LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

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Republic of Liberia

Guidelines on the Conduct of Clinical Trials in Liberia

Version No. 002

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FOREWORD

This is the second edition of the guidelines for application to conduct clinical trials in Liberia which has been drafted by a committee constituted by the Liberia Medicines and Health Products Regulatory Authority (LMHRA). These guidelines have been made under Part IV Section 2(1 j & n) and Part V Section 5 (1 & 2) of the LMHRA Act, 2010. The edition is the second on the process of Clinical Trials in Liberia to have been drafted and to be implemented under the LMHRA's Act of 2010. The Authority has a legal responsibility of ensuring that all clinical trials obtain a written authorization from the LMHRA prior to commencement of study of any kind in Liberia (Part V Section 5 (1).

It is therefore anticipated that all those who will be intending to conduct clinical trials in Liberia will herein oblige themselves with the aforementioned legal provisions and follow the procedures and requirements as set out in these guidelines. The review process had evolved through drafting the guidelines and consultation with stakeholders from various institutions through a validation work before final approval by the LMHRA Board of Directors. These guidelines therefore provide an up-to-date guidance on application requirements and standards of Good Clinical Practices (GCP) to be followed by all those who have interest in the conduct of clinical trials in the Liberia, to include research institutions, Contract Research Organizations (CROs), Principal Investigators (PIs) and Sponsors alike.

It is expected that the guidelines shall enable consistent and uniform documentation of applications and make it easier for the Authority to evaluate all clinical trials and make decisions on approval/non-approval based on clear and transparent outlined criteria. The Authority has also adopted for use the International Conference on Harmonization (ICH) of Technical requirements for Registration of Pharmaceuticals for Human Use - Tripartite Guideline for Good Clinical Practice (GCP). Applicants are therefore required to follow the LMHRA guidelines along with the current GCP guidelines when generating clinical trials data. As clinical trials are complex in nature and since review of technical guidelines in any scientific spectrum is unavoidable in order to keep pace and benefit from developments in science and technology, the LMHRA shall always welcome new ideas, opinions, and suggestions in this context that will assist in improvement of these guidelines.

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ACKNOWLEDGEMENTS

We remain grateful to the hard working committee for their tireless efforts in development of this policy document to guide all medicines and health products related clinical trials in the Republic of Liberia. This second edition of the guidelines has been drafted to outline application requirements and procedures for clinical trials in Liberia.

The Global Health Protection Program (GHPP) through it VaccTrain project have provided technical support in the review and modification of this guideline and related CT documents. The Department of Clinical Trials, Pharmacovigilance and Medicines Information of the Liberia Medicines and Health Products Regulatory Authority (LMHRA) have worked along with the VaccTrain Team to develop the final version of this guideline and other technical related CT documents. The drafting team relied on their experiences, knowledge on clinical trials, and available literatures (WHO, ICH-GCP, NIH, School of Pharmacy-University of Liberia, School of Medicines University of Liberia, Regional Center of Regulatory Excellence in Clinical Trials (RCORE) Ghana FDA, etc.).

I would like to express my profound gratitude to the second edition Drafting Committee members; led by Dr. Juwe D. Kercula, Manager for Clinical Trials Unit, Dr. James D. K. Goteh, Director, Pharmacovigilance & Clinical Trials, Dr. Ezekiel F. Hallie, Dean, School of Pharmacy, University of Liberia and the entire team for the level of hard work and resources exerted in a timely development in the draft of the second edition. I like to express my sincere thanks and appreciation to the former Managing Director of the LMHRA, Dr. David Sumo, during whose administration the first edition was developed and lastly I would also like to appreciate the technical support of the Global Health Protection Program (GHPP) through its VaccTrain project in completing the final draft of these documents, I also appreciate the following institutions: the Pharmaceutical Association of Liberia, The Liberia Medical & Dental Association(LMDA), National Research & Ethics Board (NREB), National Public Health Institute of Liberia(NPHIL) and all persons and institutions for their meaningful support to this work.

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TABLE OF CONTENTS

ABBREVIATIONS

CT	Clinical Trial
CTA	Clinical Trial Application
CoA	Certificate of Analysis
CRO	Contract Research Organisation
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator´s Brochure
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LMHRA	Liberia Medicines and Health Products Regulatory Authority
NIMP	Non- Investigational Medicinal Product
NREB (EC)	National Research and Ethics Board
PACTR	The Pan African Clinical Trials Registry
TMF	Trial Master File
PI	Principal Investigator
SR	Safety Report
WHO	World Health Organization

1. INTRODUCTION

1.1. Legal Basis

1.1.1. The regulation of clinical trials in Liberia is governed by the provisions and requirements of the Liberia Medicines and Health Products Regulatory Authority Act 2010 by which the Liberia Medicines and Health Products Regulatory Authority (LMHRA) was established.

1.1.2. Part V: SPECIFIC PROVISIONS, section 5: Clinical Studies, of the LMHRA Act 2010, stipulate that no person/organization shall conduct clinical studies in humans or animals of medicines or health products without the authorization of the Authority. In the same section it is indicated that the conditions for authorization of such clinical studies shall be stipulated in regulations promulgated by the Authority that shall provide for the issuance, renewal, suspension, cancellation and revocation of such authorizations.

1.1.3. The LMHRA regulation on Clinical Trials in Liberia details the requirements for the conduct of clinical trials for humans addressing the application, authorisation and reporting process.

1.1.4. Applicants are required to familiarise themselves with this document and the above stated law before applying for a clinical trial.

1.2. Interpretation

The interpretation of terms provided in the Liberia Medicines and Health Products Regulatory Authority Act 2010 as well as in LMHRA regulation on Clinical Trials 2019 in Liberia apply to this guideline, unless further defined in this guideline.

Terms not provided in the Act or the Regulations shall bear the following meanings in this guideline unless the context otherwise requires-

Auxiliary medicinal product is a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples are medicinal products used as rescue medication, challenge agents, to assess end-points in the clinical trial, or background treatment.

