



PHARMACY, MEDICINES & POISONS BOARD

1

PROCEDURES FOR REVIEW/EVALUATION

OF

CLINICAL TRIAL APPLICATIONS

FOR VACCINES AND BIOLOGICALS

IN

MALAWI

Guidelines for the Expert Review & Evaluation of Applications for Clinical Trials of Vaccines & Biologicals

CONTENTS

- 1 Introduction
Definition of terms and abbreviations (Document 1)
The Expert Reviewer
- 2 Outline Procedures for NRA to Review an Application
- 3 Receipt and screening of applications
- 4 Expert Review
- 5 NRA deliberation and Decision
- 6 Appeal and re-review
- 7 Notes for Evaluation of Applications for Clinical Trials

1 INTRODUCTION

The overall process for application, regulatory review and approval, and conduct of clinical trials is set out in Document 1.

This document sets out a procedure for receipt, screening, evaluation and approval of applications that have been submitted in the recommended format.

The procedures proposed below must be adapted and adopted to comply with the laws and regulations in Malawi and the capacity of the Pharmacy, Medicines and Poisons Board (PMPB).

The Application form CTA is intended to provide the information required for the PMPB to review an application.

Additional comments (in italics) are appended to assist the NRA reviewer in assessing the application.

THE CLINICAL TRIAL REVIEWER

The PMPB should appoint sufficient, suitable experts prepared to evaluate Clinical Trial applications. The Expert should be well qualified in a relevant discipline, and should have received additional training in GCP and the review of CTA forms.

The Expert reviewer should endeavour to obtain and study up-to-date internationally available documents on the structure, conduct and evaluation of clinical trials.

The following are of value at this time.

WHO TRS 924:

Guidelines for clinical evaluation of vaccines: Regulatory Expectations

European Union Directive 2005/28/EC.

Laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

It is possible that Malawi will enter into a contractual arrangement to accredit or “network” with disinterested reviewers in other countries to assist in the training of local experts, or to jointly review applications if required.

Malawi will inform the applicant of the intention to interact with specified outside expert reviewers for an identified application, and the applicant may object to such reviewer taking part in the review, for specified reasons.

2 Outline PMPB Procedures for Review of an Application

- 2.1 PMPB will designate an internal division (Registration Office) to be the “Focal point” for clinical trial applications. This may be specific for vaccines and biologicals but may include all clinical trial applications. This “Focal point” should be communicated to potential applicants.
- 2.2 That “Focal point” division must ensure that there are sufficient trained staff available to receive and screen applications.

3 Receipt and Screening of Applications.

- 3.1 The designated PMPB responsible person must enter the application into an “Applications Register”, assign a unique PMPB reference number and fill that Identification number in on the space provided on the front page of the Application form for each copy.
- 3.2 The responsible person should screen the application for completeness:
 - All documents and Appendices - see Checklist in CTA
 - Application form signed by Applicant and National Principle Investigator
 - Proof of payment of required fees
 - Application for import of unregistered and trial medicines
 - Application for export of biological specimens (if necessary)
 - Declarations in Appendix 10, complete & signed.
- 3.3 If the application is deficient in any of the documents, it should be returned to the applicant for completion.
- 3.4 Complete, screened applications should be distributed to [3] Expert Clinical Trial reviewers, designated and accredited by the PMPB.

4 Expert Review

- 4.1 The Expert reviewers will evaluate the application, following the guidelines set out below - they may be modified to be applicable to local conditions.
- 4.2 Within [14] days the Expert Reviewer will provide a written report to the “Focal Point” for collation and presentation to the PMPB CTRC (Clinical Trials Review Committee).

5 NRA Deliberation and Decision

- 5.1 The CTRC will review all the available information and provide a recommendation for approval or rejection
- 5.2 The PMPB will issue a written Approval or a Rejection (including reasons).
- 5.3 The PMPB will, at the same time, approve the application for import of medicines

6 Appeal & Re-review

- 6.1 The Applicant may appeal the rejection decision, providing additional information, or amending the application to meet the PMPB requirements.
- 6.2 This will be referred to the CTRC for a final recommendation to the PMPB.

**7 Notes on the expectations and requirements of the Clinical Trial Reviewer.
CTA form and Appendices.**
Comments are appended in italics.

CTA Section 1 Identification of the Clinical Trial Front Page

1.1 Title of the Study
The title should be fully descriptive, allowing internet search engines to detect relevant detail

1.2 Protocol number: *This should be a short, unique identifier*

1.3 Contact Person and contact details *All correspondence will be sent there.*

1.4 [Space for PMPB Reference Number]

1.5 Declaration of Intent, Signed by Contact Person & National Principal Investigator

We, the undersigned have submitted all the required documentation and have disclosed all the information required for approval of this application.

