenicity to the vaccination should be assessed. This information is usually collected immediately and some days after vaccination by observation and interview. Participants may also have a memory aid to help recollect their symptoms. It should be stated on which form these AEs will be captured (e.g. in a reactogenicity record form or AE form) to avoid double reporting.

* Describe which adverse events will be collected as reactogenicity to vaccines and in which form (solicited reports).
* Provide a definition of local versus systemic events, based on the risk profile of the vaccine.
* Describe the collection and documentation procedure for the reactogenicity.
* Describe how decisions will be made regarding the grading of severity of reactogenicity.

### Serious adverse events (SAEs)

* Describe how serious adverse events will be captured.
* Plan the data collection and documentation system to avoid double capture. Include time period of collection and note how long SAEs are collected.
* Describe how SAEs will be followed (e.g. until satisfactory resolution or until the PI deems the event to be chronic or the patient to be stable, etc).

### Suspected unexpected serious adverse reactions (SUSARs)

* State what constitutes a SUSAR.

***Example text:***

A SUSAR is different from an SAE in that it is unexpected and thought to be related to the study medicine.

## Reporting procedures

**Note**: All clinical trials on investigational products must have an AE reporting system in place.

Procedures for reporting of AEs and the duration of follow-up should be specified. The reporting will be dependent on the abnormality, the trial intervention, and the trial population and should be stated specifically. If deaths, hospitalisation, etc are expected to happen during the trial period it might be appropriate to report only unexpected SAEs expeditiously.

* Describe in detail the reporting procedures for adverse events and inter-current illnesses and to which parties (e.g. sponsor, local safety monitor, relevant ethics committees, regulatory agencies, chair of DMC/DSMB, etc) they will be reported. {6.8.3}
* Include the individual responsible for each step.
* State which forms should be completed.
* Describe how and in which time reports will be distributed.
* Describe what follow-up procedures are required and for how long. {6.8.4}
* Include specific details of reporting procedures for deaths and life-threatening events, other SAEs, and other adverse events.
* Identify additional safety issues that need to be reported in an expedited fashion.
* Describe any other AEs that merit reporting to any party.
* State the trial’s pregnancy-related policy and procedure. Provide appropriate modifications to trial procedures (e.g. discontinuation of investigational product while continuing safety follow-up, following pregnant women to pregnancy outcome).
* Provide appropriate modifications to trial procedures and/or cross-refer to the corresponding section.

## Safety oversight

* Identify clearly the type of safety oversight along with any known responsibilities for the oversight of safety in the trial.
* State in detail who is or are responsible for safety oversight (e.g. local safety monitor, TSC, DMC/ DSMB, etc) including time points, composition, where appropriate, etc.
* Describe the safety monitoring procedures.

Suspension of enrolment (for a particular group or for the entire trial) is a potential outcome of a safety review by any relevant party.

***Examples***

*Findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of adverse events.*

# Discontinuation criteria

## Participant’s premature termination

* If appropriate, provide distinct discontinuation criteria for participants and cohorts.
* State the type and timing of the data to be collected for withdrawn participants and/or cross-refer to the corresponding section.
* Describe safety findings that would temporarily suspend enrollment and/or study interventions for an individual or study group
* Describe replacement of participants which discontinue early, if allowed and/or cross-refer to the corresponding section.
* Describe the efforts to follow participants who withdrawal from the trial.

***Example text:***

The reason for participant’s premature termination will be documented on the appropriate page of the CRF and specified which of the following possible reasons were responsible for the study premature termination:

* Serious Adverse Event / SUSAR
* Non Serious Adverse Event
* Participant’s consent withdrawal
* Inappropriate enrolment
* Development of exclusion criterion
* Protocol deviation
* Migrated/moved from the study area
* Lost to follow-up  
  A 'lost to follow-up' is any participant who completed all protocol specific procedures up to the administration of the investigational product or intervention, but was then lost during the study period to any further follow-up, with no safety information and no efficacy endpoint data ever became available.
* Other, reason will be specified

**Note:** It is vital to collect safety data on any participant discontinued because of an AE or SAE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the participant should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the participant’s condition becomes stable.

