GUIDELINE FOR THE CONDUCT OF CLINICAL TRIALS IN SRI LANKA

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CLINICAL TRIALS REGULATORY DIVISION
NATIONAL MEDICINE REGULATORY AUTHORITY
No.120, Norris Canal Rd, Colombo 01000, Sri Lanka

GUIDELINE FOR THE CONDUCT OF CLINICAL TRIALS IN SRI LANKA

CONTENTS

1 PURPOSE

The aim of this guideline is to provide comprehensive guidance to assist investigators, clinicians, scientists, sponsors and research organizations to become familiar with the existing procedures and requirements for the conduct of clinical trials in Sri Lanka.

Also, one of the principal objectives of this guidance note is to help investigators better understand their responsibilities with respect to protecting human research participants and ensuring the integrity of the data from clinical investigations.

2 SCOPE

This guideline indicate the order of the material to be submitted and the minimum requirements to be completed to obtain "Letter of Authorization" for the conduct of clinical trial in Sri Lanka for which regulatory approval is needed from NMRA.

These guidelines are not intended as a comprehensive guide on Good Clinical Practice (GCP), and should be read in conjunction with National Medicines Regulatory Authority Act No.05 of 2015, National Medicines (Clinical Trials) regulations 2145/2 of 19th October 2019 and ICH GCP guidelines.

3 PROCEDURE/S

Approvals required to conduct a clinical trial

1. A clinical trial may be initiated in Sri Lanka only after:
   a) Obtaining regulatory approval from the Clinical Trials Evaluation Committee (CTEC), National Medicines Regulatory Authority (NMRA), Ministry of Health.
   b) Obtaining ethical clearance from an Ethics Review Committee (ERC), which have been recognized by the Clinical Trials Evaluation Committee, NMRA, Ministry of Health
   c) Obtaining approval or a no-objections certificate from the head(s) of the institution(s) of the trial site(s) (e.g. Director of a hospital).
   d) Registering the study in the Sri Lanka Clinical Trials Registry.

Parallel submissions can be made to both the CTEC and to the relevant ERC. However, CTEC approval to conduct a clinical trial will be granted only after clearance from one of the ethics review committees listed under 2 below has been obtained for the trial.

Ethics Review Committees (ERC) recognized by the NMRA

2. For the purpose of granting ethical clearance for trials requiring regulatory approval following Ethics Review Committees have been recognized by the CTEC :
   - ERC, Faculty of Medicine, University of Colombo
   - ERC, Faculty of Medical Sciences, University of Sri Jaewardenepura
   - ERC, Faculty of Medicine, University of Peradeniya
   - ERC, Faculty of Medicine, University of Kelaniya
   - ERC, Faculty of Medicine, University of Ruhuna
   - ERC, Faculty of Medicine, University of Jaffna
   - ERC, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka
   - ERC, Medical Research Institute, Colombo
   - ERC, Sri Lanka Medical Association, Colombo

Categories of clinical trials requiring Clinical Trials Evaluation Committee (CTEC) approval

3. Approval from the CTEC is required to conduct a clinical trial for the following categories of medicines;
   a) Unregistered medicines, and

   b) Registered medicines where the proposed clinical trial is outside of the conditions of registration. These may include changes to:
      (i) indication(s) and clinical use
      (ii) target patient population(s)
      (iii) route(s) of administration
      (iv) dosage regimen(s)

Clinical trials for other categories of medicines sponsored by non-commercial sponsors such as investigators either as individuals or collaborative groups, academic institutions, healthcare institutions and cooperative establishments are not subject to regulatory review and do not require approval from the CTEC. Such clinical trials require only ethics approval and registration with the Sri Lanka Clinical Trials Registry.

Phases of clinical trials permitted to be conducted in Sri Lanka

4. 1. Phase I / first-in-man clinical trials are not allowed in Sri Lanka at present.

   2. Applications for Phase II clinical trials shall be accepted for consideration based on the following criteria:

   a. Phase II trials where the same protocol is approved by a reference authority and the same study drug has been evaluated for the same indication.

      (Reference authorities for this purpose are FDA/USA, MHRA/UK, EMEA/European Union, Health Canada, PMDA/Japan, South Korea, TGA/Australia, HAS/ Singapore, MEB/Netherlands and SWISSMED/Switzerland)

   b. WHO sponsored Phase II trials that are on high priority globally or locally

   c. Other phase II trials to be considered case by case, provided that all of the following criteria are fulfilled;
      (i) Phase I studies have been approved by a reference authority and Phase I is successfully concluded reference country.
      (Reference authorities for this purpose are FDA/USA, MHRA/UK, EMEA/European Union, Health Canada, PMDA/Japan, South Korea, TGA/Australia, HAS/ Singapore, MEB/Netherlands and SWISSMED/Switzerland, MDSAFE/New Zealand)

      ii) For diseases not prevailing in reference countries or unable to conduct in a reference country due to a justifiable reason

      iii) Investigational product is not the first in class and the therapeutic class has a satisfactory safety record

   3. Phase III and IV trials are allowed to be conducted in Sri Lanka.

Application for approval to conduct a clinical trial

5. The Principal investigator who intends to conduct a clinical trial in Sri Lanka shall make the application to NMRA. However in situations where a sponsor or a person designated by the sponsor (eg: CRO) or any local parties involving the coordination of a clinical trial (eg: Site management organization) such details should be disclosed to the authority as specified in the application form mentioned below.
6. Application must be in filled in English language and all other data, particulars supporting documentations, 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.
   In addition, NMRA may require the applicant to submit manually (one hardcopy and soft copy on appropriate data storage device as Portable Document Format (PDF) files).