We have read the Protocol and the Investigators brochure, appended and are satisfied that the proposed activities are feasible and ethical.

We have the authority and responsibility to oversee this clinical trial, and agree to ensure that the trial will be conducted according to the Protocol and all legal, ethical and regulatory requirements in this country.

Applicant (Local Contact): NAME Date:

Signature:
Designation:

National Principal Investigator:
NAME Date:

Signature:
Designation:

This ensures that the key people responsible for the conduct of the trial fully understand and commit to comply with the regulatory requirements

CHECKLIST of REQUIRED DOCUMENTS

Fees

Proof of payment

Applications for import and/or export of materials (if required)
This is set out in the application form

CTA

Clinical Trial Application Form

A blank is provided as an addendum to Document #1

APPENDIX 1: Trial Protocol

In the format provided by the ICH Guide E6(R1)

APPENDIX 2: Investigators Brochure

In the format provided by the ICH Guide E6(R1)

APPENDIX 3: Report Summaries of prior clinical trials with this medicine

These would form part of Appendix 2 if it is in the ICH format

APPENDIX 4: Participant Information Leaflet (PIL) and Informed Consent (ICON)

*This should conform to the information provided in the CTA, Protocol and IB.
Any publications referenced from the PIL should be checked for accuracy of conclusions
Separate ICONs for genetic studies or HIV testing are usually required.
Parental-guardian ICONs are required for minor participants.*

APPENDIX 5: Certificate of GMP manufacture of the trial medicine

This is not always available for investigational products. Sufficient information should be provided that will satisfy the reviewer/s that the material as manufactured has a defined quality, and is safe, stable and consistent.

APPENDIX 6: Package Insert/s for other trial medicines.

*These may not be registered in Malawi and translations into language/s acceptable to the reviewers and the PMPB may be required.
The use of unregistered comparator or concomitant medicines may require additional justification.*

APPENDIX 7: Certificate of GMP manufacture of the placebo - if appropriate.

Sufficient information should be provided that will satisfy the reviewer/s that the material as manufactured is safe, and consistent with defined quality.

APPENDIX 8: Evidence of accreditation of the designated Laboratories

*Laboratories to be used for assay of clinical samples must provide evidence of Accreditation with a recognized control authority - to conduct the specified tests.
This applies both to the laboratories conducting safety/screening tests as well as those conducting specialized end-point assays.
In the absence of an accreditation authority, evidence of GLP compliance and of validation of the assay methods should be provided*

APPENDIX 9: Insurance Certificate specific for this trial,

*It should be current, run for the full duration of the trial (or there must be a written commitment to renew for the duration) and follow-up period. The certificate should contain a reference to the trial Protocol number and the countries to which cover is extended.
There should be reference to insurance cover including the guidelines of the ABPI.
There should be evidence of malpractice insurance for all Investigators and associated staff*

APPENDIX 10: Signed and completed Declarations by Investigators

*It is expected that Investigators will be qualified, experienced and have specific GCP training.
The Principal Investigators should have acted as sub-investigators in at least one prior clinical study
The investigator must have read the Protocol and Investigators Brochure, and must confirm that the information provided in the CTA is a true reflection of these.
The investigator must commit to comply with the Protocol.
The investigator must have no conflicts of interest, and no history of GCP non-compliance (or at least should have been absolved of wrong-doing).*

APPENDIX 11: Ethics Committee/s approval of the Protocol

*It is usual that the application will be submitted to the PMPB and IEC at the same time. Thus approval will not usually be available during the Expert Review.
The applicant should provide a copy of the application letter to the IEC as #-11.
The PMPB should receive the IEC approval timeously for inclusion in the deliberations leading to the final approval.
Any condition, amendment or additional information required by the IEC should be communicated to the NRA.*

APPENDIX 12: Full, legible copies of key, peer-reviewed published articles supporting the application.

*These are often difficult to obtain in certain countries.
It is important that these are available to confirm assertions, and conclusions drawn in the CTA, Protocol, IB, or PIL.
They may be provided in PDF format on a CD or other agreed electronic media.*

APPENDIX 13 Other appended documents

May include Power-of-Attorney agreements

CTA Section 2 Basic Administrative Data on the Application

2.1 Name and address of the registered office of the Applicant

Name:
Telephone Number/s: Fax Number/s:
E-mail address/es:
Physical Address:
Postal address:

2.2 Name and address of the registered office of the Sponsor/s

Telephone Number/s: Fax Number/s:
E-mail address/es:
Physical Address:
Postal address:

If there is no sponsor as in Investigator initiated trials - a statement to this effect.