## Study discontinuation

* Provide criteria and possible reasons for discontinuation of parts of the study or entire study (e.g. study closure due to review, discretion of the sponsor), and/or cross-refer to corresponding section, as appropriate.
* Describe findings that would temporarily suspend enrollment and/or study interventions including the objective of which is a decision as to whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed and/or cross-refer to the corresponding section.
* Describe the reporting procedure on study discontinuation.

# Statistical considerations

The statistical consideration should show how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. If interim analyses will be performed, complete instructions should be provided and its impact on the final efficacy analyses, particularly on Type I error should be discussed.

For the consolidated guideline by ICH on statistical principles for clinical trials ICH (E9) please refer to: <http://www.emea.eu.int/pdfs/human/ich/036396en.pdf>

More details can be provided in a separate statistical analysis plan written later but prior to performing any analyses.

* Describe the statistical methods to be employed, including timing of any planned interim analyses. {6.9.1}
* State the formal, testable, null, and alternate hypotheses for primary and key secondary objectives, specifying the type of comparison, if applicable (e.g. superiority, non-inferiority, dose-response, etc).
* State the level of statistical significance to be used and how it relates to the clinical significance. {6.9.3}
* Provide all information needed to validate the calculations for the number of participants planned to be enrolled. In multi-centre studies, specify the numbers of enrolled participants projected for each study site.{6.9.2}
* Give reason for choice of sample size including reflections on (or calculations of) the power of the study and clinical justification including whether the sample size provides power for addressing secondary objectives or for secondary analyses in key subgroup populations.{6.9.2}
* Describe the types of and procedures for statistical interim analyses, if any.
* Describe the criteria and statistical techniques be used for the termination of the trial or halt enrolment into all or a portion of the trial (e.g. the probability of stopping under different safety event rates and the associated number of participants that would be enrolled), and/or cross-refer to the corresponding section. {6.9.4}
* Describe the statistical techniques be used to halt enrolment into all or a portion of the trial.
* Describe the selection of participants to be included in the analyses and identify clearly the analyses cohorts (e.g. “Per Protocol” or “Intent to Treat”) as well as subsets of interest (e.g. all randomised participant, all dosed participants, all eligible participants, evaluable participants, etc). {6.9.7}
* Describe the methods to account for missing, unused or spurious data. {6.9.5}
* Discuss how outcome measures will be measured and transformed, if relevant, before analysis (e.g. is the primary variable binary, categorical, or continuous; will a series of measurements within a participants be summarised, such as by calculating the area under the curve; what are the competing risks and censoring variables for survival outcome measures, etc).
* Describe and justify procedures for reporting any deviations from the original statistical plan. {6.9.6}

# Data handling and record keeping

## Data management and processing

{6.13}

* Describe briefly reference to source documentation, instructions for completing forms, data handling procedures, and procedures for data monitoring. For details cross refer to the appropriate document, as appropriate.
* Include instructions for special data-handling or record-keeping procedures and/or cross-refer to the corresponding section.
* Describe responsibilities for data handling and record keeping.
* Describe coding dictionaries to be used and reconciliation processes, if applicable.
* Provide details regarding the type of data and indicate expectations for time for submission of CRFs.
* Indicate the types of data that will be collected and the database used.
* Indicate the schedule for data review and reports.
* Specify the length of time for the investigator to maintain all records pertaining to this trial.

## Source documents and access to source data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. It is acceptable to use CRFs as source documents.

* State what data will be collected on CRFs and what data will be collected from other sources
* Describe who will have access to records
* State that each site will permit monitoring, audits, IRB/IEC reviews, and regulatory inspections, providing direct access to source data/documents and, if required, to copy them by authorized representatives. {6.10}

***Example text:***

The Principal Investigators will maintain appropriate medical and research records for this study in compliance with the principles of good clinical practice and regulatory and institutional requirements for the protection of confidentiality of participants. The study team members will have access to records.