   The stipulated Application Form (Annex I) should accompanied by a covering letter with following essential documents:

i. Clinical trial protocol

The contents of a trial protocol that should generally include are in Annex II. However, site specific information may be provided on separate protocol page(s), or addressed in a separate documents.

ii. ***Investigator's brochure***

This document containing chemical and pharmaceutical information, animal pharmacology & toxicology data, specific pharmacological actions, pharmacokinetic data, and available human clinical pharmacology data related to the investigational product(s) as described in Annex III.

iii. ***Informed consent document(s) in English with Sinhala and Sri Lankan Tamil translations***

Consent forms prepared for trial participants in all three languages should be submitted as per the information in annex IV.

iv. ***Details relevant to the Investigational Medicinal Product (IMP) or Investigational medical device or Borderline product***

a. Current copy of certificate of Good Manufacturing Practices (GMP) of the manufacturing site should be submitted for investigational medicinal product, in case where there are more than one IMP's used each details should be submitted separately. The application should also include the Investigational Medicinal Product Dossier (IMPD) which contains all the details on the manufacture of IMP including specifications, test methods, method validation, stability data etc.

   Where a medical device is being used as the investigational product relevant certificate for quality management system according to ISO 13485 for manufacturing site with the details of the device design and development (Technical file/ Device Master File) should be submitted.
   (ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice)

b. Complete certificate of analysis for Investigational medicinal product or finished product test report / final inspection report for medical devices
c. Sample Labels (original /scanned) attached to original container

v. ***Approval from relevant Ethics Review Committee***

It is mandatory under section 4(2) of National Medicines (Clinical Trials) regulations 2145/2 of 19th October 2019 to obtain ethical approval for the clinical Study protocol, protocol Amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects, from an NMRA recognized Ethics Review Committee (ERC) as described above.

vi. ***Valid insurance certificate with insurance cover in Sri Lanka***

The amount should be indicated in US dollars and Sri Lankan rupees

vii. Undertaking responsibilities by the principal investigators

The format for PI declaration attached as an annex to the application should be filled and signed by the Principal Investigator with the application.

viii. Curriculum vitae of principal investigators with latest GCP certification

CV's of all investigator's including coordinating PI should be submitted with latest GCP certification.

ix. Global regulatory status in other countries, if available, in case of international multi-centre studies

Ethics Review Committee details of other participating countries along with the regulatory approval of other countries, or status of regulatory approval should be submitted for multicentre trials.

Following documents may also should be submitted accordingly.

x. Case Report Forms and signature sheets

xi. Lab manuals and pharmacy manuals

xii. Material transfer agreement

xiii. List of laboratories involved in the trial and a list of devices/ consumables used in the clinical trial

xiv. Records on retained samples (if any)

xv. *Justification for placebo (if any)*

xvi. Any other information as the CTEC may require

Confidentiality

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

Fees

8. NMRA would charge a processing fee for industry sponsored trials or academic sponsored trials with international sponsorship as specified in the gazette extraordinary No. 2052/33 of 05.01.2018.

Clinical Trials Evaluation Committee (CTEC)

9. NMRA may nominate the experts with requisite qualification & experience as members of Clinical Trials Evaluation Committee (CTEC) for the purpose of evaluation of clinical trial applications submitted for regulatory approval. The CTEC shall have approved Terms Of References (TOR) for its functions and responsibilities.

Composition of the committee

a. Director, Clinical Trials Regulatory Division or the person who acts on his behalf. (Ex-officio)
b. Two – three clinical pharmacologists / pharmacologists from University Departments of Pharmacology.
c. Clinical pharmacologist / pharmacologist from Medical Research Institute (MRI), Ministry of Health.
d. Four – five specialist clinicians representing different disciplines and specialities whilst possessing knowledge and expertise in clinical trials. At least one of them shall be a specialist in paediatrics.
e. One – two pharmacists from University Departments of Pharmacy who possess knowledge and expertise in clinical trials.
f. At least one- two person specialized in medical statistics.
g. Three pharmacists from CTRD, NMRA, who possess the required background.

Proceeding of the meetings of CTEC

The meetings shall be held in once a month every second Friday of the month.

Responsibilities of CTEC

i. To ensure that all clinical trials involving products conducted in Sri Lanka which require regulatory approval of the NMRA undergo ethics review by one of the recognized ethics review committee and have ethics clearance prior to being conducted.
ii. To recognize ERCs based on defined criteria, for the purpose of granting ethics approval for clinical trials which require regulatory approval of the NMRA.
iii. To review all clinical trial applications which require regulatory approval based on SOPs.
iv. To grant regulatory clearance, propose modifications to an application, withhold regulatory clearance or suspend regulatory clearance, for proposed or ongoing clinical research involving medicinal products conducted in Sri Lanka.
v. Through the NMRA, to ensure that records of the ethics approval and regulatory clearance process are maintained for all clinical trials involving medicinal products conducted in Sri Lanka which require regulatory approval.
vi. With the CTRD, to conduct GCP inspections of local trial sites before or after obtaining regulatory approval.
vii. With the CTRD, to review clinical trial guidelines and procedures for the conduct of clinical research with humans on a regular basis to ensure that they remain current.
viii. Through the NMRA, to ensure that amendments to previously reviewed clinical research projects undergo appropriate ethics and regulatory review, and accurate records of the approvals of amendments are kept.
ix. Through the NMRA, to ensure that a mechanism is in place for reporting and review of adverse events associated with clinical trials.
x. Through the NMRA, to seek legal or other advice, as required, on matters related to the protection of human participants in clinical research.

