GUIDELINES FOR THE CONDUCT OF CLINICAL TRIALS IN UGANDA

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Citation

These guidelines shall be cited as the *"Professional Guidelines on the Conduct of Clinical Trials in Uganda", Doc. No. DPS/GDL/024, Revision No.:0".*

Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional **Guidelines on the Conduct of Clinical Trials in Uganda;** Doc. No. DPS/GDL/024, Revision No.:0, made this **7th day of October 2019,** that take effect on **14th October 2019**.

Signature

Dr. Medard Bitekyerezo
CHAIRPERSON
National Drug Authority
Kampala, Uganda

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1.0 INTRODUCTION

These guidelines as outlined are drawn in conformity with the legal requirements of the National Drug Policy and Authority Act and the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014. It is required that all medicines used in Uganda are registered with the National Drug Authority (NDA), and any clinical trial using registered or unregistered medicine must receive written approval from NDA for that purpose.

The guidelines set out the procedures that should be followed by applicants who wish to conduct clinical trials in Uganda. The timelines for a regulatory decision on various applications are communicated on the NDA website and follow a stop clock mechanism from the time the completed application is received by the Directorate of product Safety.

The guidelines also set out the procedures that should be followed by applicants who wish to amend the condition(s) of approved, ongoing clinical trials in Uganda and the steps that NDA will take to evaluate and make a regulatory decision regarding the request for amendment of such trials.

These guidelines also speak to the proper management of the investigational medicinal product during the conduct of a clinical trial

Approval by NDA for conduct of the clinical trial does not absolve the applicant from compliance with all laws and regulations in Uganda. In particular, other laws may apply to import or use of infectious or genetically modified organisms.

These guidelines are with respect to drug-related clinical trials as defined under the National Drug Policy and Authority Act.

1.1 Objectives of this guideline

To guide researchers on the submission of drug-related clinical trial applications and the conduct thereof specifically: the format of submission, support documentation, key aspects during the conduct of a clinical trial

1.2 Scope

These guidelines do not address the procedures for the conduct of veterinary clinical trials which shall be covered in a separate guideline.

1.3 Policy

These guidelines are drawn under section 40 of the National Drug Policy and Authority Act and the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014, Statutory Instrument No.32.

1.4 Distribution

NDA website: http://www.nda.or.ug

A shared folder for all staff on NDA head office server (\\ndaserver\qms\guidelines);

2.0 DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines.

"Act" means the National Drug Policy and Authority Act

"Adverse Drug Reaction" means a response to an investigational drug product which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function

"Adverse Event" means any undesirable medical occurrence in a subject to whom an investigational drug product is administered, including occurrences which are not necessarily caused by or related to that product

"***Authority***" means the National Drug Authority

"Clinical Trial" means any investigation in a human subject which is intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of an investigational drug product or to identify any adverse reactions to an investigational drug product

"Clinical Trial Report" means a written description of a trial/study of any therapeutic, prophylactic, diagnostic agent conducted in human subjects, in which the clinical and statistical description, prescriptions, and analyses are fully integrated into a single report (see the ICH Guideline for structure and content of Clinical Study Reports).

"*Clinical trial application"* means the submission/dossier that includes all documentation pertaining to the conduct of a clinical trial in the country according to the regulation. The dossier includes a cover letter, a protocol, an investigator's brochure or product information, CV's of investigators, and other requirements as provided by the Act.

"Comparator Product" means an investigational or marketed product (i.e. active control) or placebo, used as a reference in a clinical trial

"Contract Research Organisation (CRO)" means a person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

"Good Clinical Practice (GCP)" means a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of trial subjects are protected.

"*Informed Consent"* means a written, signed and dated voluntary confirmation by a subject about his or her willingness to participate in a clinical trial, after being informed of all the aspects of the clinical trial that are relevant to the decision to be made by the subject regarding his or her participation in the clinical trial.

"***Inspection"*** means the act by a regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

"*Data and Safety Monitoring Board (DSMB)"* means an independent and multidisciplinary group established by the trial sponsor to review, at intervals, accumulating trial data, in order to monitor the progress of a trial and to make recommendations on whether to continue, modify or stop the trial for safety or ethical reasons. The DSMB may be synonymous with the Independent Data-Monitoring Committee (IDMC) or Data Monitoring Committee (DMC)

"Interim Clinical Trial/Study Report" means a report of intermediate results and their evaluation based on analyses performed during the course of a trial.

"Investigational Medicinal/Drug Product" means a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a registered product when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication or when used to gain further information about an approved use

"Investigator" means a person responsible for the conduct of the clinical trial at a trial site.

If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

"Investigator's Brochure" means a document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product which are relevant to the study of the investigational drug product in a subject

"Manufacture" *means* all operations that include purchase of materials and production, quality control, release, storage, shipment (from storage related to manufacturing site) of finished products, and related controls.

"Manufacturer" means a company that carries out at least one step of production as well as the final release of the finished product

"*Multi-centre Trial"* means a clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

"*Principal Investigator*" means a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the principal investigator is the responsible leader of the team.

"*Protocol"* means a document that describes the objective(s), design, methodology, statistical considerations, and organisation of a clinical trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

"Protocol Amendment" means a written description of a change(s) to or formal clarification of a clinical trial protocol

"*Registered Product"* means any product that has been granted marketing authorization by the NDA

"Serious Adverse Event" means any undesirable medical occurrence that at any dose:

a) results in death
b) is life – threatening
c) requires inpatient hospitalization or prolongation of existing hospitalization
d) results in persistent or significant disability/incapacity, or
e) results in a congenital anomaly/birth defect. Important Medical Event (IME)
f) Important Medical Event (IME) as determined by the investigator

"Sponsor" means an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial

"*Subject"* means a human participant in a clinical trial.

"*Trial Site"* means the location(s) where trial-related activities are actually conducted or implemented.

"*Unregistered Product"* means any product that has not been granted marketing authorization by the NDA

3.0 ABBREVIATIONS

ADR : Adverse Drug Reaction
AE : Adverse Event
AIDS : Acquired Immune Deficiency Syndrome
CIOMS: Council of International Organization for Medical Science
CoA : Certificate of Analysis
CRO : Contract Research Organization
CTA : Clinical Trial Application
CTC : Clinical Trial Certificate
DSMB: Data Safety and Monitoring Board
EU : European Union
GCP : Good Clinical Practice
GLP : Good laboratory Practice
GMP : Good Manufacturing Practice
IB : Investigator's Brochure
ICH : International Conference on Harmonisation
IRB : Institutional Review Board
LoA : Letter of Amendment
NDA : National Drug Authority
NIMP : Non Investigational Medicinal Product
NRA : National Regulatory Authorities
PI : Principal Investigator
REC : Research Ethics Committee
SAE : Serious Adverse Event
TRS : Technical Review Series
UNCST: Uganda National Council for Science and Technology
WHO : World Health Organisation