Authorised representatives of the sponsor, the ethics committee(s) or regulatory bodies may inspect all documents and records required to be maintained by the investigator for the purposes of quality assurance reviews, audits, inspections, and evaluation of the study safety and progress. This will include, but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

## Protocol deviations

A protocol deviation is any noncompliance with the clinical study protocol, good clinical practice (GCP), or other protocol-specific requirements. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

* Describe plans for detecting, reviewing, and reporting deviations from the protocol and/or cross-refer to the corresponding section.
* State that the PI will not implement any change to the protocol without prior agreement by the sponsor and approval by the Ethics Committee
* Indicate under which circumstances a change to the protocol might be implemented without approval (e.g. to eliminate an immediate hazard(s) to trial participants)
* Describe the documentation procedure of protocol deviations
* Describe the reporting procedure of protocol deviations

***Example text:***

A protocol deviation (PD) is any noncompliance with the clinical trial protocol, good clinical practice (GCP), or other protocol-specific requirements. The noncompliance may be either on the part of the participant or the investigator including the study team members, and may result in significant added risk to the study participant. As a result of a deviation, corrective actions will be developed and implemented promptly.

If a deviation from, or a change of, the protocol is implemented to eliminate an immediate hazard(s) to trial participant without prior ethics approval, the PI or designee will submit the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) as soon as possible to the relevant ethics committee(s) for review and approval and to the sponsor for agreement.

The PI or designee will document and explain any deviation from the approved protocol on the CRF, where appropriate, and record and explain any deviation in a file note or deviation form that will be maintained as an essential document.

Deviations from the protocol, GCP or trial specific requirements that might have an impact on the conduct of the trial or the safety of participants will be reported within 5 working days to the sponsor and relevant EC, as appropriate.

# Quality control and quality assurance

{6.11}

This section will address the plans for local quality assurance and quality control.

* Describe steps taken to ensure the collection of accurate, consistent, complete, and reliable data and/or cross-refer to the corresponding section.
* Describe how data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
* Specify the methods of training for staff.

## Study monitoring

Site monitoring is conducted to ensure that the human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet the sponsor, ICH E6 and, when appropriate, regulatory guidelines. This section will give a general description of how site monitoring will be conducted. A separate clinical study monitoring plan should be developed to describe who will conduct the monitoring, what frequency of monitoring will be done, and what level of detail monitoring will be performed, depending on the risks involved.

* Give a general description of how site monitoring will be conducted.

# Ethical considerations

* Include the guiding ethical principles being followed by the study.

***Example text:***

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the Declaration of Helsinki in its current version, whichever affords the greater protection to the participants.

## General considerations on human subject protection

{6.12}

* Describe the ethical considerations and context for the conduct of the study.
* In the event that the study is discontinued, describe procedures for participants to continue therapy, if appropriate and/or cross-refer to the corresponding section.
* Include provisions for consent if residual specimens will be maintained and specify the location(s) and protections of confidentiality.
* Include a statement that genetic testing will not be performed without prior informed consent.
* Specify any type of remuneration.

{Declaration of Helsinki 2008}

* Describe incentives for participants
* Describe provisions for treating and/or compensation for subjects who are harmed as a consequence of participating in the study and/or cross-refer to the corresponding section.

### Rationale for participant selection

* If the study intends to exclude any special populations justify the exclusion in the context of the study design and/or cross-refer to the corresponding section.
* Explain the rationale for involvement of special classes of participants, if any.

### Evaluation of risks and benefits

If an Investigator’s Brochure, Summary of Product Characteristics (SmPC) or package insert leaflet is available for investigational products, it should be used as the primary source of risk information. If the risk profile cannot be described from any of the above sources, the risk information discussion will result from the literature search and review.

* Describe in detail any potential risks.
* Describe alternative treatments and procedures that might be advantageous to the participants.
* Describe in detail the expected potential benefits, if any.   
  **Note:** Payment to participants, whether as an inducement to participate or as compensation for pain and inconvenience, is not considered a “benefit” as well as provision of medical care participants are entitled to independent from the study.
* Discuss the benefit-risk-relationship.

Include a review of relevant literature, which should be referenced. Add relevant websites, etc from which the information could be drawn (e.g. on product information) in Section “References”.

## Informed consent

Informed consent is required for all subjects participating in a clinical study. In obtaining and documenting informed consent, the investigator should comply with ICH GCP, applicable regulatory and local ethical requirements.