Conflict of Interest

All the members of the CTEC shall declare the conflict of interest at the time of their appointment, in accordance with the NMRA policy on Conflict of Interest.

Procedures for review and approval of application

10. On receipt of an application, the Clinical Trials Regulatory Division (CTRD) of NMRA will screen the application within 07 working days for its completeness. Application for conduct of clinical studies shall essentially be complete in the first instance if it includes all documents, study protocol & Investigator Brochure should be in accordance with ICH GCP Guidelines respectively, and the accepting pharmacist will complete checklist and forwarded the application for payments as may be prescribed in the relevant fees gazette.

    All applications received will be screened by CTRD and shall be scheduled for the upcoming CTEC meeting of the same month based on the category of the application to be reviewed by the CTEC.
    The CTRD shall maintain a register of all clinical trial applications received for review and the details of the application with relevant payment details.

Application Reference Number

11. Once an application received by the CTRD division the relevant details shall be entered in the Clinical Trials registry and an acknowledgement will be issued with a reference number.

Timelines for related processes, excluding stop-clock

12. Following timelines will be applicable for the below mentioned regulatory activities regarding the processing of clinical trials application submitted for review;

Processing of a clinical trial application	– 75 days
Processing of a variation (i.e. for amendments requiring NMRA approval)	– 35 days
Issuing of sample import licences of investigational and Non-investigational products	- 7 days

Priority review of a clinical trial

13. The applicant may request for priority review for an investigational product if there are unmet medical needs. The request for priority review should be made at the point of the application submission and should be accompanied with a justifications for requesting for a priority review and how the investigational product is expected to benefit patients.
    The Authority reserves the right to deny a request for priority review if it is deemed inappropriate. (Refer details for submission and processing of application for priority review – Guideline on non-routine processing of clinical trials applications and conduct of Clinical Trials during emergency situations).
    The decision for the granting of priority review would be conveyed to the applicant at the point of acceptance of the application for evaluation.

Supplementary Information and Updates

14. Any new information available for the trial such as changes in the protocol submitted to NMRA, consent form updates and additional trial sites are made, any changes to the formulation or manufacturer for the IMP must be reported to NMRA immediately.

The initial review may result in queries that need to be answered by the applicant.
The reviewers will not have direct contact with the applicant and all correspondence should be directed through the CTRD of NMRA.

Experts review (optional)

15. The application if required, maybe reviewed by experts designated / nominated by CTEC where such expertise are not within the composition of the committee. There will be confidentiality agreement with the reviewers and NMRA to ensure that the content of the application remains confidential.

Evaluation of applications will be done by the reviewers according to the guidelines and checklist provided by NMRA. The same policies are used for the evaluation of CT applications regardless of the applicant (e.g. domestic, foreign, public sector, or private sector)

The reviewers will generate a report that shall be placed before the CTEC meeting for the consideration. In case where the decision would not be obtained by a single reviewer two or more reviews may be nominated by the CTEC to review applications.

Relevant CT decisions, reports or information from other NRAs or SRAs

16. As per regulation 76 of National Medicines (Clinical trials) regulations 2145/2 shall also consider relevant clinical trial decisions, reports or information from stringent regulatory authorities and regional or international bodies such as WHO, ICH and others in making decision on clinical trial applications.

Any application for approval or registration of clinical trial will not undergo in the assessment process, if the same at any stage, has already been rejected, suspended or put on hold due to any reason, in above regional or international bodies or authorities and shall be rejected during the process of screening.

Approval

17. The CTEC will be responsible for evaluation and approval of the application, considering the reports submitted by reviewer.
The CTEC may approve or may reject the application and specify the reasons for such rejection.

If the trial is being approved by the CTEC the decision will be communicated to the applicants in writing, by the NMRA after obtaining the Ethical approval from respective ERC for the trial, by issuing the applicant a "Letter of Authorization". The period of validity of such letter will be decided by the CTEC/CTRD based on the trial protocol and other relevant details.

In case of rejection, the applicant may appeal and provide additional information where applicable and whenever required.

Updating web on clinical trial applications/ information

18. The CTRD division will maintain a data base on each received applications with their reference number, name of the trial, name of principal investigator, name of the sponsor if available, and details on the proceeding of application.

    A list of the clinical trials (approved and rejected applications), including summarized evaluation reports will be publicly available on the web site of NMRA. The web site will be updated every three months and the format of the content published in the web on such proceed trials would be as per Annex V.

    A responsible officer in the CTRD division, would fill the relevant work order format and communicate with the web manager, NMRA for web updates. Such updates shall carry information on the published formats, guidelines, procedures etc.

Inspections (Audits) by NMRA

19. An inspection or audit of clinical trial site/s may be conducted by NMRA before or after the approval of a clinical trial.

    The aim of the inspection is to evaluate the acceptability of clinical data submitted to NMRA, and to ensure that legislation, on Good Clinical Practices (GCP) and Good Clinical and Laboratory Practice (GCLP) principles are in place as per the ICH-GCP Guidelines. The nominated members from CTEC or responsible officer of NMRA may contact the PI or sponsor for the date of inspection when required.

    However in the case of complaints or reports of unexpected adverse reactions, inspections may take place at short notice or may be unannounced.
    (Refer details for conduct of GCP inspection – Guideline GCP inspections).

Amendments to the trial protocol

20. As per regulation 29 of National Medicines (Clinical Trials) regulations 2145/2 of 19th October 2019, no amendments in the approved protocol of clinical trial can be made without seeking prior approval from CTEC and relevant ERC.

