Quality Medicines for Malawi

SUBMISSION OF A CLINICAL TRIAL APPLICATION (CTA) TO PHARMACY AND MEDICINES REGULATORY AUTHORITY (PMRA)

CHECKLIST (PLEASE TICK)

1 An application to conduct a clinical trial of an investigational medicinal product shall be submitted to the Authority and accompanied by the following;

- ☐ Comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application. The location of each document should be identified by tab identifiers. In general, the name for the tab identifier should be the name of the document;
- ☐ Cover letter signed by the principle investigator or sponsor;
- ☐ Proof of payment of the application and registration fees as prescribed in PMRA fee structure in force at the time of application;
- ☐ Duly filled in, signed and stamped Clinical Trial Application form CT8;
- ☐ Current version of the study protocol signed and dated by sponsor and investigator- *In the format provided by the ICH Guide E6(R1) and(or) in line with SPIRIT 2013 checklist as in* ***attachment 1*** *below*;
- ☐ Investigator's brochure where applicable-*In the format provided by the ICH Guide E6(R1);*
- ☐ Certificate of GMP manufacture of Investigational Medicinal Product (IMP) and(or) Placebo or evidence of manufacture quality, safety and consistency;
- ☐ Mock up labels for the IMP;
- ☐ Blank Case Report Forms (CRFs) and Serious Adverse Events (SAEs) reporting form to be used in the study;
- ☐ Investigational Medicinal Product Dossier (IMPD) or alternative as provided in ***attachment 2*** below;
- ☐ Stability data of the IMP and auxiliary medicine(s) for climatic zone IVa if not registered in Malawi by PMRA;
- ☐ Evidence of registration of the IMP or auxiliary medicines in a country with Stringent Regulatory Authority (SRA) and (or) Certificate of Pharmaceutical Product (CoPP) i.e. if IMP/auxiliary medicines are not registered by PMRA;
- ☐ Summary of Product Characteristics (SmPC) for IMP and auxiliary medicines;
- ☐ Pharmacy plan; refer to PMRA guidelines on Investigational drugs;
- ☐ Report summaries of prior clinical trials with this medicine. *These would form part of IB if it is in the ICH format;*
- ☐ Capacity building plans including training and updating of staff involved in the trial;
- ☐ Informed consent form according to ICH;
- ☐ Declaration of intent by the national principal investigator or contact person (see PMRA template);
- ☐ Signed and completed declaration by investigators (see PMRA template);

- Investigators CVs including that of pharmacist(s);
- Financial declaration by Sponsor and Principal Investigator (see PMRA template);
- Ethical clearance certificate from an independent ethics review committee recognized by the laws of Malawi;
- Certified copy of clinical trial insurance for study participants endorsed by National Commission Science and Technology (NCST);
- Malpractice insurance for investigators and associated staff endorsed by NCST;
- Evidence of accreditation or equivalent of the designated laboratories (refer to GCL Practice guidelines 2009);
- Completed PMRA Material Transfer Agreement Form (Form CT 12) on Shipping of Samples;
- Description of the site facilities. Pictorial presentations may be included;
- Evidence of registration of investigators with appropriate bodies e.g. Medical council of Malawi;
- Evidence of registration of Pharmacists with PMRA;
- Evidence of GCP training by investigators and pharmacists in the last three (3) years;
- Electronic or soft copy of the Clinical Trial Application dossier to be sent to registration@pmra.mw, info@pmra.mw;
- Three (3) hard copies of the Clinical Trial Application dossier in lever arch file to be sent to the Director General PMRA;
- Each section of the Clinical Trial Application dossier above should be well demarcated for ease of reference by PMRA reviewers.
- Any other requirement as may be determined by the Authority.

Note: For an item that is not ticked or submitted as per checklist above, please provide justification(s) for not submitting the document.

2 An application to conduct a clinical trial may be made by a sponsor or the sponsor's agent who shall submit a power of attorney attesting that he is a duly appointed agent (see PMRA template).

ATTACHMENT 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No.	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items on https://www.spirit-statement.org .Amendments to the protocol should be tracked and dated.

ATTACHMENT 2

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

1 The IMPD shall give information on the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.

1.1. **Data relating to the investigational medicinal product**

Introduction

2 Regarding data, the IMPD may be replaced by other documentation which may be submitted alone or with a simplified IMPD. The details of this 'simplified IMPD' are set out in section 1.2 'Simplified IMPD by referring to other documentation'.

3 Each section of the IMPD shall be prefaced with a detailed table of contents and a glossary of terms.

4 The information in the IMPD shall be concise. The IMPD must not be unnecessarily voluminous. It is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points.

Quality data

5 Quality data shall be submitted in a logical structure such as that of Module 3 of the ICH Common Technical Document format.

Non-clinical pharmacology and toxicology data

6 The IMPD shall also contain summaries of non-clinical pharmacology and toxicology data for any investigational medicinal product used in the clinical trial in accordance with international guidance. It shall contain a reference list of studies conducted and appropriate literature references. Wherever appropriate, it is preferable to present data in tabular form accompanied by a brief narrative highlighting the main salient points. The summaries of the studies conducted shall allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

7 Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as that of Module 4 of the ICH Common Technical Document format.

8 The IMPD shall provide a critical analysis of the data, including justification for omissions of data, and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

9 The IMPD shall contain a statement of the good laboratory practice status or equivalent standards.

10 The test material used in toxicity studies shall be representative of that of the clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material shall be subject to the controls necessary to ensure this and thus support the validity of the study.

Data from previous clinical trials and human experience

11 Data from previous clinical trials and human experience shall be submitted in a logical structure, such as that of Module 5 of the ICH Common Technical Document format.

12 This section shall provide summaries of all available data from previous clinical trials and human experience with the investigational medicinal products. It shall also contain a statement of the compliance with good clinical practice of those previous clinical trials.

Overall risk and benefit assessment

13 This section shall provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the investigational medicinal product in the proposed clinical trial unless this information is already provided in the protocol. In the latter case, it shall cross-refer to the relevant section in the protocol. The text shall identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults shall take account of the specific provisions set out in this Regulation.

14 Where appropriate, safety margins shall be discussed in terms of relative systemic exposure to the investigational medicinal product, preferably based on 'area under the curve' (AUC) data, or peak concentration (Cmax) data, whichever is considered more relevant, rather than in terms of applied dose. The clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials shall also be discussed.

1.2. **Simplified IMPD by referring to other documentation**

15 The applicant may refer to other documentation submitted alone or with a simplified IMPD.

Possibility of referring to the IB

16 The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the reference safety information and the summaries of pre-clinical and clinical parts of the IMPD. In the latter case, the summaries of pre- clinical information and clinical information shall include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision on the potential toxicity of the investigational medicinal product and the safety of its use in the proposed clinical trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the pre-clinical and clinical information shall be submitted as part of the IMPD.

Possibility of referring to the SmPC

17 The applicant may submit the version of the SmPC valid at the time of application, as the IMPD if the investigational medicinal product is authorized (either registered in Malawi or registered in any country with Stringent Regulatory Authority (SRA).

1.3 **IMPD in cases of placebo**

18 If the investigational medicinal product is a placebo, the information requirements shall be limited to quality data. No additional documentation is required if the placebo has the same composition as the tested investigational medicinal product (with the exception of the active substance), is manufactured by the same manufacturer, and is not sterile.