Guidance on information provided to participants and informed consent is provided by the Gambia Government/MRC Joint Ethics Committee on the MRC intranet <http://open.mrc.gm/SCC/home.asp>

* Describe the procedures for obtaining and documenting informed consent, including the circumstances in which consent will be sought and obtained.
* Identify different consent forms that are needed including e.g. screening, study participation, screening for human immunodeficiency virus, future use of specimens, assent form for minors and/or cross-refer to the corresponding section.
* State special circumstances regarding obtaining consent and prepare provisions for special populations and/or cross-refer to the corresponding section.
* State the protections for vulnerable participants.
* Discuss how assent of minors will be obtained for the particular study, if applicable.

## Participant confidentiality

* Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention and/or cross-refer to the corresponding section.
* Describe whether participant identifiers will be attached to data or whether samples/data will be coded or unlinked and/or cross-refer to the corresponding section.
* State possible persons that might have access to records, in addition to the trial monitor and/or cross-refer to the corresponding section.
* State whether personally identifiable information will be released to third parties and/or cross-refer to the corresponding section.

## Future use of stored specimen

* If residual specimens will be maintained after the study is completed, include the provisions for consent and the options that are available for the participant to agree to the future use of his/her specimens.
* Specify the location(s), if other than the clinical site, where specimens will be maintained, if the ethics committee will review future studies.
* Specify protections of confidentiality for any future studies with the stored specimens (e.g. specimens will be coded, bar-coded, etc).

# Financing and insurance

{6.14} and {Declaration of Helsinki 2008}

* Indicate the sponsoring and funding parties and describe the financing procedure and/or refer to the document it is addressed.

{6.14}

* Describe insurance procedure, if applicable, or refer to the document it is addressed.  
  **Note:** In The Gambia no insurance is required by legislation.

{Declaration of Helsinki 2008}

* Indicate the institutional affiliations and any potential conflicts of interest

# Publication policy

{6.15}

* Specify the dissemination of results and/or cross-refer to the corresponding section or refer to the document it is addressed.
* State whether any confidentiality is to be respected by any party.
* Indicate the intellectual or industrial property rights.
* Outline the publication and authorship policies or refer to the corresponding document.
* State how trial results will be communicated to participants.

**Note:** Electronic copies of any original research papers accepted for publication in a peer-reviewed journal, which are supported in whole or in part by MRC funding, must be deposited at the earliest opportunity, and certainly within six months of publication, in UK PubMedCentral. The condition is subject to compliance with publishers’ copyright and licensing policies. Whenever possible, the article deposited should be the published version.

# References

* Include a list of relevant references to literature and data.

## Documents attached to this protocol

* Tick boxes and enter versions and dates as appropriate.

|  |  |
| --- | --- |
| **1.** | **Subject information sheet** |
| **2.** | **Informed consent form** |
| **3.** | **SAE report form** |
| **4.** | **Protocol deviation report form** |
| **5.** | **Data management plan** |
| **6.** | **Statistical plan** |
| **7.** | **Study monitoring plan** |
| **8.** | **Clinical quality assurance plan** |
| **9.** | **DMC/DSMB charter/plan** |
| **10.** | **Financial plan** |

Supplements, appendices and other documents

Examples of documents that might be provided as supplements or appendices to the protocol, as attachments or as related documents or other documents referred to in the protocol (supporting documents).

Supplements and protocol appendices

* Sub-studies or other adjunct studies (e.g. pilot studies, add-on studies, etc)
* Graphic outline
* Toxicity grading scales

Related documents

* Application form (Proposal)
* Models of case report forms
* Models of questionnaires
* Site roster
* Study specific SOPs
* User’s guides or manuals
* Repository instructions
* Biosafety precautions
* Laboratory handling

**\*Schematic of Study Design**: {6.4.2}

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

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

Instructions for progressing to next phase (if applicable):

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

***Example 2:***Flow diagram

Prior to

Total N: Obtain informed consent. Screen subjects by criteria; obtain history document.

Enrollment

Randomize

Clinical and AE assessment

Perform pregnancy test; collect blood for assays;

**Administer Study Product/Intervention**

Time Point or

Study Visit 1

Time Point or

Study Visit 2

Time Point or

Clinical and AE assessment

Study Visit 3

Time Point

or Study Visit …

**Assessment of Final Study Outcome Measures**

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

Appendix: Schedule of events

***Example:***

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

(X) – As indicated/appropriate

* List the tests applicable to your specific protocol.
* Provide a list of tests to be done