    If amendment is essential, it is recommended that the application should be withdrawn and the complete amended version should be re-submitted. If the CTEC requires amendments, only the revised section may be replaced.

    If the amendment may affect the safety of the trial participants (e.g. changes to dose, regimen, concomitant medication, monitoring, etc.) the amendment must be submitted in full, and should approved by the CTEC and relevant ERC prior to implementation.

    If the amendment is unlikely to impact on participant safety (e.g. change of investigator - except Principle Investigator, end point assay, laboratory, statistical analysis, etc.) the full detail of the change must be submitted in writing, and the only notification of CTEC may be required.

Information to be supplied when submitting a protocol amendment;
i. An amended form as may be published in the NMRA web site should be completed.
ii. A **Bold Heading** should note that this is an Amendment and the date.
iii. Each amendment should be BOLD and in a BOX at the relevant position in the text.
iv. Summary of changes should be submitted in a tabulated format with the authorized signatures.
v. The amended supporting documents should be appended, including any new relevant publications.

The CTRD will review the application together with supporting documents and will referred to CTEC in its very next meeting for expert review and consideration for approval of the amendment(s) (Refer details for processing of amendments - Guideline for amendments to clinical trials)

Periodic reports to CTEC

21. The CTEC may require the holder of a "Letter of Authorization" during a clinical trial to provide any information or report at such times and in such manner as the CTEC may require.

Reports of Serious Adverse Events

22. Any clinical trial related adverse reaction shall be reported immediately to the CTRD of NMRA and to the relevant ERC. The PI shall report to NMRA, relevant ERC and the sponsor of all serious adverse events (SAEs), both expected and unexpected, as soon as possible but not later than seven (7) calendar days upon receiving notice of such event.

Sponsor shall bound the investigator to report all serious adverse events immediately to him except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. For reported deaths of a subject, the investigator shall supply the sponsor, NMRA and the Ethics Committee with any additional information requested.

The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators.
(Refer guideline for the submission of serious adverse events – Guideline on safety reporting)

Progress and Final reports

23. The holder of a Letter of Authorization should submit to the CTEC a notification of trial initiation, progress reports during the conduct of trial within six (06) months as well as final report of the clinical trial after the completion of the trial or such longer period as the CTEC may allow.

In the case of a clinical trial lasting for more than 6 months, an interim report shall be submitted at 6 months' intervals until the completion of the trial or as may be directed by the CTEC. This summary reports should provide a brief description of the study, number of participants exposed to the drug, dose and duration of such exposure, details of adverse reactions, if any, and reason(s) for discontinuation in case of a prematurely discontinued trial subjects or the clinical trial.

The PI shall submit an End of Study Summary Report pertaining to the sites conducting the trial to NMRA, within 3 months from the Last Patient out (LPO)/ Last Patient Last Visit (LPLV) date. In case of a multi-center trial within the country, with different end times, a report on each site shall be submitted before the end of the 3rd month from the last subject out.
A Final Report on the trial findings shall then be submitted not later than 3 months of completion of the whole trial. The format and contents of such reports shall be as in the format of Annex VI.

Product Accountability and Disposal

24. The destruction of unused investigational products should be carried out after completion of clinical trial and should be notified to the NMRA of such activity. Investigational product Accountability / Disposal report shall be submitted to CTRD of NMRA within 3 months from the Last Subject Out date.

The report will be placed in very next meeting of the CTEC and the report should include;

i. Date the trial started and ended and the reference number of the Letter of Authorization

ii. Clinical trial sites and details of PI including the person for handling of investigational product

iii. Date(s) and quantity received for each trial product

iv. Balance of the study medical product

v. Written evidence of re - export of the unused drug supplies to country of origin (whichever applicable).

Note: This guideline does not cater for radioactive substances. If such substances, the international guidelines for radioactive substances will be applied.

Archiving of Documentation

25. The sponsor and investigator must ensure that all significant documents concerning the trial (including the Trial Master File) must be stored for at least 5 years after completion of the trial. The documents must be stored longer than this, if any other legislation so requires, e.g. if the trial results are to be used in connection with an application for a marketing authorisation for a medicinal product, or if this is agreed with the sponsor.

The media used for storage of documents etc. must be appropriately secured and must be protected from loss and damage in the required storage period. Any changes to the documents etc. must be documented. In addition, the sponsor and investigator must ensure that the documents are stored in a manner that makes them easily available for control.

The list of source data must be prepared before the trial is initiated. It must be signed and dated by the principal investigator or by a person whom the principal investigator has assigned this task. The list must be available in the Investigator's Trial Master File.

Insurance cover for self-sponsored academic trials

Research Insurance

It is a requirement of any organization undertaking research with human participants that they hold appropriate insurance to cover the eventuality of an individual coming to harm, as a result of the research, and making a successful legal case for damages.

Compensation to Subjects and Investigators

1.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

1.2 Financing and Insurance Financing and insurance if not addressed in a separate agreement.

1.3 Insurance statement (where required) to document that compensation to subject(s) for trial-related injury will be available - located in Files of Investigator/ Institution Sponsor

Compensation to study participants

1. Any organization undertaking research with human participants should ensure that systems for compensation is in place through insurance or in some other manner in the event of any physical damage, health issue or death suffered by a subject resulting from participation in a clinical trial.
2. The requirement for insurance coverage shall be based on risk involved in the study to the participant and the assumed liability.
3. A justification should be submitted, if there is no insurance cover to compensate the participants, in an event of an injury to a participant.
4. A statement should be included in the study protocol to the effect that the participant will be provided with best possible medical care if any adverse drug reaction occur
5. Clinical trials conducted before marketing authorization of a pharmaceutical product, i.e. phase II and III trials pose a higher degree of risk to the participants. For such trials, a mandatory condition requiring the sponsor to obtain and maintain insurance to provide compensation shall be applied.
6. Clinical trials on pharmaceutical products already approved for marketing and with a known safety profile shall be considered for exemption of an insurance cover, which shall be determined on a case by case basis.