Comparator Product is a medicinal or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Placebo is an inactive substance or sham form of a therapy administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation or procedure.

1.3. Purpose

1.3.1. In pursuance of the CT Regulation 2019, this document provides guidance to sponsors and investigators for the application procedures to conduct clinical trials (CTs) in Liberia and the reporting requirements.

1.4. Scope

1.4.1. This guideline applies to medicines and medicinal products as defined in the LMHRA Act 2010 and CT Regulation 2019 to be used in a CT as investigational medicinal products (IMPs) or health products, whether they are unauthorised or marketed products or not, and to non-investigational medicinal products used in the context of a CT (auxiliary medicines).

1.4.2. It does not apply to non-interventional clinical research studies.

2. GENERAL CONDITIONS FOR CLINICAL TRIALS

2.1 Classification of Clinical Trials

2.1.1. Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of medicines, is given below:

Phase I

2.1.2. These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in humans.

Phase II

2.1.3. These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III

2.1.4. These are trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV

2.1.5. These are studies performed after marketing of the medicine. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorisation was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in premarketing studies. **Note:** After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new medicines.

Application for a Clinical Trial Authorisation from the LMHRA

2.2.1. Before commencing a CT in Liberia, the applicant (Sponsor or Sponsor´s legal representative or Prinicipal investigator or Sponsor-Investigator) Principal Investigator (PI) must obtain a written permission from the National Research and Ethics Board (NREB) and autorisation from the LMHRA in accordance with the requirements laid down in the CT Regulation 2019.

2.2.2. Two Clinical Trial Application (CTA) procedures are possible in Liberia: (i) parallel process where CTA is submitted to the LMHRA and the NREB at the same time and (ii) sequential process where a written permission to conduct a CT has been obtained from NREB before submitting CTA to the LMHRA.

2.2.3. In case of any unclarities regarding the requirements for conduct of CTs, the applicant is encouraged to request a pre-submission meeting with the LMHRA. The applicant, who wishes to meet with officers of the LMHRA before submitting an application or during the

conduct of a study, shall submit an official letter of request to the LMHRA indicating:

- Purpose for the meeting
- Agenda for the meeting
- Names of the CT team expected to meet with the LMHRA

The LMHRA shall consider the request and respond appropriately

2.2.4. For the LMHRA to issue a CT approval, the applicant should submit a signed cover letter including list of documents submitted and their version number and date as part of the CT application dossier to the LMHRA. Its subject line should contain the invariable sponsor protocol number with the title of the trial.

2.2.5. The cover letter should be addressed to:

The Managing Director
Liberia Medicines and Health Products Regulatory Authority
2nd & 3rd Floors, Clay Building
Sekou Toure Avenue, Mamba Point
Monrovia, Montserrado County
Republic of Liberia

2.2.6. The applicant shall state in the cover letter if the given CT has already been assessed by any other national regulatory authority or international body and the outcome of the assessment. If applicable, the cover letter may contain request for authorisation of import of IMP , related product or auxilary medicine to be used in the CT into Liberia (see Section 3.2).

2.2.7. The CTA form must be completed and duly signed and dated by the applicant. The CTA form (Annex 1) is available at the LMHRA website: *www.lmhra.gov.lr*

2.2.8. The CTA dossier shall in addition contain following documents:

1. CT protocol
2. A list of the planned CT sites and the planned number of study participants to be recruited at the sites located in Liberia;
3. Details of the site(s) where the CT is to be conducted and a duly justified written statement on the suitability of the CT sites adapted to the nature and use of the investigational medicinal product (IMP) and including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic/institution at the CT site or by some other responsible person;
4. Participant information sheet, Informed consent form(s), assent form in case minors are to participate in the CT and informed consent procedure for CTs in humans
5. Product information if the IMP is registered: summary of product characteristics, patient information leaflet/package insert and labelling
6. Investigator's brochure (IB) containing relevant chemical, pharmaceutical, pre–clinical pharmacological and toxicological data and where applicable, human or animal pharmacological and safety and efficacy clinical data about the IMP;
7. If applicable, synopsis of previous trials with the IMP(s)
8. If applicable, electronic copies of key peer reviewed publications following the International Committee of Medical Journal Editors (ICMJE) recommendations to support the application
9. Copy/-ies of recruitment advertisement(s) (if applicable) and questionnaires
10. Investigational medical product dossier (IMPD) (If applicable)
11. Content of the labelling of the IMP(s)
12. Product information and certificate of analysis (CoA) for the concomitant and rescue medications
13. Good Manufacturing Practice (GMP) certificate issued from the National Regulatory Authority of the country where the IMP is manufactured, translated into English language
14. CoA of the IMP(s)

15. Certificate(s) of accreditation for the central laboratories
16. Signed declaration by the applicant
17. Signed declaration by the PI
18. Workload forms for investigators
19. Signed curriculum vitae for all key staff participating in the conduct of the CT, e.g. principal investigator, principal and/or co-investigators, study coordinator, regional and local monitor, contract research affiliate etc.
20. Signed declaration(s) by each investigator(s)
21. Signed joint financial declaration between the sponsor and the PI
22. Signed declaration by the sub-investigators and key staff participating in the CT
23. Signed declaration by the CT monitor(s)
24. Signed declaration by the Sponsor/ Sponsor-Investigator of the trial referred to in CT Regulation 2019 that they are familiar with and understand the protocol and will comply with GCP as determined by the LMHRA during the conduct of the CT;
25. Proof of registration on The Pan African Clinical Trials Registry (PACTR) or other WHO primary accessible registry
26. Active CT insurance (Phase I, II, III)
27. Proof of sponsor indemnification for investigators and trial site
28. Good Clinical Practice (GCP) certificates for the investigators
29. Proof of registration of the key investigators with a professional statutory body (if applicable)
30. Proof of residence in Liberia of the PI
31. Proof of professional indemnity (malpractice insurance)
32. Study budget
33. In case of parallel submission, proof of submission of the CTA to the NREB
34. The written permission of the NREB in case of sequential submission, and in case of parallel submission the updated versions of documents or information as requested by the NREB, for the conduct of the CT, if applicable
35. Information on the composition of the Data and Safety Monitoring Board (DSMB), including the list, terms of reference and curriculum vitae of its members justifying their expertise as members of the DSMB
36. Summary of product characteristics or other professional information for all registered medicines used in the trial, or the international equivalent thereof if the medicines are not registered in Liberia;
37. Recruitment arrangements;
38. If applicable, request for authorisation of export of biological samples out of Liberia as well as the respective material transfer agreement
39. Summary of the CT (100-150 words) to be made publicly available at the LMHRA website.
40. Proof of payment of the appropriate application fee as per the LMHRA's prescribed fee schedule for Clinical Trial Authorisation.