4.0 PROCEDURES FOR SUBMISSION OF APPLICATIONS

4.1 When to apply?

4.1.1 Clinical Trials requiring a Clinical trial Application

In line with regulation 3 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, an application for the conduct of a clinical trial is required for studies using drugs as defined by the National Drug Policy and Authority Act that are registered under the Act or not registered under the Act that intend to**:**

a) Investigate a new medicine or vaccine including pharmacokinetic, bioequivalence and first-in-human studies, that has not yet received any marketing authorization anywhere in the world

b) Investigate registered medicines where the proposed use is outside the registered aspects of the medicine including; indication and clinical use of the medication, route of administration, target population, dosage and dosage form.

c) Do comparative bioavailability trials

d) Generate information on the absorption, distribution, metabolism and excretion of one or more medicinal products;

e) Use an investigational medicinal product on human participants.

f) Studies using medical devices to deliver a drug or medicinal product to a human participant

For clinical trials involving the use of herbal medicinal products, please refer to the "*Guidelines on clinical trials involving the use of herbal medicinal products".*

4.1.2 Clinical trials requiring Notification to the Authority

There are some studies that require notification to the National Drug Authority although these will not require regulatory review and issuance of a Clinical Trial Certificate. These include:

i) Medical devices which are specifically excluded from applying for clinical trial authorization by the Authority (except in section 8.1.1 (6) above). However a synopsis of the study shall be submitted to the Authority for verification purposes. There is no provision under the current Act or Regulations to authorize clinical trials involving investigational medical devices.

ii) Socio-behavioural studies using registered drugs or medicinal products.

iii) Studies where the objectives and end-points of the research are not about the product and the product has received marketing authorization in Uganda or a country with a stringent regulatory authority.

4.2 Where to Apply

The application to conduct a clinical trial in Uganda shall be submitted to;

The Secretary to the Authority

National Drug Authority

P.O. BOX 23096 Kampala

Rumee towers, Plot 19. Lumumba Avenue

Telephone: (+256) 417 788 100/1 0417 799 124 0417 788 129

Fax: (+256) 41-255758/343921

E–mail: ndaug@nda.or.ug

Application forms and guidelines can be downloaded from the website: www.nda.or.ug. using the link https://www.nda.or.ug/application-forms/

4.3 Who can apply

The Sponsor or authorized person who is to conduct a drug related clinical trial in Uganda shall make the application. Based on the Clinical Trial Agreement between the Sponsor and the Principal Investigator (PI), the Authority will liaise with the PI who is the representative of the sponsor in the country.

The principal investigator should be (local) that is resident in Uganda and should be licenced by a relevant body in Uganda. The qualifications of the Principal Investigator should be in line with the proposed study with careful consideration of the population and the product.

4.4 Application Fee

Every application for conducting a clinical trial shall be accompanied with a non-refundable fee. The applicable fees are contained in The National Drug Policy and Authority (Fees) Regulations, 2014, Part 9. Details for payment are detailed in the table below.

National Drug Authority: TIN 1000054563

BANK	STANBIC BANK UGANDA
ACCOUNT NUMBER USD	9003008068851
ACCOUNT NUMBER UGX	903005759829
SWIFT CODE	SBICUGKX
ACCEPTABLE FORMS OF PAYMENT	CASH IN THE BANK, RTGS, EFT, TT,CHEQUE

N.B The prescribed fees for clinical trial applications in Uganda may change from time to time as determined by the Authority.

4.5 Application Format

Application for authorization of the conduct of a clinical trial shall be made on prescribed forms which shall be available on the NDA website (www.nda.or.ug) using the link https://www.nda.or.ug/application-forms/ . Only one copy of the completed clinical trial application form shall be submitted for each application. The complete application package shall consist of the documentation listed in Appendix II of this document.

The signed Clinical Trial Application (CTA) form shall be submitted in the format set out in the Clinical Trial Application Form (Appendix I of this guideline). The text and diagrams must be clear and legible (12 pt Times New Roman font). Upon signing the application, all the investigators accept the responsibility that all applicable regulations and requirements will be adhered to and shall be responsible for ensuring that the trial is based on and implemented according to well – founded ethical and scientific principles,

which are expressed in the Helsinki Declaration and its current revisions as well as in the local and international guidelines for GCP.

4.6 Presentation of the Application

The application should be bound in a single volume (or series of volumes clearly indicated) and the pages of the CTA numbered sequentially. The appended documents should be bound together with the application, with tabbed sections identifying each appended document or in electronic format as guided by the Authority.

4.6.1 Supporting documents;

a) Clinical Trial Application Form

Every person intending to conduct clinical trial will complete a clinical trial application form. This form is available on the NDA website under the forms section.

b) Trial Protocol

The trial protocol is a formal document that specifies how a clinical trial is to be conducted. It describes the objective(s), design, methodology, statistical considerations, and administrative structure of the trial sponsor

c) Investigator's Brochure
d) Participant Information Leaflet and Informed Consent
e) Certificate of GMP manufacture of the trial medicine or other evidence of manufacture quality, safety and consistency
f) Package Insert(s) for other trial medicines.
g) Certificate of GMP manufacture of the placebo - if appropriate.
h) Evidence of accreditation of the designated Laboratories or other evidence of GLP and assay validation.
i) Insurance Certificate specific for the trial sourced from a local provider or in consultation with NDA
j) Signed and completed Declarations by all Investigators
k) Approval of Ethics Committees for the Protocol
l) UNCST Approval
m) Full, legible copies of key, peer-reviewed published articles supporting the application.
n) Sample of the label for the imported products
o) Letter of authorization from the manufacturer/product owner;

In line with regulation (3) of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014, the applicant needs to provide evidence of authorization by the manufacturer of the product or the agent of the manufacturer. If the agent provides this authorization, there is a need to provide evidence of power of attorney of the by the agent of the manufacturer. There is a need for the manufacturer of the product or their agent to consent authorise the use of investigational product in the proposed study.

a) Pharmaceutical Data on dosage form This documents gives details on the characteristics of the finished product, the manufacture of the product quality control of the product, stability of the product detailing the acceptance limits
b) Duly signed declaration of the Monitor
c) Materials transfer: Applications for import and/or export of biological materials (if required)
d) Clinical trial Agreement between the Sponsor and the Principal Investigator
e) Other supporting documents; Depending on the proposed study and the nature of the investigational product, the NDA may ask for additional information to support the protocol.

4.7 Language

Application for Clinical Trial Import Licence must be in English. All other data, particulars supporting documents, product labels and package inserts must also be in English.

When supporting documentation is not originally in English, a copy of the document in its original language, accompanied by authenticated translation in English shall be submitted.

4.8 Trial registration

Clinical Trial registration with a publicly accessible clinical trial registry is a requirement for all industry funded clinical trials that are to be conducted in Uganda. Details of registration should be provided at the time of application. This is to avoid duplication of effort and also to reduce reporting bias (publication bias and selective reporting bias)

4.9 Confidentiality

National Drug Authority commits to maintain the confidentiality of any information submitted as part of a clinical trial application, supporting documents or associated correspondence.

5.0 PROCEDURES FOR REVIEW AND APPROVAL OF APPLICATIONS

Reviews for clinical trials will be done following a first-in first-out principle except for applications for clinical trials that are to be conducted in public health emergencies such as disease outbreaks which may be exempted as detailed in section 10.4.1.

In line with regulation 6 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014, the Authority will consider and verify the application for conformity to these Regulations.