   A risk assessment analysis shall be conducted to determine the risk level to the trial participants, based on severity of known adverse events for the investigational product, which may be classified as mild, moderate or severe

4 DEFINITIONS

(a) Adverse Event (or Adverse Experience)

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

(b) Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

(c) Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

(d) CIOMS-I format

A format for reporting adverse drug reactions according to the Council of International Organizations for Medical Sciences.

(e) Clinical Trial

Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions may include but are not restricted to substances such as drugs, cells and other biological products, vaccines, surgical procedures, radiological procedures, or any other item claimed to have therapeutic benefit. The terms "clinical trial" and "clinical study" are synonymous

(f) Contract Research Organization (CRO)

A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

(g) Ethics Review Committee

An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non- medical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics review committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

(h) Final Report

means a comprehensive description of the trial after its completion including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethical, statistical and clinical appraisal

(i) Good Clinical Practices (GCP) Guidelines

means identified ethical and scientific quality requirements which are internationally recognized and which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety, and well-being of the study participants are protected, and the results of the clinical trials are credible;

(j) Good Manufacturing Practices (GMP)

means that part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP Guidelines published by WHO

(k) Informed Consent

Voluntary written assent of a study subject's willingness to participate in a particular clinical trial and its documentation. Such consent shall be taken only after information about the clinical trial, including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available and the rights and responsibilities of the study subject has been provided to the potential study subject

(l) Investigational Medicinal Product (IMP)

Any pharmaceutical product or placebo being tested or used as a reference in a clinical trial.

(m) Investigational product labeling

Labeling developed specifically for products involved in a clinical trial

(n) Investigator

A doctor or dentist, as the case may be, responsible for the conduct of the clinical trial and for the rights, health and welfare of the participants in the 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;

(o) Investigator' Brochure

A collection of data for the investigator consisting of all the relevant information on the investigational medicinal product(s), including chemical and pharmaceutical data and toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the investigator's brochure must be updated.

(p) Legal representative

In relation to a person who is to be used as a study subject in a clinical trial, an individual or judicial or other body authorized under the law to grant consent on behalf of that person, to the participation of such person in the clinical trial

(q) Phase I clinical trials

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.

(r) Phase II clinical trials

The clinical trials 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.

(s) Phase III clinical trials

The clinical 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.

(t) Phase IV clinical trials

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization 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. 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 pharmaceutical products.

(u) Principal Investigator (PI)

A doctor or dentist, as the case may be, having specialized in the area of study and specified in an approval as the person responsible for the conduct and supervision of a clinical trial.

(v) Protocol

A document that states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

(w) Sponsor

an individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

(x) Study Participant

an individual who participates in a clinical trial, either as a recipient of the investigational product under investigation or as a control. The individual may be a healthy person who volunteers to participate in a trial, a person with a condition unrelated to the use of the investigational product, a person (usually a patient) whose condition is relevant to the use of the investigational product.

5 RELATED LEGISLATION AND DOCUMENTS

- National Medicine Regulatory Authority Act No. 05 of 2015
- National Medicines (Clinical Trials) Regulations 2145/2

6 FEEDBACK

- Staff and customers may provide feedback about this document by emailing p4@nmra.gov.lk or p9@nmra.gov.lk

7 APPROVAL AND REVIEW DETAILS

	NAME	SIGNATURE
Prepared by		
Reviewed By		
Recommended By		
Approved by		

Next Review Date	05/10/2023

Annex I

NATIONAL MEDICINES REGULATORY AUTHORITY
MINISTRY OF HEALTH

APPLICATION FOR ISSUING A LETTER OF AUTHORIZATION TO CONDUCT A CLINICAL TRIAL

SECTION 1: TRIAL INFORMATION	
1.1 Title of clinical trial (*as stated in the protocol document)*	
1.2 Protocol number Protocol date (Current)	

1.3 Phase of clinical trial to be conducted

- ☐ **Phase 1**
- ☐ Phase 2
- ☐ Phase 3
- ☐ Phase 4

Describe if necessary:

1.4 Type of sponsorship

- ☐ Commercial
- ☐ Non-commercial

1.5 Details of sponsor

Name of sponsor:

Name of contact person:

Address of sponsor:

Telephone number:

Fax number:

Email:

1.6 Therapeutic Area	
1.7 Disease Type	

1.8 Previous CTA Application Number (Involving the Same Study Drug)

Not Applicable ☐

TRIAL SUMMARY	
1.9 Participants	☐ Healthy volunteers, ☐ Patients, or ☐ Both healthy volunteers and patients
1.10 Design	☐ Single-blind, ☐ Double-blind, ☐ Open-label, or ☐ Others - *please specify:*
1.11 Allocation	☐ Randomised ☐ Non-randomised
1.12 Type of investigational product	☐ Medicine ☐ Medical Device ☐ Borderline product
1.13 Involves concurrent use of	☐ Placebo ☐ Comparator drug ☐ Concomitant drug ☐ Comparator device ☐ Comparator border line product ☐ Not applicable (*i.e. trial does not involve the use of placebo, comparator or concomitant drug/device/borderline product)*
1.14 Name(s) of investigational product(s) used	
1.15 Name(s) of comparator drug(s)/device/borderline product	
1.16 Name(s) of Concomitant Drug(s)	
1.17 Administration of investigational product **(If tick medicine or borderline in 1.12)** <u>Study drug administration schedule</u> ☐ Single-dose, ☐ Multiple-dose, ☐ Cyclical dose, or ☐ Others, *Please specify in section 1.19*	<u>Duration of study drug dosing / treatment</u> ☐ For multiple or cyclical dose, state treatment period: Days Weeks Years ☐ Continue treatment until disease progression or unmanageable toxicity *Describe if necessary in section 1.19*
1.18 Duration of follow-up post-dosing of study drug(s)	Days Weeks Years Other, please describe:
1.19 Describe the design of the trial if necessary to supplement information in above for sections 1.9 to 1.18 if necessary. ☐ Not Applicable	
1.20 Location(s) of trial Centres	☐ Only Sri Lanka ☐ Sri Lanka / International If international, name other participating countries
1.21 Details of clinical trial registration:	
1.22 Number of trial sites in Sri Lanka	☐ Single centre ☐ Multi-centre State number of centres:

1.23 Proposed number of trial participants to be recruited from Sri Lanka	
1.24 Total proposed number of trial participants as per protocol	Globally:
1.25 Duration of study in Sri Lanka Planned start Date Planned end Date	Days Weeks Years
1.26 Is advertisement / recruitment programme included in this application?	☐ Yes ☐ No
1.27 Is there a Data Safety Monitoring Committee for this study?	☐ Yes ☐ No
1.28 Is this a US IND study?	☐ Yes ☐ No
1.29 Objective And Significance of Clinical Trial 1.30 Benefit / impact of this clinical trial for Sri Lanka	
1.31 Details of accredited ethics committee in Sri Lanka relevant to the study	
1.32 Status of the Ethical approval ☐ Approved ☐ Pending approval	

SECTION 2: STUDY DRUG(S) TO BE INVESTIGATED (This will appear if tick "Medicine" in 1.12)		
2.1 Investigational medicine	**1**	**2** *This column to be used only when > 1 study drug is indicated in section 1.13*
2.2 Active ingredient / generic name or code designation		
2.3 Brand name (if any)	☐ Not Applicable	☐ Not Applicable
2.4 Dosage form		
2.5 Strength		
2.6 Route of administration		
2.7 Pharmacological class		
2.9 Class of Study Drug Class I New investigational drug without any clinical trial conducted yet Class II New investigational drug with on-going phase 1, 2 or 3 clinical trials Class III Approved drug undergoing clinical trial for new indication(s), method of administration and, or dosages, etc. Class IV Approved drug whereby a marketing authorisation has been granted and used in this trial as a study drug, comparator drug or concomitant drug for approved indications, using approved method of administration and dosages.		
	☐ Class I ☐ Class II ☐ Class III ☐ Class IV	☐ Class I ☐ Class II ☐ Class III ☐ Class IV

2.10 For class III and IV study drugs, state the countries in which the drug has been granted marketing authorisation		
2.11 For product registered in Sri Lanka, provide the product licence No.	☐ Not Applicable	☐ Not Applicable
2.12 Name of the manufacturer	Name: Address:	

SECTION 2: STUDY MEDICAL DEVICE (S) TO BE INVESTIGATED (This will appear if tick "Medical Device" in 1.12)		
2.1 Investigational Medical Device	**1**	**2** *This column to be used only when > 1 study drug is indicated in section 1.13*
2.2 Approved name of the device		
2.3 Brand name (if any)	☐ Not Applicable	☐ Not Applicable
2.4 Intended use		
2.5 Strength/Sizes/ Models (if applicable)		
2.6 Device Class (As per NMRA classification) Class I ☐ Listed device ☐ Class II ☐ In vitro diagnostic device ☐ Class III ☐ Class IV ☐		
2.7 Are there any trials conducted for this device in foreign countries?	☐ Yes ☐ No	
2.8 For product registered in Sri Lanka, provide the product licence No.	☐ Not Applicable	☐ Not Applicable
2.9 Details of the Manufacturer	Name: Address:	

SECTION 2: STUDY BORDERLINE PRODUCT(S) TO BE INVESTIGATED (This will appear if tick "Borderline product" in 1.12)		
2.1 Investigational Borderline product	**1**	**2** *This column to be used only when > 1 study drug is indicated in section 1.13*
2.2 Active ingredient / generic name or code designation		
2.3 Brand name (if any)	☐ Not Applicable	☐ Not Applicable
2.4 Dosage form		
2.5 Strength		
2.6 Route of administration		
2.7 whether the product is classified as a borderline in NMRA ?	☐ Yes ☐ No	

2.8 Class of Study Drug Class I General sale Class IIA Pharmacy only Class IIB Prescription only		
	☐ Class I ☐ Class IIA ☐ Class IIB	☐ Class I ☐ Class IIA ☐ Class IIB
2.8 Are there any trials conducted for this device in foreign countries	☐ Yes ☐ No	
2.10 For product registered/classified in Sri Lanka, provide the product licence No.	☐ Not Applicable	☐ Not Applicable
2.11 Details of the manufacturer	Name: Address:	