2.2.9. The head of the clinic/hospital or institution or another responsible person of the CT site (medical superintendent or medical officer) should sign and date a statement on the suitability of the CT site issued by him/her.

2.2.10. The contents and format of the CT Protocol and IB should follow the requirements as laid down in the International Council for Harmonisation Guideline for Good Clinical Practice (ICH-GCP guideline).

2.2.11. All investigators shall be trained in GCP documented by the provision of training certificates not older than three (3) years at the time of application. Any other training or experience from previous CTs and patient care as needed for the conduct of the trial shall be provided to prove their qualifications. The PIs should have acted as PI or at least as an investigator in at least one prior CT.

2.2.12. The investigators must have no conflicts of interest, and no history of GCP noncompliance or malpractice, or at least should have been absolved of wrong-doing. In case of any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators this must be declared.

2.2.13. The protocol should contain a statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements and signed and dated by both, the Sponsor/ sponsor's representative and PI to document the investigator's and sponsor's agreement to the protocol. If the protocol is not signed and dated by both parties, a corresponding declaration as stipulated in the CT Regulation 2019, signed and dated by both shall be provided to the LMHRA with the application.

2.2.14. The study insurance certificate or professional indemnity insurance should be current and valid for the full duration of the trial and follow-up period. If the validity is shorter, a written commitment for renewal for the duration of the trial is required. The certificate should contain a reference to the clinical trial/ CT protocol number and the countries to which the cover is extended. The insurance cover should be provided from an internationally recognised company.

2.2.15. The IMPD as laid down in the CT Regulation 2019 is required for placebo and an IMP that has no marketing authorisation in any country or is not prequalified by World Healht Organization (WHO). For confidentiality reasons, the IMPD or equivalent can be submitted directly by the sponsor to the LMHRA.

2.2.16. If a GMP certificate for the IMP is not available for justifiable reasons, sufficient information must be provided that will satisfy the LMHRA that the product has a defined quality and is safe, stable and consistent.

2.2.17. For an IMP that has a marketing authorisation, the IMPD may not be required if proof of compliance with GMP, a CoAfor each batch of the IMP and in case of a biological, a Batch Release Certificate is provided, and other relevant information from non-clinical and clinical experience is contained in the IB.

2.2.18. If a comparator other than placebo that is not a registered medicine is to be used a justification for the use of the comparator is required.

2.2.19. For related products used in a CT relevant product information must be provided to the LMHRA.

2.2.20. Laboratories to be used for assay of clinical samples must provide evidence of accreditation by a recognised body 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 Good Clinical Laboratory Practice compliance, where applicable and of validation of the assay methods should be provided.

2.2.21. The applicant can apply for a written permission to conduct a CT to the NREB at the same time as for approval by the LMHRA (parallel submission, as specified in the CT Regulation 2019). In this case the Applicant must submit the the application letter to the NREB at the time of submission to the LMHRA and provide the favourable opinion of the NREB and, where applicable, updated versions of documents or information as requested by the NREB, when available. The LMHRA can reach a decision on the application only when those documents are provided.

2.2.22. All documentation submitted shall be in English. If documents are written in another language, including e.g. product information for auxiliary medicines, a certified translation is required.

2.2.23. The application form and documents should be submitted both, electronically and as hard copies (four sets).

2.2.24. The LMHRA may ask the applicant to supply other information as may be required to enable reaching a decision on the application (see section 5).

2.2 Clinical Trial Amendments

Changes to the approved CTs can be made. Depending on the nature of a change, amendments to the trial are regarded as substantial or non-substantial/ minor amendments.

Substantial Amendments

2.2.1 Amendments to a CT are regarded as 'substantial' where they are likely to have a significant impact on the safety or physical or mental integrity of the CT participants, and/or the scientific value of the trial. Annual update of IB is not per se a substantial amendment. However, the sponsor has to verify whether the update relates to changes which are to be considered as substantial. In that case, the rules for notification of substantial amendments apply to the change.

2.2.2 Any substantial amendments to the CT protocol, the CT arrangements or the IMP or related product deemed to be ammendment shall be approved by the LMHRA and the NREB before such amendments are carried out.

2.2.3 The submission of amendment(s) shall be indicated in a signed cover letter identifying the CT, sponsor / applicant, and shall include:

- possible consequences for CT participants already included in the trial; and
- possible consequences for the evaluation of the results.

2.2.4 The amendment(s) shall be described in a completed CT Amendment form (Annex 2) and the new version of the documents identified with an updated version number and date shall be provided. CT Amendment form **(Annex 2)** is available at the LMHRA website: www.lmhra.gov.lr

2.2.5 The submited document should clearly present scientific arguments justifying classification of an amendment to the LMHRA / NREB. Where applicable, supporting information shall be included with the submission.

2.2.6 Written approval from the NREB is required before LMHRA can reach a decision on an amendment.

2.2.7 The LMHRA shall respond within 20 calendar days upon receipt of the written decision from the NREB. The LMHRA may reject or accept the changes or recommend a revision of sponsor´s classification.