5.1 Validation of the completeness of application package

An application will be screened for completeness as per the requirements of these Regulations and where the Authority is not satisfied with the information provided, the applicant will be advised in writing to provide further information or clarification. The applicant shall submit their responses in writing or in any other format as advised by the Authority, in the timeframe determined by the Authority and addressed to the Secretary to the Authority.

Incomplete applications will not be received at the NDA Registry.

5.2 Clinical Trial Application Code

A complete application for authorization of a clinical trial shall be allocated a Clinical Trial Application (CTA) code. The CTA code shall be quoted in all subsequent correspondence with the Authority including applications to amend the protocol, applications for annual renewal, notifications as well as submission of safety reports.

5.3 Additional information

Any new information that becomes available regarding the product such as new adverse effects, changes in formulation or the manufacturer for the active ingredients or finished products must be submitted to the NDA as soon as possible. Unless otherwise stated, additional information that is submitted prior to issuance of a clinical trial certificate shall be considered as part of the submission and reviewed accordingly.

The NDA may request for further supplementary information or documentation when appropriate. Additional information requested by NDA should be submitted within the stated timeline, usually 4 weeks or in the specified time communicated by the secretariat.

The Secretariat may grant additional time to provide information upon request by the applicant on a case by case basis.

In the event that the requested information is not submitted by the applicant, the application will be archived within 50 working days. The applicant will need to resubmit their application for it to be reviewed.

5.4 Types of regulatory review of submitted documentation

Applications that have been verified as complete will be subjected to any of the three (3) types of reviews listed below depending on the applicable criteria;

5.4.1 Internal Review:

These are reviews conducted by the NDA Secretariat shall be further subdivided into;

5.4.2 Expedited Reviews:

These shall apply wherein a regulatory decision shall be given to the applicant within 30 working days and this is applicable for only if one of the following criteria are met.

a) Clinical trial applications for investigational drugs to provide treatment where no therapy exists.

b) Clinical trials conducted in an emergency for example during a disease outbreak.

c) Clinical trial applications that do not explicitly meet criterion (1) or (2) above and are led by the Ministry of Health in the interest of a public health intervention

The Secretariat reserves the right to determine which application may undergo this kind of review where the criteria may be unclear.

5.4.3 Routine Reviews:

These reviews shall be conducted according to the current NDA service delivery timelines as published on the NDA website.

5.4.4 Expert Review:

The application may be reviewed by external reviewers co-opted by NDA following internal procedures.

5.4.5 Joint Reviews

These reviews are carried out jointly with other regulatory bodies that is the NDA, UNCST, UNHRO and the primary REC. These reviews will be coordinated by the Uganda National Council for Science and Technology as Secretariat.

It should be noted that in the review of CTAs if there are issues pertaining to ethics and UNCST, NDA will endeavour to notify the UNCST on such issues including but not limited to discrepancies in compensation, inconsistent versions of protocol of ICF, missing risk information in the ICF, issues pertaining to appropriate insurance cover. In some cases pending issues may hinder issuance of a regulatory decision from the National Drug Authority and a regulatory decision will be issued once these issues have been resolved.

5.5 Regulatory Decision and Timelines

In line with regulation 6 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, there will be three outcomes from the review of the application submitted;

a) Authorization of the clinical trial and subsequent award of the Clinical Trial Certificate(CTC);

b) Request for additional information to support the application.

c) Rejection of the clinical trial application with reasons

The Approval for importation of trial related medicines will be dependent on the award of the clinical trial certificate for the conduct of the clinical trial.

The regulatory decision shall be communicated to the applicant in writing and the timelines for the various regulatory decisions shall be published on the NDA website. These timelines shall not include the time taken by the applicant to respond to any requests for additional information from the Authority. A stop-clock mechanism shall thus apply each time the Authority requests for additional information.

5.6 Documentation Submitted to the National Drug Authority

5.6.1 Errors or omissions

Errors or omissions made on documents furnished to the Authority that are administrative such as typos, administrative changes grammatical errors/changes, revisions to document versions and dates(that do not consist of a protocol amendment), need not be submitted to the authority. However in exceptional circumstances where it is a Sponsor requirement (and the applicant needs to provide evidence of this along with the submission) the stamp of receipt at the Registry will suffice as acknowledgement of receipt of the said notification by the NDA.

5.6.2 Errors on Documents from NDA

Errors made on responses given by the authority shall be addressed by an acknowledgement letter referring to the particular document in which the error was made. No authorizations will be re-issued except in extra ordinary circumstances.

5.6 Conclusion of a clinical trial

In line with regulation 12 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, the Sponsor or the Principal Investigator shall notify the Authority upon conclusion of a trial within ninety calendar days using the format prescribed by the Authority. This notification shall be accompanied by;

1. The final clinical trial report as specified in Appendix X.
2. Evidence of destruction or shipment of remaining investigational medicinal product or any other course of action approved by the Sponsor.

The definition of the end of the study will be as defined by the specific study protocol. The National Drug Authority requires that the PI submits an end of study notification according to the end defined in the study protocol.

In the event of a sponsor-initiated termination of a clinical trial before the planned end of the study, the sponsor shall within fifteen calendar days inform the Authority in writing of the termination or suspension and the reason(s) for the termination or suspension and provide evidence of notification to the REC of record and the UNCST.

5.7 Annual Renewal of Authorization to Conduct a Clinical Trial

Clinical Trial Certificates awarded will be valid for a year from the day of award. Annual renewal of authorization to conduct the clinical trial shall be required for the trial prior to expiration of the validity. The requirements for application of annual renewal are listed in Appendix VII of this document. For studies that have completed follow-up for the last

participant where there is no product nor human subject, oversight will be deferred to the only primary IRB and UNCST.

6.0 APPROVAL OF THE TRIAL BY THE UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

In line with regulation 5 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014 an applicant shall prior to making an application to the Authority for authorisation to conduct a clinical trial, get approval to carry out the clinical trial, from the Uganda National Council of Science and Technology or from an institution authorised by the Uganda National Council of Science and Technology. For studies authorized by an institution other than UNCST, the Authority will withdraw from review applications that are not given a favourable opinion by the UNCST.

7.0 AMENDMENTS TO THE TRIAL PROTOCOL

In line with regulation 10 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014 the applicant shall apply to deviate from the conditions of the clinical trial certificate as an amendment application. In line with regulation 11 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014 where the Authority, on its own initiative, makes amendments to the conditions for conducting a clinical trial for safety reasons or the scientific validity of the clinical trial, the Authority shall give notice of fifteen calendar days to the Sponsor or the Principal Investigator and request them to submit a written response to the proposed amendments.