- 2.3 Name and address of the site of the **Manufacturer/s**
Telephone Number/s: Fax Number/s:
E-mail address/es:
Physical Address:
Postal address:

CTA Section 3 Medicines to be used in the trial

- 3.1 Investigational Vaccine or Biological medicine
- 3.1.1 Identifier or name of investigational medicine (code if applicable)
 - 3.1.2 Registration number in (country)
 - 3.1.3 Manufacturer/s (Include all sites)
 - 3.1.4 Active ingredient, complete composition, potency and presentation
 - 3.1.5 Evidence of manufacture under conditions compliant with current codes of Good Manufacturing Practice
 - 3.1.6 Release Specifications and tests. Include Certificate of Analysis.
 - 3.1.7 Evidence of stability of trial medicines for duration of the trial
 - 3.1.8 Current approved Package Insert if available.
If the manufacturer is based in Malawi, then they must comply with the local requirements for a manufacturer of medicines for human use.
Evidence for stability of the medicines at the specified conditions, for the duration of the use period is essential.
- 3.2 Comparator, Concomitant and Rescue medications (and Placebo)
- 3.2.1 Proprietary name and INN
 - 3.2.2 Active ingredient/s, composition, and presentation
 - 3.2.3 Registration number/s (country)
 - 3.2.4 Approved Package inserts to be appended to application
 - 3.2.5 Evidence that Placebo is manufactured under GMP.
- 3.3 Details of handling Trial medicines
- 3.3.1 Shipping, delivery and distribution of trial medicines
 - 3.3.2 Details of storage requirements, and arrangements for cold-chain maintenance and monitoring during distribution.
 - 3.3.3 Details of dispensing trial medicines and Waste disposal procedures.
 - 3.3.4 Packaging and Labelling
Evidence of Pharmaceutical control for the dispensing of medicines is usually expected - compliant with the law in Malawi.
This may not be the case for routine vaccines - but should be required for novel and unregistered products.
- 3.4 Estimates of quantities of each medication (presentation) to be used for the trial, and for which an import permit is needed.
It is important that the quantities are specified to ensure that this trial process is not used as a method for pre-registration introduction of the medicine into Malawi

CTA Section 4 Sites & Investigators

- 4.1 National Principal Investigator or co-ordinator (Responsible person)
- Name: Qualifications
- Contact Details
- Physical address
- Declaration of Capacity & Interests [Appendix 10]

For each Site list the following:

- 4.2 Site Identifier (Name)
Physical Address: (for rural sites include GPS coordinates)
Telephone & Fax numbers
E-mail address
 - 4.2.1 Description of the site facilities & Staff
 - Clinic and counselling rooms
 - Emergency facilities
 - Facilities for special examinations (if required)
 - Capacity to collect, prepare, store and transport clinical samples
 - Storage and handling facilities for medicines
 - Name and qualifications of person with responsibility for dispensing medicines

Some novel vaccines and biologicals may require stringent storage conditions (e.g. -70°C) during early development phases, before sufficient stability data are available. Thus storage and monitoring of conditions may be critical.
- 4.3 Site Principal Investigator
 - Name: Qualifications
 - Contact Details
 - Physical address
 - Declaration of Capacity & Interests [Appendix 10]
- 4.4 Site Sub-investigators and trial specific support staff
 - Name: Qualifications
 - Contact Details
 - Physical address
 - Declaration of Capacity & Interests [Appendix 10]
- 4.5 For Hospital or Public Health Clinic Sites
 - Responsible Administrator Contact Details
 - Append Signed Letter of Agreement for this Trial to take place.
- 4.6 Append signed Agreement/s between the Investigators and the Sponsor/s and/or Clinical Research Organization specific for this clinical trial. Appendix 13.

CTA Section 5 PARTICIPANTS

- 5.1 Numbers of Participants
 - 5.1.1 Total number to be enrolled, world wide
 - 5.1.2 Total number to be enrolled in this country
 - 5.1.3 Number of trial sites in this country
 - 5.1.4 Intended numbers of participants at each site - evidence of availability.
- 5.2 Duration
 - 5.2.1 Estimated trial duration: First enrolment to End of Trial.
The end-of-trial and its relationship to delivery of the final report should be defined.
 - 5.2.2 Duration for individual Participant
 - Screening period
 - Intervention period
 - Follow-up period
- 5.3 What is the intended remuneration/compensation per participant.
PMPB should consider discussion with local IECs to establish an understanding of a reasonable, but non-coercive, remuneration for different types of clinical trial.