Non-substantial/ minor Amendments

2.2.8 Non-substantial/ minor amendments can be implemented immediately by the sponsor and should always be documented and notified to the LMHRA/ NREB. For example, a change of the contact person or in the contact details of the contact person (e.g. a change of e-mail or postal address) is not considered as a substantial amendment, if the sponsor and legal representative remain identical. However, the sponsor should ensure that the LMHRA is aware of this change as soon as possible, in order to allow the LMHRA to exercise its CT oversight function.

2.2.9 Following cases are not considered as amendments:

- A change to the documentation submitted to the LMHRA during the ongoing assessment of the request for CT authorization by the LMHRA, and
- A change to the documentation submitted to the NREB during the ongoing assessment of the request for authorization by the NREB.
- Progress reports including safety data as well as annual updates of investigator´s brochure are not per se an amendment and thus do not have to be notified as a substantial amendment to the LMHRA. However, the sponsor has to verify whether the data presented requires a change to the documentation submitted with the request for authorization of a CT. If this amendment is substantial, the rules for notification of substantial amendments apply to these changes.

2.3 Clinical Trials in Case of Emergency Situations

2.3.1 Under certain circumstances LMHRA may accept an expedited application and review process for CTs. Examples of such situations are epidemics or other urgent public health interests that require fast utilisation of new medicines or health products and/or fast gathering of information on products.

2.3.2 The following documents must at least be submitted in such situations together with a cover letter and completed application form, both signed and dated by the applicant:

- CT protocol;
- IB or a corresponding product information containing available chemical, pharmaceutical, pre–clinical pharmacological and toxicological data and where applicable, human or animal pharmacological and safety and efficacy data about the IMP;
- CoA;
- A list of the planned CT site(s) and the planned number of CT participants at the site(s);
- The name, position and full contact details of the Sponsor and PIs who will be responsible for the sites where the trial is to be conducted and who shall be registered with the relevant statutory health council, where applicable;
- In the case of trials involving human participants, proof of current, relevant and appropriate -
    - Study insurance for all participants undertaken by the applicant; or
    - Professional indemnity insurance for Investigators;
- Information provided to CT participants and process of obtaining consent;
- Recruitment arrangements
- A clearly defined scope of the evaluation process including screening, verification, etc.
- Proof of CTA submission to the NREB.
- Proof of payment of the appropriate application fee as per the LMHRA's prescribed fee schedule for Clinical Trial Authorisation.

2.3.3 If the IMP, related product or any auxiliary medicine for the given CT needs to be imported, the application for import permit can be included in the cover letter for the CTA and must include at least the following information:

- The title and identification numbers of the CT for which the application is made;
- The planned CT sites and the planned number of CT participants at the sites;
- Description of the IMP(s), related product or any auxiliary medicine by name or code, strength and dosage form;
- Unit of issue, total quantity, batch number and expiry dates of the products;

2.3.4 The LMHRA will review expedited application as soon and fast as possible. Not more than 14 working days for approved products while 21 days for new products.

3. INVESTIGATIONAL MEDICINAL PRODUCTS

3.1 Labelling

3.1.1. IMPs must be manufactured and labelled in accordance with the CT Regulation 2019.

3.1.2. If the primary container takes the form of blister packs or small units such as ampoules, the secondary packaging should be provided bearing a label with the required particulars. The primary container should nevertheless bear the following:

- name of the sponsor, contract research organisation (CRO) or investigator;
- route of administration (may be excluded for oral solid dosage forms) and in the case of open trials, the name/identifier of the IMP and strength/potency;
- batch and/or code number to identify the contents and packaging operation;
- a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
- the trial subject identification number/treatment number and where relevant, the visit number.

3.1.3. If it becomes necessary to change the expiry/use-by date, an additional label should be affixed to the IMP which should state the new use-by date and repeat the batch number. It may be superimposed on the old date, but for quality control reasons, not on the original batch number.

3.1.4. The operation should be performed at an appropriately authorised manufacturing site, but when justified, may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, if available, the PI or by the CT monitor(s) who should be appropriately trained.

3.1.5. The provisions listed above may apply for auxiliary medicinal products.

3.2 Importation, Exportation and Destruction

3.2.1. If the IMP, or any auxiliary medicinal product must be imported, the CT must be approved by the LMHRA before the import can be authorised.

3.2.2. IMPs, or auxiliary medicines may only be imported if they are not locally available or if the need for importation is otherwise justified. The justification must be stated in the application letter for permit of import.

3.2.3. Application for import permit must include at least the following information:

- The title and identification number of the CT for which the application is made;
- The planned CT sites and the planned number of subjects at the sites;
- Description of the IMP(s) by name or code, strength and dosage form;
- Unit of issue, total quantity, batch number and expiry dates of the product(s)
- Justification of the quantity of the IMP, or any auxiliary medicines to be imported relative to the timelines in the CT protocol.
- Letter of authorisation of the CT

3.2.4. A parallel submission for approval of the CT and application for import permit is possible. In this case, application for import permit can be included in the CT application package.

3.2.5. If the IMP, related product or any auxiliary medicines are to be exported out of Liberia upon completion of the CT, exportation must be authorised by the LMHRA.

3.2.6. Application for export permit shall be submittied to the LMHRA and must include at least the following information:

- The title and identification number of the CT concerned
- Description of the IMP(s), related product or any auxiliary medicine concerned
- Unit of issue, total quantity, batch number and expiry dates of the products concerned
- Justification of the quantity of the IMP, related product or any auxiliary medicines to be exported

3.2.7. If IMP, or auxiliary medicine used in a CT is to be destroyed at any time point, respective destruction procedure shall be provided to the LMHRA as part of the CT protocol.