7.1 The Application Form

In line with Regulation 10(2) and 10(3) of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014 an application for amendment of the conditions of a clinical trial shall be made using the Application form for amendment of conditions of a clinical trial which is available on the NDA website (www.nda.or.ug). The application shall be accompanied by a cover letter signed by the applicant together with all the required supporting documentation listed in Appendix VI of this document. Furthermore,

a) The proposed changes shall be listed in the cover letter accompanying the application and a clear step-by-step justification for each proposed change(s) provided.

b) The possible consequences with regard to the benefit: risk balance for participants already enrolled into the trial shall be summarized in the cover letter.

c) The subject of the cover letter shall be “Application to amend CTA XXX” where XXX is the CTA code number assigned by NDA at authorization of the clinical trial and indicated on the clinical trial certificate. (*This code number applies to all clinical trials authorized from April 2016. All trials authorized prior to this date shall be referenced with the full protocol title and the study acronym where applicable in parenthesis*).

d) Only one copy of the completed form shall be submitted to the Authority.

7.2 Supporting documentation

All applications to amend a clinical trial shall be accompanied by:

a) Valid evidence of approval from the Research Ethics Committee (REC) and where applicable such as additional clinical trial site, change in Principal Investigator, evidence of approval by the Uganda National Council for Science and Technology (UNCST). This is in line with Regulation 10(3) and Schedule 1 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014.

b) Proof of payment of the prescribed fees

c) For addition of new site(s), an agreement between the sponsor and additional site, a detailed explanation of the infrastructural capacity of the site to support the research activities (staff, space, equipment etc) and the Site Investigator at the new site.

d) For change in Principal Investigator of the clinical trial, an updated curriculum vitae of the new Principal Investigator including evidence of training in Good Clinical Practice (GCP) and an indication of their current workload or time contribution to the clinical trial.

e) For applications to change the sample size, the applicant shall provide the justification for the change, any implications on the scientific validity of the study and mitigation measures in case there are indeed implications. For increase in the sample size, the applicant shall provide evidence of capacity to support the additional subjects in terms of laboratory capacity for additional samples, sufficient budget to cater for compensation of additional participants, clinical trial insurance to cover the additional subjects, additional study staff to handle the additional workload etc.

f) Applications to amend the shelf life of an investigational product shall be accompanied by stability data, among other requirements to support the change

g) Where an amended Participant Information Leaflet & Informed Consent form may be required any additional risks or safety issues should be highlighted.

h) The amended supporting documents should be appended, including any new relevant publications.

7.3 Procedures for Review and Approval of Applications to Amend the Conditions of a Clinical Trial

7.3.1 Completeness of application form, supporting documents and fees

In line with regulation 10(4) of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014 upon receipt, the application shall be screened for completeness. Applications to amend the conditions of a clinical trial shall essentially be complete in the first instance if it includes all required documents and appendices and one copy of the complete checklist.

Applications which are incomplete will not be evaluated however, a letter documenting the deficiencies in the application will be issued to the applicant.

7.3.2 Supplementary Information and Updates

Any new information available for the product such as adverse effects, updates to the Investigator Brochure, changes in formulation or manufacturer for the active ingredients or finished products shall be notified to NDA. The NDA may request for further supplementary data or documentation where applicable.

7.3.3 Regulatory decision

The Authority will consider the favourable opinion of the Research Ethics Committee(s), the UNCST and other relevant information.

The Authority may request the applicant to submit an interim clinical trial study report to support the decision.

NDA may approve or reject the application and specify the reasons for rejection.

NDA may take other regulatory action such as an inspection of the clinical trial site or investigational product manufacturing facility for regulatory and protocol compliance prior to making a decision on an application for amendment of the trial.

This decision will be communicated to the applicant in writing.

7.4 Categorization of Major Amendments To The Trial Protocol

Amendments may be major/substantial and minor/non-substantial. Major amendments require written approval from the NDA prior to implementation with the exception of urgent safety measures. In line with regulation 19 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014, the sponsor or PI shall submit a written notice of the changes implemented as urgent safety measures for regulatory review using the Amendment Application Form and indicate these measures as "immediate notifications". Letters of Amendment (LoA) that require a change in the conditions of an on-going clinical trial that meet the criteria of a major or substantial amendment will be evaluated as such. Appendix IV of this guidance provides additional guidance on examples of major/substantial amendments.

8.0 INSPECTION BY THE NATIONAL DRUG AUTHORITY

In line with regulation 7, sub-regulation 1(c), regulations 15 and 23 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, the Authority may at any reasonable time conduct inspections of the trial site prior to or after issuance of a clinical trial certificate. The purpose of these inspections is to assess the staff and facilities to be used or that are being used for the conduct of the clinical trial, to verify the availability of the necessary resources and feasibility of conducting the study at the proposed site(s). These inspections shall assess the compliance of the trial conduct with the conditions of the certificate.

The aim is to evaluate the acceptability of clinical data submitted to NDA, and to ensure that legislation, Good Clinical and Laboratory Practice (GCLP) principles and practices as elaborated in the National Guidelines for Research involving Humans as Research Participants, July 2014 and in this guideline are adhered to. The NDA Secretariat may contact the PI or sponsor notifying them of the date(s) of inspection.

The Secretariat will conduct inspections routinely, or as a result of a trigger. In addition, the inspections may be done jointly with the UNCST and/or the REC.

8.1 The Inspections will include - but are not limited to:

a) The facilities and staff used for the trial: as approved by the NDA
b) Compliance with the approved Protocol
c) management of the IMP
d) All amendments to the Protocol which may have been approved
e) Accurate, complete and current records according to the Protocol
f) Verifying that Serious Adverse Events are reported as required by the Protocol
g) Verifying that inspections intended to monitor and audit the trial are conducted as required by the Protocol and the reports are available for inspection.

The "*Guidelines on Good Clinical Practice"* shall provide additional guidance on the requirements for compliance.

9.0 REPORTS AND FINAL REVIEW

9.1 Notification of Adverse Events

In line with regulations 21 and 22 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, the PI shall report to the NDA all serious adverse events (SAEs), both expected or unexpected, as soon as possible but no later than seven (7) calendar days upon receiving notice of such an event.

Additional follow up information shall be made available to NDA as soon as possible, but in any case not later than fifteen (15) calendar days.

Suspected unexpected serious adverse reaction (SUSARs) reports originating from other studies using the same product internationally shall be submitted within fifteen (15) calendar days following notification of the PI by the sponsor.

A line listing of Adverse events that have occurred during the reporting period shall be submitted with the application for renewal of authorization to conduct a clinical trial.

9.2 Protocol Deviation reports

Protocol deviation is defined as a departure from the approved protocol's procedures made with or without prior IRB approval. Such departures may be major or minor/administrative in nature

Examples of protocol violations may include the following:

a) Inadequate or delinquent informed consent
b) Inclusion/exclusion criteria not met
c) Unreported serious adverse events
d) Improper breaking of the blind
e) Use of prohibited medication
f) Incorrect or missing tests
g) Mishandled samples
h) Multiple visits missed or outside permissible windows
i) Materially inadequate record keeping
j) Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
k) Subject repeated non-compliance with study requirements

9.3 Classification of deviations

a) **Emergency deviations** are those occurring in an emergency, such as when a departure from the protocol is required immediately to protect the life or physical well-being of a participant. In such cases, there is no time to prospectively seek the approval of the authority. The Authority must be notified as soon as possible, but not later than 5 days after the emergency situation occurred.
b) **Major deviations** are deviations from the protocol that have may affect the safety if the participant or the credibility of the data. These are gross violations of the approved study protocol and these should immediately be reported. Corrective action should be taken to prevent re-occurrence.
c) **Minor or administrative deviations** are those which do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects." If a protocol deviation occurs which meets this definition, the deviation should be reported to the National Drug Authority at the time the continuing review application.