CTA Section 6 History of Previous and in-progress trials

- 6.1 List the titles of previous trials with this (or similar) medicines in Malawi
- 6.2 List the titles of previous trials with this (or similar) medicines in other countries
- 6.3 Append Interim or Final report-summaries of these trials to this application. (This may be cross-referenced to the Investigators Brochure or APPENDIX 3)
- 6.4 Include a letter or certificate from the regulatory authorities in countries where previous trials have been undertaken (including those in-progress) that these trials have been GCP compliant.

Much of this information should appear in the IB and may be cross-referenced.

CTA Section 7 Ethics review

- 7.1 Provide the local IEC approval of the Protocol for each site - [Appendix 11]
It is important that the IEC is local and has the capacity to monitor the conduct of the trial.
- 7.2 What GCP Guidelines have been followed in compiling this protocol?
The applicant should define the guidelines followed - this enables a cross-check.
- 7.3 Will GCP training be provided for local staff and investigators?
This is an element of capacity building of local expertise that should be encouraged.

CTA Section 8 Trial conduct monitoring and reports

- 8.1 Describe the Safety and Monitoring Plan for each site.
- 8.2 Describe the system to be used to detect, record, assign causality and the actions for Adverse events.
It is important that there is a plan and the capacity to monitor and audit the trial, and that correct records are maintained, and are available for inspection.
- 8.3 Describe the actions to be taken following reports of Serious Adverse Events.
- 8.4 Describe the composition and remit of the Data Safety Monitoring Board or similar body. Include conditions for Pause- or Stop- recommendations.
The DSMB must be properly constituted and empowered with guidelines to recommend pause or termination to the trial for safety reasons.
- 8.5 When will Interim Reports be submitted?
- 8.6 Final Report - Estimated due-date?
The applicant must commit to making the required reports to PMPB.

CTA Section 9 INSURANCE

- 9.1 Provide a copy of the current insurance certificate. Appendix 9
- 9.2 Provide evidence that each member of the Investigator team is covered by relevant Malpractice insurance for this trial. Appendix 10.
This should include reference to the protocol number of this trial, and a statement that compensation will be at least in accord with the ABPI Guidelines.

CTA Section 10 Description of the Trial

This information should all be in the Investigators Brochure.

Brief synopsis repetition of the information in the CTA provides easier review.

- 10.1 Is the Title of the Trial fully descriptive?
- 10.2 Summarized Rationale for this Clinical Trial, including relevance to Malawi.
It is expected that there is a possibility that the population from which the participants are drawn will benefit from the product or findings of this clinical trial at some time in the future.
- 10.3 BRIEF Background information should include
The disease or condition and local epidemiology, properties of the medicine - hypothesis for action
Description of risks of the protocol and the potential harms of the medicine.
Pre-clinical animal toxicology test results in-animals and in-vitro that establishes probable safety and efficacy in humans *
Prior Clinical trial report summaries that establishes probable safety and efficacy in humans *
Include evidence that the formulations used in the pre-clinical and previous studies are identical to that in this application. Any variations should be highlighted and justified. *
Published reviews or reports relevant to this disease and this type of medicine
* : Cross reference to the detail in the IB.
- 10.4 Objectives of this trial
(List as Primary and Secondary objectives and provide justification)
- 10.5 Trial Design: Describe and justify each component.
- 10.4.1 Phase Placebo or comparator
Randomization and blinding
Other detail
- 10.4.2 Time sequence - A Table of screening, intervention and follow-up visits will be of assistance.
- 10.4.3 Participants
Eligibility Inclusion criteria - list and justify each
Exclusion criteria - list and justify each
- 10.4.4 Treatment regimens for each group.
The table in 10.4.2 above can be used to set this out
- 10.4.5 Follow-up, sampling collection and monitoring plans
Immediate monitoring - intermediate monitoring - long term
Diary cards, Telephone access to investigators.
- 10.4.6 The intention for long-term extension of access to trial-treatment to those participants that may benefit should be defined.