3.2.8. The CRO/ Sponsor shall bear the cost of disposal of the IMP

4. CLINICAL TRIAL APPLICATION REVIEW AND DECISION PROCESS

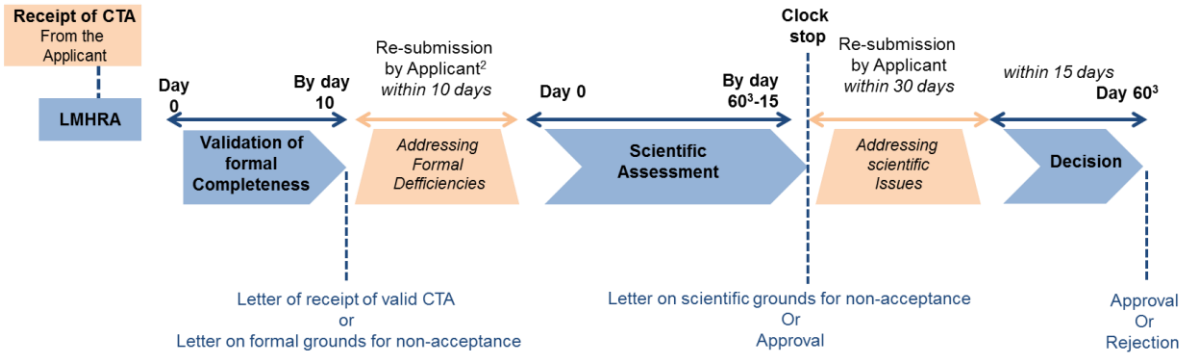
4.1. Timelines as defined per CT Regulation 2019 apply. During the assessment process, the LMHRA may consult international bodies or other Agencies who already assessed the particular CT.

4.2. The LMHRA shall inform the applicant in writing about the receipt of a valid clinical trial application or the formal grounds for non-acceptance within 10 working days from the receipt of the CTA. The applicant shall address formal grounds for non-acceptance within 10 working days. The LMHRA shall inform the applicant in writing about the outcome of the assessment of the clinical trial application within a maximum of 60 working days after validation of a formally complete clinical trial application, or as defined in **Table 1**. This excludes time taken for applicant to respond to queries from the Agency. If changes are required and the applicant fails to modify the application correspondingly within a maximum of 30 working days, following the reasoned objections, the application shall be deemed to be rejected.

4.3. During evaluation, additional documents or changes may be requested through a query letter. Once a query has been raised and issued to the applicant, the process stops until when LMHRA receives a written response to the query.

4.4. If LMHRA requries changes to the application and the applicant fails to modify the application correspondingly within a maximum of ninety (90) days following the reasoned objections, the application shall be deemed to be rejected.

4.5. In general, CT applications should be processed as per the prescribed timelines presented in Figure 1



[1]CTA submission to the LMHRA and NREB can be done in parallel or sequentially. [2]Appplicant: Sponsor/ Legal representative of Sponsor or PI or Sponsor-investigator who submitted CTA. [3]Day 60- Different timelines may apply for specific types of investigational medicinal products (see Table 1)

Figure 1: Graphic display of the periods (counted as working days) and process of Clinical Trial Authorization (CTA) in Liberia[1] by LMHRA.

Table 1: Timelines for the evaluation of the scientific content of CTA by LMHRA for different types of IMPs, unless otherwise specified by the LMHRA on case-by-case basis.

Type of IMP	Period for the evaluation of the scientific content of CTA
Pharmaceuticals	45 working days
Biological and biotechnology medicinal products	60 working days
Genetically modified organisms	90 working days

4.6. During the CT assessment process, relevant CT decisions, reports or information from other national regulatory authorities (NRAs) or regional and international bodies can be recognized or used by the LMHRA.

4.7. All CTAs shall be evaluated with the same set of criteria based on the up-to-date scientific knowledge and ethics standards, regardless of the applicant.

4.8. Persuant to the LMHRA Act 2010, a CT certificate shall be issued to the applicant by LMHRA upon approval indicating the LMHRA CT number. The CT certificate may contain conditions required by LMHRA with the respect to the conduct or reporting of the CT.

4.9. If the CT application was rejected, the applicant can appeal which shall be made in writing to the Managing Director within sixty (60) days of receipt of the rejection notice.

4.10. No information given in a CTA shall be disclosed by the LMHRA to a third party except:

- with the written consent of the applicant; or
- in accordance with the directive of the Board of Directors of LMHRA

5. INSPECTION OF CLINICAL TRIALS SITES

5.1 LMHRA may conduct inspections as stipulated in the CT Regulation 2019. The LMHRA may inspect CT sites and/or the sponsor's/ CRO premises and/or the manufacturer to secure the compliance of CTs with the GCP provisions before, during or after a CT is conducted.

5.2 The NREB representatives may accompany the LMHRA in conduct of inspections of CT sites. May inlcude other relevant regulatory authorities CT site, the LMHRA shall notify the PI and/or sponsor/CRO and/or manufacturer in writing. However, if LMHRA has reasonable cause to believe that the approved protocol is being violated, an unannounced inspection may be conducted.

5.3 Following inspections, an inspection report shall be prepared by LMHRA and be made available to the PI and/or sponsor while safeguarding confidential aspects. It may be made available to the NREB and other regulatory authorities at their reasoned request.

6. ADVERSE EVENTS AND CLINICAL TRIAL REPORTS

6.1 The PI/ Sponsor shall report serious adverse events (SAE)/ serious adverse drug reactions (SADR) suspected to be related to the IMP and indicate the timelines allocated for related investigations as stipulated in the CT Regulation 2019 state location in the regulation by using a Suspected SADR Report form provided by the LMHRA (Annex 3), available from the LMHRA website: www.lmhra.gov.lr

6.2 The PI/ Sponsor should report any SAEs/ SADRs suspected to be related to the IMP (which occurred in Liberia) immediately, and in any event, no later than 3 calendar days after becoming aware of the event.

6.3 In case of multi center trials involving CT sites outside of Liberia, the Sponsor/PI shall submit all SAEs/ SADRs deemed to be related to the IMP within 15 calendar days to the LMHRA.