It is desirable to identify any important protocol deviation with respect to the time when it occurred, its cause and influence on the trial result.

a) The frequency and type of protocol violations,
b) Missing values, and

c) Other problems should be documented in the clinical study report.

Reporting of deviations is dependent on the nature of the deviation that has occurred.

Emergent deviations will be reported within five days of occurrence of the deviation

Major deviations will be reported within 15 days of occurrence specifying the corrective action taken or intended to be taken following the deviation.

Minor deviations may be reported as a line listing during the submission of the Annual Progress report during renewal of authorization of the study.

9.4 Trial Progress Reports

In line with regulation 12(2) of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014, the Authority may during the course of a clinical trial, request the sponsor to submit an interim report of the clinical trial. Where a sponsor is requested to submit an interim report, the sponsor shall make the report using the prescribed format for a clinical trial report.

9.5 End of Trial reports

The definition of the end of the study will be as defined by the specific study protocol. The National Drug Authority requires that the PI submits an end of study notification according to the end defined in the study protocol.

End of trial reports will be submitted once the trial data can answer the study endpoints. In line with regulation 12 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014 The National Drug Authority defines the end of the trial as a time when the trial ends and end points are available.

9.5 Maintenance of Records

In line with regulation 18 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014 and the ICH-GCP Guidance on Good Clinical Practice, it shall be the responsibility of both the investigator and the sponsor to ensure the safety of all essential documents related to the trial. Documents may be stored in electronic (soft and scanned) or hard copies. The holder of the clinical trial certificate/applicant should inform NDA in writing prior to destroying the documents. Documents shall be retained for a minimum period of 20 years in line with the above regulation

10.0 THE INVESTIGATIONAL MEDICINAL PRODUCT

In line with regulation 7(c) and 9 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, the principal Investigator or sponsor shall apply for a Clinical Trial Certificate from the NDA prior to importation/manufacturing of a local product, for clinical trial use.

10.1 Importation

Products including placebos that are not registered with NDA and are intended for importation for purpose of clinical trial use must be for applications that have already been awarded a Clinical Trial Certificate (CTC).

A product with a marketing authorization (registered product) when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication or when used to gain further information about an approved use in a clinical trial also requires award of a clinical trial certificate. Once all the documentation is in place, the applicant should follow the Guidelines for Verification of Applications for Importation of Drugs for Emergency or Extraordinary Circumstances (Doc. No.: INS/GDL/038).

10.2 Manufacture

In line with regulation 8(3) and (4) of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014 all investigational medicinal products(IMPs), including active comparators and placebos, shall be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and evidence of this shall be submitted with the clinical trial application. Acceptable evidence of manufacture under GMP standards shall either be from the list of countries considered as stringent regulatory authorities under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) or from the National Drug Authority, Uganda.

Where a product contains a narcotic or psychotropic substance, applicants must possess the necessary approval under the current applicable legislations.

10.3 Labelling of the Investigational Medicinal Product (IMP)

In line with regulation 17 of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, an IMP shall be labelled as specified in Form 38 of the regulations that is available on the NDA website using the link below https://www.nda.or.ug/application-forms/

10.4 Use of the IMP

a) The product shall only be supplied to the investigator(s) at the trial site(s) named in the application for which a CTC has been issued for the purpose and use as stated in the said application. No change in investigator, trial site or trial protocol shall be made without notification to and approval by the NDA using the prescribed processes.

b) The holder of the certificate shall ensure that adequate precautions are taken for all study medication(s), such as storage as per the manufacturer's prescribed storage conditions in a secure and access-controlled location, to prevent theft, misuse, accidental or illegal distribution. Temperature and where prescribed, humidity monitoring shall be done for all areas where IMPs are stored.

c) The holder of the certificate shall ensure that the study medication(s) are supplied only to subjects involved in the said trial.

10.5 Responsibility of the Principal Investigator

a) The Principal Investigator (PI) shall be responsible for the product and all information supplied in support of his/her application for CTC of his/her study using the said IMP(s). They shall be responsible for updating any information relevant to the product/application.

b) In the event where the PI is not the manufacturer and where confidentiality considerations prevent disclosure of certain information to the PI, such information may be furnished to NDA through the PI in a sealed envelope marked CONFIDENTIAL or sent to the Clinical Trials Unit with the necessary password protection on clinicaltrials@nda.or.ug.

10.5.1 The Sponsor shall:

a) ensure timely delivery of the investigational product(s) to the investigator(s);

b) Maintain records that document shipment, receipt, disposition, return and destruction of the investigational product(s);

c) Maintain a system for retrieving investigational product(s) and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim);

d) Maintain a system for the disposal of unused investigational product(s) and document the process.

e) Not supply or ship the investigational medicinal product until all the required documentation has been obtained.

f) ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP and is coded and labelled in a manner that protects blinding, if applicable.

g) state for the investigational medicinal product(s) acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any.

h) Ensure that the investigational product(s) are stable over the period of use. This stability data should be available on request and for inspection purposes. If non-compliance with the specifications becomes evident in the stability studies during the period of use in the clinical trial, the sponsor should notify the investigators and arrange to take appropriate action;

i) Maintain sufficient quantities of the investigational product(s) used in the trial to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent that stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

10.5.2 The Pharmacist of Record shall;

a) Maintain instructions for handling of Investigational Medicinal Product(s) and trial related materials (if not indicated in the protocol or investigator's brochure).

b) Maintain shipping records for the Investigational Medicinal Product(s) and trial related material as well as receipt date(s) of product delivery and quantity. This record should also contain the exact batch numbers, expiration dates and codes assigned to the product and the trial subject.

c) Documentation regarding allocation of treatment, randomization and code breaking.

d) Investigational Medicinal Product(s) accountability at site (pharmacy or investigator):

e) Date and quantity dispensed or returned, identification of recipients (patients code or authorised persons).

f) Documentation about relabelling, if applicable.

g) Records of the date and quantity returned to the sponsor. Return receipt should also contain batch numbers, expiration dates and codes assigned to the product and the trial subject.

h) Documentation of destruction of Investigational Medicinal Product according to the NDA guidelines.

i) Documentation of re-export, where applicable.

10.5.3 Other obligations

In line with regulation 3 (f) and 7(1) (f) of the National Drug Policy and Authority (Conduct of Clinical trials) Regulations, 2014, the terms of agreement between the sponsor and the Principal Investigator and the financial declaration by sponsor and the principal investigator made using Form 33 of the regulations should be in place and these should be submitted to NDA.

Any person who knowingly supplies any false or misleading information in connection with his application for Clinical Trial Certificate commits an offence under section 60 of the National Drug Policy and Authority Act.

10.6 Non Investigational Medicinal Products (NIMPS)

As a general rule, the documentation, importation and manufacture requirements in the clinical trial application that apply for the IMPs also apply to the NIMPs with the exception of the investigator's brochure and the authorization from the manufacturer if these products are going to be used within the acceptable indications for the IMPs.