SECTION 3: DETAILS OF PLACEBO (This will appear if tick "Placebo" in 1.13)		
3.1 Brand name (if any)	☐ Not Applicable	
3.2 Dosage form		
3.3 Route of administration		
3.4 Composition		
3.5 Details of Manufacturer	Name: Address:	

SECTION 3: COMPARATOR DRUG(S) TO BE USED IN CLINICAL TRIAL (Optional)	
☐ Not Applicable, check box here if no comparator drug is used	
3.1 COMPARATOR DRUG	**1**
3.2 Active ingredient / generic name or any code designation	
3.3 Brand name (if any)	☐ Not Applicable
3.4 Dosage form	
3.5 Strength	
3.6 Route of administration	
3.7 Pharmacological class	
3.8 Class of study drug	☐ Class II ☐ Class III ☐ Class IV
3.9 For Class III & IV study drug, state the countries in which the drug has been granted marketing authorisation	
3.10 For product registered in Sri Lanka, provide the product licence number	☐ Not Applicable

SECTION 4: CONCOMITANT DRUG(S) TO BE USED IN CLINICAL TRIAL (Optional)	
☐ Not applicable, check box here if no concomitant drug is used	
4.1 CONCOMITANT DRUG	**1**
4.2 Active ingredient / generic name or any code designation	
4.3 Brand name (if any)	☐ Not Applicable
4.4 Dosage form	
4.5 Strength	
4.6 Route of administration	
4.7 Pharmacological class	
4.8 For product registered in Sri Lanka, provide the product licence number	☐ Not Applicable

SECTION 5: INFORMATION ON LOCAL TRIAL CENTRE(S), PRINCIPAL INVESTIGATOR(S), AND RESPONSIBLE EC/IRB		
5.1	**Trial centre**	**Trial centre**
5.2 Name of trial centre		
5.3 Name of Principal Investigator		
5.4 SLMC reg number of PI		
5.5 Speciality / board certification		
5.6.1 Institution		
5.6.2 Department		
5.6.3 Address of institution		
5.7 Designation of PI		
5.8 Telephone number		
5.9 Fax number		
5.10 E-mail address		
5.11 Address of trial centre (if different from above listed institution)		
5.1	**Trial centre**	**Trial centre**
5.2 Name of trial centre		
5.3 Name of Principal Investigator		
5.4 SLMC reg number of PI		

5.5 Speciality / board certification		
5.6.1 Institution		
5.6.2 Department		
5.6.3 Address of institution		
5.7 Designation of PI		
5.8 Telephone number		
5.9 Fax number		
5.10 E-mail address		
5.11 Address of trial centre (if different from above listed institution)		
5.1	**Trial centre**	**Trial centre**
5.2 Name of trial Centre		
5.3 Name of Principal Investigator		
5.4 SLMC reg number of PI		
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5.6.1 Institution		
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5.6.3 Address of institution		
5.7 Designation of PI		
5.8 Telephone number		
5.9 Fax number		
5.10 E-mail address		
5.11 Address of trial centre (if different from above listed institution)		
5.1	**Trial centre**	**Trial centre**
5.2 Name of trial centre		
5.3 Name of Principal Investigator		
5.4 SLMC reg number of PI		
5.5 Speciality / board certification		
5.6.1 Institution		
5.6.2 Department		
5.6.3 Address of institution		
5.7 Designation of PI		
5.8 Telephone number		
5.9 Fax number		
5.10 E-mail address		

5.11 Address of trial centre (if different from above listed institution)		

Is a Contract Research Organisation (CRO) involved in the conduct of the clinical trial in Sri Lanka? ☐Yes ☐No

If Yes, has the CRO entered into a legal agreement with a recognized institution with clinical trial experience in Sri Lanka?

☐Yes☐No

If Yes to both, please complete section 6

SECTION 6: INFORMATION ON CONTRACT RESEARCH ORGANISATION (CRO)	
6.2.1 State the number of CRO(s) involved in this clinical trial:	
6.3.1 Company name	
6.3.2 Company address	
6.3.3 Telephone number	
6.3.4 Fax number	
6.3.5 Please list the types of services engaged and provide the following information	☐ Monitoring ☐ Data Management ☐ Central laboratory ☐Others (Please specify):
6.3.6 Is the CRO also the Local Sponsor for this Clinical Trial?	☐Yes ☐No

If there are more than one CRO involved in this clinical trial, please add rows for sections 6.3.1 to 6.3.6 here.

SECTION 7: SUPPORTING TRIAL DOCUMENTS
1. Detailed protocol *
2. Investigator's Boucher
3. Participants information sheets and Informed Consent Forms (submit in three languages)*
4. COA for investigational medicinal product (Please upload final product test report for medical device)*
5. GMP certificate and/or IMPD (investigational medicinal product dossier/device master file)*
6. ERC approval Letter
7. Insurance certificate
8. Acceptance of responsibilities *

9. CV's and latest GCP certificates of the investigator(s)*
10. Global status of the trial (please upload ERC details of other participating countries and regulatory approval of other countries, if available)
11. Case Report Forms and signature sheets
12. Samples of label(s) attached to IMP containers *
13. Lab manuals and pharmacy manuals
14. Material transfer agreement
15. List of medical devices used in the clinical trial
16. Records on retained samples (if any)
17. Justification for placebo (if any)
18. Any other documents

SECTION 8: Acceptance of responsibilities

The PI / National Coordinator should be a Sri Lanka based scientist.