6.4 The applicant shall provide a progress report on the CT to LMHRA by using the Progress Report template (Annex 4) at least annually, unless otherwise stipulated in the CT certificate. The report should contain recruitment status, safety updates and DSMB reports as well as update on the use and results collected on biological samples exported out of Liberia (if applicable).The report form is available at the LMHRA website: www.lmhra.gov.lr

6.5 The applicant shall inform the LMHRA of CT suspension or premature termination of a CT within 10 working days and provide the reasons clearly explaining such decision.

6.6 The applicant shall notify the LMHRA within 30 calendar days from the end of a CT. The definition of the end of the trial should be documented in the CT protocol.

6.7 The applicant shall submit a closeout report with disposal certificate to LMHRA within 90 days from completion of the CT by using a template (Annex 5) available at the LMHRA website: www.lmhra.gov.lr

6.8 The applicant shall submit a comprehensive end of study report conforming to the ICH E3 guideline as revised, within 1 year from the end of the CT. The report shall containin any adverse events reported by PIs.

7. CLINICAL TRIAL FILES AND ARCHIVING

8.1. The PI shall keep an Investigator Site File (ISF) and the sponsor a Trial Master File (TMF) containing the essential documents relating to the CT which allow verification of the conduct of the CT and the quality of the data generated, taking into account all characteristics of the CT.

8.2. The files shall be readily available, and directly accessible upon request to the LMHRA.

8.3. The sponsor and the investigator shall archive the contents of the TMF and ISF, respectively, for at least 25 years after the end of the CT including the medical files of study participants.

8. FINAL PROVISIONS

8.1 This guideline is the first version published by the LMHRA and will become effective on **August 20, 2021.**

8.2 This guideline will be reviewed within 3 years of becoming effective.

9. ANNEXES

Annex No.	**Title** (as referenced on the attachment)
Annex 1	Clinical Trial Application - Form
Annex 2	CT Amendment – Form
Annex 3	SADR report – Form
Annex 4	CT Progress Report – Form
Annex 5	Closeout report - Form

10. REFERENCES

- Liberia Medicines and Health Products Regulatory Authority Act 2010
- Regulation on Clinical Trials in Liberia
- International Council for Harmonisation (ICH), Integrated Addendum to ICH E6 (R1), Guideline for Good Clinical Practice E6 (R1), 2016
- World Health Organization, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, WHO Technical Report Series, No. 850, Annex 3, 1995

11. DOCUMENT HISTORY

Version:	Issue Date:	Reasons for Change:

Annex 1 Clinical Trial Application – Form

African Vaccine Regulatory Forum (AVAREF) - Clinical Trial Application Form

Annex 2 CT Amendment – Form

NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE LMHRA AND FOR THE OPINION OF THE NREB OF LIBERIA

For official use

Date request received:	Non acceptance/ negative opinion: ☐ Date: ……. (dd/mm/yyyy)
Date procedure started:	Authorization/positive opinion: ☐ Date: ……. (dd/mm/yyyy)
LMHRA registration number of the trial: NREB registration number of the trial:	Withdrawal of amendment application: ☐ Date: ……. (dd/mm/yyyy)

To be filled in by the applicant:
This form is to be used both for a request to the LMHRA for authorization of a **substantial** amendment and to the NREB for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

A TYPE OF NOTIFICATION

A.1. Notification for authorization to the competent authority (LMHRA)	☐
A.2. Notification for an opinion to the ethics committee (NREB)	☐

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1. Does the substantial amendment concern several trials involving the same IMP?		Yes ☐ No ☐
B.1.1. (If yes, please specify)		
B.2. Full title of the trial		
B.3. Sponsor's protocol code, number, version, date		

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1. Sponsor	
C.1.1. Name	
C.1.2. Organization	
C.1.3. Address	
C.1.4. Telephone number	
C.1.5. Fax number	
C.1.1. E-mail	
C.2. Legal representative of the sponsor for the purpose of this trial (if different from the sponsor)	
C.2.1. Name	
C.2.2. Organization	
C.2.3. Address	
C.2.4. Telephone number	
C.2.5. Fax number	
C.2.6. E-mail	

D APPLICANT IDENTIFICATION (please tick the appropriate box)

D.1. Request for the competent authority (LMHRA)	
D.1.1. Sponsor	☐
D.1.2. Legal representative of the sponsor	☐
D.1.3. Person or organization authorized by the sponsor to make the application	☐

D.1.4. Complete applicant details as below:

D.1.4.1. Organization	
D.1.4.2. Name of person to contact	
D.1.4.3. Address	
D.1.4.4. Telephone number	
D.1.4.5. Fax number	
D.1.4.6. E-mail	
D.2. Request for the Ethics Committee (NREB)	
D.2.1. Sponsor	☐

D.2.2. Legal representative of the sponsor	☐
D.2.3. Person or organization authorized by the sponsor to make the application	☐
D.2.4 Investigator in charge of the application if applicable • D.2.4.1 Co-coordinating investigator (for multicenter trial) • D.2.4.2. Principal investigator (for single center trial)	☐ ☐

D.2.5. Complete applicant details as below:

D.2.5.1. Organization	
D.2.5.2. Name of person to contact	
D.2.5.3. Address	
D.2.5.4. Telephone number	
D.2.5.5. Fax number	
D.2.5.6. E-mail	

E AMENDMENT IDENTIFICATION

E.1. Type of substantial amendment	
E.1.1. Amendment to information in the CT application form	Yes ☐ No ☐
(If yes, please refer to relevant sections and submit either the revised CT application form with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text)	

E.1.2. Amendment to Protocol	Yes ☐ No ☐
(If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text)	

E.1.3. Amendment to initial request for an ethical opinion	Yes ☐ No ☐
(If yes, please refer to relevant sections of the main application form)	

E.1.4. Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the clinical trial	Yes ☐ No ☐
(If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold)	

E.1.5. Amendment to other documents or information		Yes ☐ No ☐
(If yes, please specify)		

E.1.6. This amendment concerns mainly urgent safety measures already implemented	Yes ☐	No ☐
E.1.7. This amendment is to notify a temporary halt of the trial	Yes ☐	No ☐
E.1.8. This amendment is to request the restart of the trial	Yes ☐	No ☐