This refers to the following categories of medication:

10.6.1 Rescue medication; Rescue medications are medicines identified in the protocol as those that may be administered to the patient when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.

10.6.2 Concomitant medicinal products systematically prescribed to the study patients: This type of NIMP is given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested, and is therefore not the object of the study.

For any additional NIMPs, the applicant should seek guidance from the Authority prior to submission of their application.

10.7 Notification of Change of Information to NDA

The holder of the clinical trial certificate shall inform NDA of any change in information, or any information received by them that casts doubt on the continued validity of the data on the IMP which was submitted with, or in connection with the application for the CTC.

10.8 Discontinuation of Trial

The holder of the clinical trial certificate shall inform NDA of any decision to discontinue the trial to which the certificate relates and shall state the reason for the decision.

10.9 Post Trial Access of the IMP

Post-trial access programmes included in the protocol will be considered for approval and these requests will be reviewed as part of the application. Requests for post-trial access of the investigational medicine that are not included in the protocol and that emerge at the end or after the trial has ended shall be required to submit additional information included in Appendix VIII of this guideline.

11.0 NOTES ON THE APPENDICES

This section comprises recommended formats for some of the supporting documents as well as additional guidance on the regulatory requirements.

a) Failure to enclose the necessary details and supporting documents may result in a delay in the processing, or rejection of an application.

b) Headings set out for each Appendix are minimum general requirements. These may not be applicable in all circumstances, neither are they exhaustive.

c) Interpretation of these guidelines shall be done in the context of or related to the proposed use of the product.

d) Where a heading is not applicable or information is not available, indicate clearly in the appropriate section.

e) Additional information to that specified in the guidelines may be submitted to support the application for the clinical trial authorization. Such data shall be presented in a well compiled manner as additional appendices, with a summary of the particulars.

These guidelines do not preclude any other information required by NDA. Such additional information may be supplied to NDA on request.

12.0 REFERENCES

ICH-GCP Guidelines for Good Clinical Practice E6(R2)

National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition)

National Drug Policy and Authority (Conduct of Clinical Trials) Regulations No. 32, of 2014.

The Rules Governing Medicinal Products in the European Union, Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Volume 4, European Union

Medicines Control Authority of Zimbabwe. Guidelines for Good Clinical Practice in Zimbabwe (2012).

Medicines Control Authority of Zimbabwe. Pharmacy Guidelines for Investigational Drugs.

13.0 DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and/or reasons for revision
07.Oct. 2019	0	DPS/GDL/024	*Authors:* Dr. Evans Tusubira Helen Byomire Ndagije Huldah Nassali *Reviewers:* Dr. Rachel Kyeyune Bakyayita Sheila Ampaire Sharon Kiggundu Florence Wanyenze Dr. Ian Mugisa Julius Mayengo Victoria Nambasa Daisy Nabatanzi	This is the first issue of this document

APPENDIX I: THE CLINICAL TRIAL APPLICATION FORM (CTA)

CTA Section 1 Identification of the Clinical Trial

1.1 Title of the Study

1.2 Protocol number, Date, Version:

--- --- ---

1.3 Contact Person and contact details

1.4 [Space for NDA Reference Number] ---

1.5 Declaration of Intent signed by the 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.

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 Uganda.

Applicant (Local Contact):

NAME Date:

Signature:----------

Designation----------

Principal Investigator: Date:

NAME ----------

Signature:----------

Designation----------

CHECKLIST OF REQUIRED DOCUMENTS

Item	Requirement
Fees	Proof of payment
Materials transfer:	Applications for import and/or export of materials (if required)
CTA	Clinical Trial Application Form
APPENDIX 1:	Trial Protocol
APPENDIX 2:	Investigators Brochure
APPENDIX 3:	Participant Information Leaflet and Informed Consent
APPENDIX 4:	Certificate of GMP manufacture of the trial medicine or other evidence of manufacture quality, safety and consistency[1]

[1] *Note:*

Certificate of Good Manufacturing Practice (GMP) for the investigational product or statement on GMP from the manufacturer/re-packer (whichever is more relevant).

- *The GMP certificates or other documents must be issued by an authority recognised by NDA i.e. the authorities listed in the WHO certification Scheme On The Quality Of Pharmaceutical Product Moving In International Commerce,*
- *Or the statement on GMP can be issued by the Quality Assurance Department where the product is manufactured.*
- *For local product, the manufacturing licence is required.*
- *For a comparator product, the following is required:*

i) *a GMP certificate*

ii) *If not available one of the following can be submitted:*
   - *Approval letter from the regulatory authority*
   - *Annual Registration of Drug Establishment*
   - *Package insert*

iii) *For a repacked product, a statement of GMP must be submitted by the re-packer.*

3*REC/IRB approvals of study protocols should be submitted along with the CTA to NDA and should include:*

- *Details of REC/ IRB membership*
- *Statement of compliance with the requirements in the ICH Guide*
- *A relevant minute of the meeting that approved the study protocol*
- *Any amendments to the trial protocol required by the REC/IRB*
- *Any conditions included in the approval*
- *The final decision*

APPENDIX 5:	Package Insert/s for other trial medicines.
APPENDIX 6:	Certificate of GMP manufacture of the placebo - if appropriate.
APPENDIX 7:	Evidence of accreditation of the designated Laboratories or other evidence of GLP and assay validation.
APPENDIX 8:	Insurance Certificate specific for the trial in consultation with NDA
APPENDIX 9:	Signed and completed Declarations by all Investigators
APPENDIX 10:	Approval of Ethics Committees for the Protocol3
APPENDIX 11:	Full, legible copies of key, peer-reviewed published articles supporting the application.
APPENDIX 12:	Sample of the label for the imported products
APPENDIX 13:	Letter of authorization from the manufacturer/product owner
APPENDIX 14:	Pharmaceutical Data on dosage form
APPENDIX 15	Duly signed declaration of the monitor
APPENDIX 16	Clinical trial agreement between the sponsor and the principal investigator
APPENDIX 17:	Other supporting documents

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	E-mail address	Physical Address	Postal address
Applicant						
Sponsor4						
Manufacturer						

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

CTA Section 3 Medicines to be used in the trial

3.1 Investigational medicine

3.1.1 Identifier or name of investigational medicine (code if applicable)

3.1.2 Registration number

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 (See Attachment 4 for details of the required information.)

3.1.6 Release Specifications and tests. Include Certificate of Analysis.

3.1.7 Current approved Package Insert if available.

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 [Appendix 6]

3.2.5 Evidence that Placebo is manufactured under GMP. [Appendix 7]

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 where necessary and monitoring during distribution.

3.3.3 Details of dispensing trial medicines and Waste disposal procedures.

3.3.4 Packaging and Labelling of the medical products

3.4 Estimates of quantities of each medication (presentation) to be used for the trial, and for which an import permit is needed.

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]	

4.2 For each Site list the following:

4.2.1 Site Identifier (Name)

Physical Address: (for rural sites include GPS coordinates)

Telephone & Fax numbers

E-mail address

4.2.2 Description of the site facilities & Staff

a) Clinic and counselling rooms
b) Emergency facilities
c) Facilities for special examinations (if required)
d) Capacity to collect, prepare, store and transport clinical samples
e) Storage and handling facilities for medicines
f) Name and qualifications of person with responsibility for dispensing medicines

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 Trial to take place.