As Coordinating Principal Investigator/ Principal investigator I undertake;

1.1. responsibilities for the research being conducted as described in this application and subject to any condition that may be imposed by the Regulatory Authority,
1.2. to ensure that the integrity and rights of any patient participating in the trial are not violated,
1.3. to ensure that the investigational product(s) are used only in accordance with the approved protocol,
1.4. that information would remain confidential and access to the information will be limited to authorized persons,
1.5. to manage code procedures and documentation with meticulous care,
1.6. to collect record and report data properly,
1.7. to ensure proper safety reporting procedures and to report any serious or unexpected adverse events occurring during the study to the Regulatory Authority,
1.8. to be medically responsible for those subjects who are under my care for the duration of trial and to ensure that appropriate medical care is maintained after the trial,
1.9. to ensure that suitable treatment will be provided in the case of a injury of a subject attributable to the clinical trial,
1.10. to notify any changes in the research protocol to the Regulatory Authority,
1.11. to submit a progress report when half way in the study to the Regulatory Authority,
1.12. to submit the final report of the trial to the Regulatory Authority irrespective of the outcome of the trial, and
1.13. To return unused investigational products to the Regulatory Authority or sponsor or destruct as per the protocol at the conclusion of the trial.

* Delete where applicable

_____
Signature

_____
Name (in block letters)

_____
Date

Contents to be included in the Clinical Trial Protocol

1.1 General Information

1.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
1.1.2 Name and address of the sponsor and monitor (if other than the sponsor).
1.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
1.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
1.1.5 Name and title, address, and telephone number(s) of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
1.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
1.1.7 Name(s) and address (es) of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

1.2 Background Information

1.2.1 Name and description of the investigational product(s).
1.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
1.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.
1.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
1.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
1.2.6 Description of the population to be studied.
1.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

1.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

1.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.
A description of the trial design, should include:
1.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
1.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
1.4.3 A description of the measures taken to minimize/avoid bias, including:
(a) Randomization.
(b) Blinding.

1.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
1.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
1.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
1.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
1.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.
1.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

1.5 Selection and Withdrawal of Subjects
1.5.1 Subject inclusion criteria.
1.5.2 Subject exclusion criteria.
1.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
(a) When and how to withdraw subjects from the trial/ investigational product treatment.
(b) The type and timing of the data to be collected for withdrawn subjects.
(c) Whether and how subjects are to be replaced.
(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

1.6 Treatment of Subjects
1.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
1.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
1.6.3 Procedures for monitoring subject compliance.

1.7 Assessment of Efficacy
1.7.1 Specification of the efficacy parameters.
1.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

1.8 Assessment of Safety
1.8.1 Specification of safety parameters.
1.8.2 The methods and timing for assessing, recording, and analysing safety parameters.
1.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
1.8.4 The type and duration of the follow-up of subjects after adverse events.

1.9 Statistics

1.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

1.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

1.9.3 The level of significance to be used.

1.9.4 Criteria for the termination of the trial.

1.9.5 Procedure for accounting for missing, unused, and spurious data.

1.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

1.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

1.10 Direct Access to Source Data/Documents.

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

1.11 Quality Control and Quality Assurance

1.12 Ethics

Description of ethical considerations relating to the trial.

1.13 Data Handling and Record Keeping

1.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

1.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

1.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

ANNEX III

Investigator's Brochure (IB)

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This document delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

1.2 Contents of the Investigator's Brochure

1.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

1.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

1.2.3 Table of Contents

1.2.4 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

1.2.5 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

1.2.6 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned.

1.2.7 Nonclinical Studies

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Nature and frequency of pharmacological or toxic effects

- Severity or intensity of pharmacological or toxic effects

- Time to onset of effects

- Reversibility of effects

- Duration of effects

- Dose response

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

i. Single dose.
ii. Repeated dose
iii. Carcinogenicity
iv. Special studies (eg: irritancy and sensitization)
v. Reproductive toxicity
vi. Genotoxicity (mutagenicity)

1.2.8 Effects in Humans

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans.

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related product.

A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

1.2.9 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The investigator should obtained with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

1.2.10 References on Publications and reports

These references should be found at the end of each chapter

Informed Consent Template

1. Checklist for study Subject's informed consent documents

1.1 *Essential Elements:*

1. Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the Subject's participation
3. Description of the procedures to be followed, including all invasive procedures and
4. Description of any reasonably foreseeable risks or discomforts to the Subject
5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.
6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
9. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the Subject for participating in the trial
12. Subject's responsibilities on participation in the trial
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled
14. Any other pertinent information

1.2 *Additional elements, which may be required*

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.
(b) Additional costs to the Subject that may result from participation in the study.
(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.
(d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.
(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus), if the Subject is or may become pregnant), which are currently unforeseeable
(f) Approximate number of Subjects enrolled in the study.

2. Format of informed consent form for Subjects participating in a clinical trial

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject's Initials/ NUMBER : _____ Subject's Name: _____

Date of Birth / Age: _____
Please initial box (Subject)

For further regulatory requirement on informed consent, please refer Part III of National Medicines (Clinical Trials) Regulations, October 2019

Annex V

Format of the contents published in the web on proceed clinical trials

Reference No.	Trial title	Principal investigator	Sponsor	Investigational product	Status of the trial/out come

Format and contents to be included in the study status reports of clinical trials

Date :
Study Code :
Protocol No :
Protocol Title :
Submitted by (name of Principal Investigator/s) :
Name and address of Trial sponsor :
Name and address of Contract Research Organization (if any) :
Name and address of Site management organization :

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Section II – safety update

Site number	Site name	Total No of SAE (time period/site)	Subject number	Details of the event	Relationship of the event	No. of times the event had occur

Declaration of the PI

Name of the PI

Designation

Date