E.2. Reasons for the substantial amendment		
E.2.1. Changes in safety or integrity of trial subjects	Yes ☐	No ☐
E.2.2. Changes in interpretation of scientific documents/value of the trial	Yes ☐	No ☐
E.2.3. Changes in quality of IMP(s)	Yes ☐	No ☐
E.2.4. Changes in conduct or management of the trial	Yes ☐	No ☐
E.2.5. Change or addition of principal investigator(s), co-ordinating investigator	Yes ☐	No ☐
E.2.6. Change/addition of site(s)	Yes ☐	No ☐
E.2.7. Other change	Yes ☐	No ☐
E.2.7.1. (If yes, please specify)		
E.2.8. Other case	Yes ☐	No ☐
E.2.8.1. (If yes, please specify)		

E.3. Information on temporary halt of trial	
E.3.1. Date of temporary halt (dd/mm/yyyy)	
E.3.2. Recruitment has been stopped	Yes ☐ No ☐
E.3.3. Treatment has been stopped	Yes ☐ No ☐
E.3.4. Number of patients still receiving treatment at time of the temporary halt in Liberia	(……...….)
E.3.5. Briefly describe (free text):	
E.3.5.1. Justification for a temporary halt of the trial	
E.3.5.2. The proposed management of patients receiving treatment at time of the halt	
E.3.5.3. The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product	

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN LIBERIA

G.1 Type of change	
G.1.1. **Addition of a new site**	
G.1.1.1. Principal Investigator (provide details below)	
G.1.1.1.1. Name, Given Name	
G.1.1.1.2. Qualifications	(MD……...)
G.1.1.1.3. Professional address	
G.1.2. Removal of an existing site	
G.1.2.1. Principal Investigator (provide details below)	
G.1.1.1.1. Name, Given Name	
G.1.1.1.2. Qualifications	(MD……...)
G.1.1.1.3. Professional address	
G.1.3. Change of coordinating investigator (provide details below of the new coordinating investigator)	
G.1.3.1. Name, Given Name	
G.1.3.2. Qualifications	(MD……...)
G.1.3.3. Professional address	
G.1.3.3. Name of the previous coordinating investigator	
G.1.3. Change of principal investigator at an existing site (provide details below of the new principal investigator)	
G.1.3.1. Name, Given Name	

G.1.3.2. Qualifications	(MD……...)
G.1.3.3. Professional address	
G.1.3.3. Name of the previous principal investigator	

H CHECKLIST OF DOCUMENTS TO BE SUBMITTED WITH THIS NOTIFICATION FORM *(Tick as appropriate)*

H.1. Cover Letter on official headed paper, including list of modified documentation with new version numbers and dates	☐
H.2. Revised Protocol/amended document with new version number and date with amended data highlighted	☐
H.3. Revised information sheets and consent forms with new version number and dates and amended data highlighted	☐
H.4. Other supporting documentation	☐
H.5. Proof of payment of requested fees	☐

I DECLARATION

This declaration should be signed before the application will be considered valid

- I confirm that the information contained in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.
- I undertake to abide by the ethical principles outlined in the Declaration of Helsinki, and the International Conference on Harmonization's Good Clinical Practice Guidelines (ICH GCP)

I.1 Applicant of the request for the competent authority (LMHRA) – as stated in section D.1	☐
I.2. Applicant of the request for the Ethics Committee (NREB) – as stated in section D.2	☐

Signature: ……

Print name: ……..

Date of submission: …… (dd/mm/yyyy)

Annex *3* SADR Report – Form

For official use only

National/Central Office

Date report received: ……..…… (dd/mm/yyyy)	Checked by:	Designation:
Comments (include results of Casualty Assessment):		

Please complete all sections as much as possible:

F PATIENT INFORMATION

A.1. Name		
A.2. Age/Date of birth	……..…… .. /……..(dd/mm/yyyy)	
A.3.Gender: M ☐ F ☐	If female, pregnant? Yes ☐ Nein ☐	If pregnant, age of pregnancy:
A.4. Clinical trials site		
A.5. Weight		
A.6. Community		
A.7. Telephone number		

G DETAILS OF ADVERSE REACTION(S) AND ANY TREATMENTS GIVEN

B.1. Description of the Adverse Reaction

B.1. Date SADR started	……..(dd/mm/yyyy)
B.2. Time SADR started	☐☐Hr ☐☐Min
B.3. Signs and symptoms *Give a summary of the case, indicating any prior disease(s) or condition and patient's medicines before vaccination/therapeutic intervention*	

B.2. Please attach a separate sheet(s) of all relevant laboratory tests and data when necessary

H REACTION INFORMATION

C.1. Seriousness *(Check all appropriate to Adverse Reaction)*

C.1.1. Is SADR serious	Yes ☐ No ☐ If serious, complete below
C.1.2. Death: ☐ Date of death if dead: ……	C.1.5. Hospitalization: ☐ (*Please specify):*
C.1.3. Life threatening: ☐	C.1.6. Congenital anomaly: ☐
C.1.4. Disability: ☐	C.1.7. Others ☐ *(Please specify):*

C.2. Outcome

C.2.1. Recovering ☐	C.2.4. Not recovered ☐
C.2.2. Recovered ☐	C.2.5. Unknown ☐
C.2.3. Recovered with sequelae ☐	

I SUSPECT VACCINE/DRUG INFORMATION

D.1. Details of all vaccines/Drugs administered *(Attach sample or product label if available)*

IMP,Brand, Generic Name	**Batch Number**	**Expiry Date**	**Dosage Regimen**	**Manufacturer**

D.2. Vaccine/Drug administration

D.2.1. Date started: ……..…… (dd/mm/yyyy)	D.2.2. Date stopped: …… (dd/mm/yyyy)
D.2.3. Route of administration:	D.2.4. Number of days given:
D.2.5. Indications for use	
D.2.6. Did reaction subside after stopping intervention?	Yes ☐ No ☐
D.2.7. Was product reused after detection of SADR?	Yes ☐ No ☐
D.2.8. Did reaction reappear after reintroduction?	Yes ☐ No ☐

J CONCOMITANT MEDICATION

(Include complementary medicines consumed at the time and/or 3 months before. Exclude those used to treat reaction)

Name of medication	Daily dose	Date started	Date stopped/ongoing	Reasons for use

K REPORTER DETAILS

Signature: ……

Name (Print): …….