4.6 Append Signed Agreement/s between the Investigators and the Sponsor/s and/or Clinical Research Organization. (Appendix 13)

CTA Section 5 PARTICIPANTS

5.1 Numbers of Participants as stipulated in the table below

5.1.1 Total number to be enrolled, worldwide

5.1.2 Total number to be enrolled in Uganda

5.1.3 Number of trial sites in Uganda

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 Final Report

5.2.2 Duration for individual Participant

a) Screening period

b) Intervention period

c) Follow-up period

5.2 What is the intended compensation for time and other inconvenience per participant? This should not be confused with compensation in terms of damage

CTA Section 6 History of Previous and in-progress trials

6.1 List the titles of previous trials with this (or similar) medicines in Uganda

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 in 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.

CTA Section 7 Ethics review

7.1 Provide the local IRB/REC approval of the Protocol for each site [Appendix 11]

7.2 What GCP Guidelines have been followed in compiling this protocol?

7.3 Will GCP training be provided for local staff and investigators?

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.

8.3 Describe the actions to be taken following reports of Serious Adverse Events.

88.4 Describe the composition and remit of the Data Safety Monitoring Board or similar body. Include conditions for Pause- or Stop- rules.

8.5 When will Interim Reports be submitted?

8.6 Final Report - Estimated due-date?

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

CTA Section 10 Description of the Trial

10.1 Is the Title of the Trial fully descriptive?

10.2 Summarized Rationale for this Clinical Trial, including relevance to Uganda

10.3 BRIEF Background information should include:

a) The disease or condition and local epidemiology

b) Properties of the medicine - hypothesis for action

c) Description of risks of the protocol and the potential harms of the medicine.

d) Pre-clinical animal toxicology test results in-animals and in-vitro that establishes probable safety and efficacy in humans [2]*****

e) Prior Clinical trial report summaries that establishes probable safety and efficacy in humans *****

f) 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. *****

g) Published reviews or reports relevant to this disease and this type of medicine

10.4 Objectives of this trial (List as Primary and Secondary objectives and provide justification)

10.5 Trial Design: Describe and justify each component.

10.5.1 Phase

Placebo or comparator

Randomization and blinding

Other detail

[2]* *Cross-reference to detail in the Investigator's Brochure.*

10.5.2 Time sequence –

A Table of screening, intervention and follow-up visits will be of assistance.

10.5.3 Participants

Eligibility

Inclusion criteria - list and justify each

Exclusion criteria - list and justify each

10.5.4 Treatment regimens for each group.

The table in 10.5.2 above can be used to set this out

10.5.5 Follow-up sampling collection and monitoring plans; Immediate monitoring - intermediate monitoring - long term monitoring Diary cards

Telephone access to investigators

10.6 Outcomes Measurements and Analysis

10.6.1 Describe each outcome/variable (including safety) and explain or justify

10.6.2 Describe the samples that will be collected and the analyses to be conducted on each sample

10.6.3 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)

10.6.4Describe the intended statistical analysis to be conducted. Provide evidence that the clinical trial is powered to provide the intended outcome

10.7 Are any sub-studies intended? Provide full details

10.8 Are any genetic studies (HLA-typing or gene-marker analysis) intended? Provide full details, and justify this. Is there a separate consent form for this?

10.9 Will clinical samples be stored for any period beyond the duration of this trial?

10.9.1 What is the purpose of such archiving?

10.9.2 What controls are to be placed on their confidentiality and possible future use?

10.10 Participant Information Leaflet and Informed Consent Form

10.10.1 Append a copy of the participant information leaflet and consent form (Appendix 4)

10.10.2 In what languages will this be available?

10.10.3 For the subjects who are minors, append the consent form of the parents or guardians of the minors.

10.10.4 Are there separate consent forms for sub-studies or genetic studies?

CTA SECTION 11: Publication Policy

11.1 Provide details of the investigators and sponsors intentions and freedom to publish the outcomes of this clinical trial.

APPENDIX II: CLINICAL TRIAL APPLICATION CHECKLIST

Protocol title/CTA……

CHECKLIST OF REQUIRED DOCUMENTS

Item	**Requirement**	
Fees	Proof of payment	
Materials transfer:	Applications for import and/or export of biological materials (if required)	
CTA	Clinical Trial Application Form	
APPENDIX 1	Trial Protocol	
APPENDIX 2	Investigators Brochure	
APPENDIX 3	Participant Information Leaflet and Informed Consent	
APPENDIX 4	Certificate of GMP manufacture of the trial medicine or other evidence of manufacture quality, safety and consistency[3]	
APPENDIX 5	Package Insert(s) for other trial medicines.	
APPENDIX 6	Certificate of GMP manufacture of the placebo - if	

	appropriate.	
APPENDIX 7	Evidence of accreditation of the designated Laboratories or other evidence of GLP and assay validation.	
APPENDIX 8	Insurance Certificate specific for the trial sourced from a local provider or in consultation with NDA	
APPENDIX 9	Signed and completed Declarations by all Investigators	
APPENDIX 10:	Approval of Ethics Committees for the Protocol2 UNCST Approval	
APPENDIX 11:	Full, legible copies of key, peer-reviewed published articles supporting the application.	
APPENDIX 12:	Sample of the label for the imported products	
APPENDIX 13:	Letter of authorization from the manufacturer/product owner	
APPENDIX 14:	Pharmaceutical Data on dosage form	
APPENDIX 15:	Duly signed declaration of the Monitor	
APPENDIX 16:	Clinical trial Agreement between the Sponsor and the Principal Investigator	
APPENDIX 17:	Other supporting documents	

Note:

Certificate of Good Manufacturing Practice (GMP) for the investigational product or statement on GMP from the manufacturer/re-packer (whichever is more relevant).

- *The GMP certificates or other documents must be issued by an authority recognised by NDA i.e. the authorities listed in the WHO certification Scheme On the Quality of Pharmaceutical Product Moving In International Commerce,*

  Or the statement on GMP can be issued by the Quality Assurance Department where the product is manufactured.

- *For local product, the manufacturing licence is required.*
- *For a comparator product, the following is required:*

i) *a GMP certificate*

ii) *If not available, one of the following can be submitted:*

- *Approval letter from the regulatory authority*
- *Annual Registration of Drug Establishment*
- *Package insert*

iii) *For a repacked product, a statement of GMP must be submitted by the re-packer.*

[2]*IRB approvals of study protocols should be submitted along with the CTA to NDA*

Doc. No.: DPS//FOM/284
Revision No.: 1
Effective Date: 14 Oct 2019

APPENDIX III: APPLICATION FORM FOR AMENDMENT OF CONDITIONS OF A CLINICAL TRIAL

THE NATIONAL DRUG POLICY AND AUTHORITY (CONDUCT OF CLINICAL TRIALS) REGULATIONS, 2014

Please complete each section of this application form electronically as a Word Document and as a scanned signed PDF file. Please ensure that the electronic and the printed versions of the completed form accompany your submission.