- 10.5 Outcomes Measurements and Analysis
 - 10.5.1 Describe each outcome/variable (including safety) and explain or justify
 - 10.5.2 Describe the samples that will be collected and the analyses to be conducted on each sample
 - 10.5.3 Provide evidence that the Laboratories that will conduct the Safety screening, and the End-point assays are accredited and competent to do the assays. APPENDIX 8.
 - 10.5.4 Describe the intended statistical analysis to be conducted. Provide evidence that the study is powered to provide the intended outcome.
- 10.6 Are any Sub-studies intended. Provide full details.
- 10.7 Are any genetic studies (HLA-typing or gene marker analysis) intended? Provide full details, and justify this. Is there a separate Informed Consent Form for this.
There is a general concern that the archived samples of participants may be “mined” for genetic elements that will not be included in the Informed Consent provided.
- 10.8 Will clinical samples be stored for any period beyond the duration of this trial?
 - 10.8.1 What is the purpose of such archiving?
 - 10.8.2 What controls are to be placed on their confidentiality and possible future use?
- 10.9 Participant Information Leaflet (PIL) and Informed Consent (ICON)
 - 10.9.1 Append a copy of the PIL & ICON to be used [Appendix 4]
 - 10.9.2 In what languages will this be available?
 - 10.9.3 Append the Parent / guardian consent form, in the case where minor participants will be included.
 - 10.9.4 Separate ICON for sub-studies or Genetic studies.
- 11 Publication Policy
Provide details of the Investigators and Sponsors intentions and freedom to publish the outcomes of this study. (Required by some countries).

CHECK of APPENDED DOCUMENTS

- FEES** Proof of payment
Application for the Import Permit medicines for this study if required
Application for the export of biological materials (clinical samples) if required
- APPENDIX 1:** Trial Protocol
- APPENDIX 2:** Investigators Brochure
- APPENDIX 3:** Report Summaries of prior clinical trials with this medicine
- APPENDIX 4:** Participant Information Leaflet (PIL) and Informed Consent (ICON) as intended for use in this study.
Separate consent for Sub-studies or Genetic Analysis. Guardian/parental consent for minor age participants
- APPENDIX 5:** Certificate of GMP manufacture of the trial medicine or sufficient information on the manufacture and control that enables the reviewer to assess that cGMP has been assured.
Certificate of Analysis - Release test results.
- APPENDIX 6:** Package insert leaflets from concomitant and comparator medicines.
- APPENDIX 7:** Certificate of GMP manufacture of the placebo.
Certificate of Analysis
- APPENDIX 8:** Evidence of accreditation of the designated Laboratories to conduct the safety-screening tests and the end-point assays.
- APPENDIX 9:** Insurance Certificate specific for this trial, including reference to compensation according to ABPI guidelines.
- APPENDIX 10:** Signed and completed Declarations by Investigators
Example format - see below
Evidence of Malpractice Insurance
Evidence of recent GCP training
Declaration of Capacity & Interests
- APPENDIX 11:** Approval of Local Research Ethics Committee/s.
Include REC composition and Process.
In the case of parallel submission include the application letter
- APPENDIX 12:** Full, legible copies of key, peer-reviewed published articles supporting the application.
- APPENDIX 13:** Other supporting documents

APPENDIX 10: FORMAT for Declarations by Investigators

Trial Protocol Number.

NAME: Role in Trial

Trial Title:

Site: A current Curriculum Vitae is attached.

1 I am aware of the responsibilities of my role as
in clinical trial number
as required by the legal, ethical and regulatory requirements of Malawi

2 I have read and understand the attached Protocol, Investigators Brochure and supporting documentation and I will comply with the procedures and requirements included in them.

3 I have read the attached Clinical Trial Application form as submitted to the regulatory authority in Malawi and confirm that the information is complete, true and accurate, and conforms to the Protocol and supporting documentation.

4 I will not commence with this trial before written authorization has been received from the Pharmacy, Medicines and Poisons Board of Malawi and the relevant Ethics Committee/s. I will provide the IEC and PMPB with reports as required.

5 I will obtain Informed consent from all participants, or if they are not legally competent, from their legal representatives, parents or guardian.
I will ensure that every participant (and other involved person, such as relatives) will be treated in a dignified manner and with respect.

6 I DECLARE: I have no conflict of interest in terms of financial interests or personal relationships that may inappropriately influence my responsibilities and conduct of this trial.
Initials:

7 I DECLARE: I have not previously been associated with any clinical study that has been terminated, or study-site that was closed, due to failure to comply with Good Clinical Practice.
Initials:

8 I have the malpractice insurance, that will provide cover for my activities in this clinical trial, as required in Malawi
Malpractice Insurance Number

9 I have received suitable, recent training in Good Clinical Practice in Malawi context.

10 SIGNED DATE

WITNESS: NAME DATE