Profession/Designation: ……...

Name and address of Institution: ……

Telephone: …… E-mail: ……..

Date of submission: …… (dd/mm/yyyy)

Annex 4 CT Progress Report – Form

LIBERIA MEDICINES AND HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

Clinical Trials Quarterly/ Annual Progress Report Form

ADMINISTRATIVE INFORMATION

1. CLINICAL TRIAL (CT) STATUS

Check one category only:

- ☐ Enrolment has not begun
- ☐ Actively enrolling participants
- ☐ Enrolment closed on: (insert date): participants are receiving treatment/intervention
- ☐ Enrolment closed on: (insert date): participants are in follow-up only.
- ☐ Analyzing data
- ☐ Data analysis completed

2. INFORMATION ON CT PARTICIPANTS AND ACTIVITIES

a. Number of CT participants consented and screened.....
b. Total number of CT participants consented and screened who are eligible for the study.....
c. Number of CT participants to which the investigational product(s) has been administered.....
d. Number of CT participants left to be enrolled in the coming months (years).....
e. Number of participants who have discontinued the study:
- ☐ by Investigator:
- ☐ voluntarily:
- ☐ due to SAE:

f. Have there been any Serious Adverse Events (SAEs)? _____

g. Total number of SAEs: _____ (attach line list of SAEs documented for the reporting period)

Have these SAEs been reported to the LMHRA? _____

.....

i. Have there been any changes to the protocol since the LMHRA approved? _____ ☐ ☐

☐ ☐

j. Is this amendment submitted to the LMHRA? _____

If No, explain ☐ ☐

☐ ☐

.....

k. Date for the end of the study
l. Date for the final study report

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3. UPDATE ON MANAGEMENT AND RESULTS OBTAINED ON BIOLOGICAL SAMPLES EXPORTED FROM LIBERIA

4. Update on DSMB reports (if applicable)

5. Comments (if any)

6. List of Attachments:

- Data and Safety Monitoring Board reports issued during the reporting period (List by date of issuing and provide as attachment)
- Safety update reports for the reporting period

SIGNATURE	
Signature	Date

Return this form and all supporting documentation to:

THE MANAGING DIRECTOR
LIBERIA MEDICINES AND HEALTH PRODUCTS
REGULATORY AUTHORITY (LMHRA)
2nd & 3rd Floors, Clay Building
Sekou Toure Avenue, Mamba Point
Monrovia, Montserrado County
Republic of Liberia

Annex 5 Closeout report – Form

A. SITE INFORMATION

A.1. Trial Details	
A.1.1. Protocol Title:	
A.1.2. Protocol Identification number:	
A.1.3. Clinical Trial Certificate number:	
A.1.4. Name and address of Clinical Site:	
A.1.5. Name, address, telephone number and e-mail address of Principal Investigator:	
A.1.6. Name, address, telephone number and e-mail address of Sponsor:	
A.1.6. Date of last recruitment:	
A.1.7. Date(s) of Report:	

A.2. Site Staff Details		
Name	**Title**	**Contact**
A.2.1.	Local monitor	
A.2.2.	Site Coordinator	
A.2.3.	Pharmacist	
A.2.4.	Other	

B. CLINICAL SITE CLOSE-OUT CHECKLIST

Instructions: *Please provide comment(s) for each of the items listed below. Additional sheets may be attached if necessary.*

Objective	**Comments**
B.1.1. All regulatory and other essential documents (refer to Appendix IV of LMHRA Guidelines for the conduct of Clinical Trials, **(Reference number)** are up-to-date and on file	*Provide list of documents on file at the site*
B.1.2. Notification of all relevant oversight bodies of closure of Study	
B.1.3. Signed, informed consent is on file for each study participant	*Provide list of participants (use codes/ study IDs)*
B.1.4. Documentation of all protocol violations/deviations and/or appropriate note-to-files in the relevant essential Document	*Provide list*
B.1.5. Appropriate follow-up and reporting of all SAEs to LMHRA	*Provide number of SAEs reported. Summary of outcome for SAEs listed is relevant*
B.1.6. Completion of all Case Report forms for each participant	
B.1.7. Entry/ submission of all relevant data into database/ to sponsor/ coordination center. If not complete, indicate the timeline for accomplishing this and document in the comments section	
B.1.8. Status of all outstanding data edits, queries or delinquent forms and timeline for their resolution	
B.1.9. Tentative date for submission of full Clinical Study	
B.1.10. Requirements for retention of study records. Indicate if each requirement has been fulfilled.	
B.1.11. Drug accountability • Quantity of IMPs received • Quantity of IMPs utilized in the study • Quantity of IMPs destroyed (attach copy of destruction certificate(s)) • Quantity of IMPS onsite/ returned to sponsor	
B.1.12. Status/ shipment/ analyses of all participant specimen according to protocol requirements (including plans for future shipments or period of time thy will be stored on- site	
B.1.13. If blinded study drug was used, confirm that the tear-off labels were not opened. For any that were opened, documentation should be obtained noting the reason for unblinding.	

C. ADDITIONAL COMMENTS

C.1 Status of past observations/ recommendations made during monitoring / GCP inspections.
(Have corrective measures been implemented for all observations and recommendations?). Provide summary of measures implemented for each point)

C.2. Outstanding issues or activities to be implemented.
(Include problems identified, if any, and recommendations/ action items for corrections)

Prepared by *(print name)*: ……..……

Signature: ……..……Date:……..……..……(dd/mm/yyyy)