1.0 APPLICATION DETAILS

1.1 Amendment category: (tick all applicable options)

☐ Major amendment ☐ Immediate notification

☐ Minor amendment ☐ Letter of Amendment (LoA)

1.2 Clinical Trial Application Number: *e.g. CTA 0015*

☐

1.3 Details of the approved original protocol:

Date of approval of original protocol (dd/mm/yyyy)	
Principal Investigator approved for the clinical trial	

Number of sites approved for the clinical trial	
Number of subjects approved for the clinical trial	

1.4 Applicant details

Applicant[4] **(Sponsor or Principal Investigator)**	

Application Form for Amendment of Conditions of a Clinical Trial

Contact person responsible for this application	Title/Designation: First name: Surname name:
Contact person's job title	
Contact person's postal address	
Contact person's email address	
Contact person's phone number	

[4] ***Applicant***
An applicant is the Sponsor or Principal Investigator who was issued a Clinical Trial Certificate. The applicant shall therefore be responsible for signing the application form.

2.0 SUMMARY OF PROPOSED CHANGES

For multiple amendments reproduce this section and provide separate summaries for each proposed amendment.

2.1 Amendment title, number and nature of supporting documentation

e.g. *Major amendment # 1:*

Change in the shelf life of the investigational medicinal product from 12 months to 24 months— stability data to support the change is attached

Major amendment #2: To change the dose or regimen of the investigational medicinal product- Amended Informed Consent Form and Updated Investigator Brochure attached; 5 peer-reviewed publications and pre-clinical/clinical data to support the change attached

2.2 Summary of current and proposed details:

Current details	**Proposed details**
Application Form for Amendment of Conditions of a Clinical Trial	
e.g Current shelf life 6 to 12 months Current sample size: 100 infants Current Protocol version and date	Proposed: 12 to 24 months Proposed sample size: 150 infants Amended Protocol version and date

2.3 Reason/rationale for change(s): *Please itemize the rationale for each change if more than one*.

2.4 Multi-centre trials: Will this amendment apply to all approved site(s)? If No: Specify the sites for which the amendment will apply

2.5 Date of implementation (*for Immediate Notifications only*)

2.6 Additional investigators or Change of Principal Investigator:

Name of additional or new Principal Investigator	
Physical address and contact information of Investigator	
Proof of ICH-GCP training attached	Yes/No:
Summary of on-going or planned studies at the site involving the Investigator:	Provide details of studies, including numbers of participants of the clinical trial, whether the investigator is involved in research on a full-time or part-time basis, and any other details that may affect the capacity of the site at any one time
Date of approval by IRB	
Date of approval by UNCST	

Please attach an up to date curriculum vitae of additional investigator(s) or new Principal Investigator and a signed declaration of intent.

3.0 Documentation checklist

The following documents have been submitted together with this application form:

Note: All documents must be provided for this application to be valid.	

Valid ethical approval of the proposed change(s)	☐ *Yes* ☐ *No*
Evidence of payment of amendment fees (NDA receipt)	☐ *Yes*
Supporting documentation (Detail the kind of documents submitted e.g Stability data, Curriculum vitae, Memorandum of Understanding/Contractual agreement, Certificate of accreditation of laboratory X, Budget for FY 2017/2018)	☐ *Yes*

4.0 Declaration *(by Applicant)*

I declare that:

☐ For each change all conditions as stipulated in the ***NDA Guidelines on Amendments to Conditions of a Clinical Trial*** for the change(s) requested are fulfilled.

☐ There are no changes being made other than those applied for in this submission, except for possible editorial changes. Any other changes will be applied for separately.

☐ The information submitted is true and correct.

APPLICATION FORM FOR AMENDMENT OF CONDITIONS OF A CLINICAL TRIAL

Name: _____ Title/Designation_____

Signature: _____ Date: _____

APPENDIX IV: CATEGORIZATION OF AMENDMENTS

Substantial amendments *related to the protocol:*

a) Purpose of trial
b) Design of trial
c) Informed consent
d) Recruitment procedure
e) Measures of efficacy
f) Schedule of samples
g) Addition or deletion of tests or measures
h) Number of participants
i) Age range of participants
j) Inclusion criteria
k) Exclusion criteria
l) Safety monitoring
m) Duration of exposure to the investigational medicinal product(s)
n) Change of posology of the investigational medicinal product(s)
o) Change of comparator
p) Statistical analysis

Amendments related to the trial arrangements:

a) Change of the principal investigator or addition of new ones (NB this means the lead investigator in each center)
b) Change of the coordinating investigator
c) Change of the trial site or addition of new sites
d) Change of sponsor or legal representative
e) Change of the CRO assigned significant tasks

f) Change of the definition of the end of the trial

Amendments related to the IMP For example:

a) Addition to stability data/change of expiry date
b) Change of formulation
c) Additional toxicology data
d) Change to route of synthesis

Changes to investigational medicinal product quality data concerning:

a) Change of name or code of IMPs
b) Immediate packaging material
c) Manufacturer(s) of active substance
e) Manufacturing process of the active substance
d) Specifications of active substance
e) Manufacture of the medicinal product
f) Specification of the medicinal product
g) Specification of excipients where these may affect product performance
h) Shelf-life including after first opening and reconstitution
i) Major change to the formulation
a) Storage conditions
b) Test procedures of active substance
c) Test procedures of the medicinal product
d) Test procedures of non-pharmacopoeial excipients

<u>Note</u>: This categorization is not exhaustive; proposed changes to the clinical trial that do not clearly fall into any of these categories will be evaluated on a case-by-case basis and the outcome communicated to the client in writing.

APPENDIX V: CTA AMENDMENTS SCREENING FORM

Screening Checklist for Protocol Amendments **Protocol title:**			
	N	**Y**	**Comment**
Signed Cover letter summarizing proposed amendment(s) and justification for change(s)			
Completed amendment form (Form 36)			
Submission of Protocol Amendment in tracked changes and clean copy clearly indicating protocol version number			
Valid evidence of payment of amendment fees			
Ethical approval of proposed amendment			

APPENDIX VI: CHECKLIST FOR APPLICATION FOR AUTHORIZATION OF RENEWAL OF CONDUCT OF A CLINICAL TRIAL

Protocol title:			
Item #	**Description**	**Y/N**	**Comment**
1.	Signed Cover letter clearly indicating protocol title		
2.	Valid ethical approval of the study		
3.	Annual progress report clearly indicating reporting period		
4.	DSMB report /Interim Analysis and line listing of SAEs during the reporting period		
5.	Investigational Product Accountability for the reporting period and projected need for the next period		

APPENDIX VII: REQUIREMENTS FOR POST TRIAL ACCESS APPLICATION FOR STUDIES THAT HAVE BEEN COMPLETED

1. Confirmation of end of study (NDA acknowledgement of End of Study)
2. NDA approval of protocol that states post-trial access for participants
3. Verification certificates for the previous imports done for post-trial access
4. Signed sponsor agreement or commitment to provide drugs for post-trial access
5. Up to date IMP accountability
6. List of patients, quantity of drug received by each and details of Physician/ clinician in charge
7. Copy of certificate of suitability of premises for the area where the products will be stored.