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## **GUIDELINE FOR AMENDMENTS (CHANGES) TO CLINICAL TRIALS**

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NATIONAL MEDICINE REGULATORY AUTHORITY  
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# GUIDELINE FOR AMENDMENTS TO CLINICAL TRIALS

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## 1 PURPOSE

The aim of this guideline is to provide comprehensive guidance to assist clinicians, scientists, sponsors and research organizations to become familiar with the prerequisites and procedures relevant to implementing amendments to an approved clinical trial, particularly amendments to the clinical trial protocol or any other essential trial documents, changes to trial sites and/or investigators.

## 2 SCOPE

This guideline applies to documents and data submitted with the clinical trial application which require amendments prior to initiation of the trial or during the conduct of the trial. The guideline stipulates the type of changes that require prior approval of the National Medicines Regulatory Authority (NMRA) and type of changes which require notification

This guideline should be read in conjunction with the National Medicines (Clinical Trials) Regulations.

## 3 PROCEDURE

Amendments to a clinical trial either before initiation or during the conduct of a trial may be necessary. Amendments to clinical trials can be sponsor initiated or can be requested by the Authority.

These amendments may be simple modifications such as correcting errors in documents or substantial changes such as modifications to the study design. NMRA adopts different procedures in allowing sponsor-initiated changes depending on the significance of the change on the safety of the trial participants or the scientific validity of the clinical trial.

All amendments to a clinical trial shall be submitted to NMRA via eNMRA web portal <https://enmra.nmra.gov.lk/>. If there is a practical difficulty in submitting the amendment via eNMRA (e.g. amendments to clinical trial applications which were processed via manual route), they may be emailed or handed over as a hardcopy to the Clinical Trials Regulatory Division (CTRD) of the NMRA. The amended documents shall be submitted as soon as is practicable, unless timelines for submission are specified by NMRA.

### **3.1 Amendments recommended by the Clinical Trials Evaluation Committee (CTEC)/National Medicines Regulatory Authority (NMRA)**

The CTEC may require amendments to be made to the conduct of the trial to ensure compliance with Good Clinical Practice guidelines or to ensure the safety or scientific validity of the trials. Where an amendment is required, the NMRA will serve notice to the holder of the letter of authorization that a specified amendment is required within the stipulated timeline, and will give the reason for the proposed change.

The sponsor may make a written representation to the NMRA within the timeline, which may be taken into account in the final decision.

The recommendations for changes by the NMRA are usually made during the review of the clinical trial application. However, NMRA has the authority to make recommendations for changes to a clinical trial after initiation of the trial, especially in order to address urgent safety measures.

### **3.2 Amendments initiated by the sponsor/ principal investigator**

Amendments initiated by the sponsor should be communicated to the NMRA through the holder of letter of authorization. For academic trials without the involvement of a commercial sponsor, it is the holder of letter of authorization who initiates the change.

Amendments to approved trials should be submitted on the standard form 'Application for Amendments to a Clinical Trial' (see annexure I). Changes to documents should be accompanied by the updated version as well as a summary of changes in tabulated form. Ethics approval for the amendment if already obtained should be enclosed with the submission. Amendments which require prior approval of NMRA carry a processing fee as stipulated in the fees regulations of NMRA.

#### **3.2.1 Amendments to the clinical trial which do not require prior approval from NMRA**

Any amendment to a clinical trial protocol which relates only to administrative and logistic changes or minor amendments and additional safety assessments to which an Ethics Review Committee has already granted approval shall not require an approval of the Authority.

Any such amendments should be recorded accordingly and should be readily available for inspection at the trial site.

#### **3.2.2 Amendments to the clinical trial which shall be communicated as notifications.**

Any amendment to the clinical trial which relates to changes to the following shall be communicated as a notification to NMRA and the relevant ERC:

- inclusion of additional study sites;
- amendments which are made to the investigator's brochure (IB);
- amendments to the informed consent form (ICF) and the patient information sheet;
- change of a principal investigator if he is not the holder of the letter of authorization;
- recruitment of additional study participants

#### **3.2.3 Substantial amendments to the clinical trial which require prior approval of NMRA and the relevant ERC prior to implementation.**

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the clinical trials.

These amendments are regarded as "substantial" as they are likely to have a significant impact on the safety or physical or mental integrity of trial participants, or the scientific value of the clinical trial or the conduct or management of the clinical trial or the quality or safety of the investigational product used in the clinical trial.

The below examples of aspects of trials where amendments may need to be notified to NMRA & require prior approval of NMRA. There may be other aspects of the trial where amendments meet the criteria for substantial amendments.

- Changes to the medicinal products
- Dosage form or dose administered
- Changes to the pharmaceutical quality documentation of the IMP
- Changes to the manufacturing of the medicinal product that may affect the safety of the product
- Amendments related to the trial arrangement- Change of the coordinating principal investigator, change of sponsor or legal representative, Change of the CRO assigned significant tasks Change of the definition of the end of the trial

The following amendments require prior approval of NMRA and the relevant ERC before implementing the amendment:

- change of principal investigator if he is the holder of the letter of authorization for the clinical trial;
- substantial amendments to the protocol;
- changes to the investigational medicinal product that are likely to impact its quality and/or safety. E.g., change of manufacturer, change of shelf life

It is up to the sponsor to assess whether an amendment is to be regarded as substantial based on above criteria and to comply with the submission requirements. The sponsor shall consult NMRA for advice when in doubt.

After submission, the CTEC shall review substantial amendments to the protocol. NMRA shall approve, recommend further changes, or disallow the amendment with reasons to do so, based on CTEC recommendations.

### **3.3 Amendments to the Clinical Trial Protocol**

The clinical trial protocol may be amended if any amendments become necessary before initiation or during the conduct of a clinical trial.

The title page of the amended protocol should indicate the new version number, the date, and the number of the last version. In addition, each page must have “footers” indicating the current version number and date. The amended protocol should be agreed upon and signed by the persons who are signatories to the relevant protocol.

#### **3.3.1 Substantial amendments to the protocol**

Substantial amendments in the protocol could be the results of changes:

- to the purpose, design or methodology of the study, or to background information likely to have a significant impact on its scientific value;
- to the procedures undertaken by participants other than additional safety assessment to which ERC has already granted approval;
- likely to have a significant impact on the safety or physical or mental integrity of participants; or to the risk/benefit assessment for the study;

Prior approval of NMRA and the relevant ethics review committee should be obtained before implementation of a substantial amendment to the protocol.

### **3.4 Amendments to the Investigator’s Brochure (IB)**

The IB is required to be validated and updated at least once a year. Revisions should be clearly indicated and justified. Any specific change in the ‘expectedness’ of an adverse drug reaction including any increase in the specificity or severity of a previously expected reaction should be addressed in the reference safety information (RSI).

New information that might alter the perception of the trial and its risks, such as a serious finding must be communicated in writing to all investigators; the ethics review committee and NMRA. The new version of the IB should be distributed as soon as practical to all concerned.

Amendments to the IB should be notified together with the updated version and summary of changes. In addition to the title page, each page should indicate the version number and date in the “footer”. However, the amended IB does not require prior approval of the NMRA.

### **3.5 Amendments to study documentations such as patient information sheets, Informed Consent Forms (ICFs), questionnaires etc.**

Changes to study documents such as patient information sheets and consent forms may be necessary due to various reasons which include minor changes such as correction of spelling or grammatical errors and alterations necessitated due to administrative changes.

Also, the sponsor may require introducing new site-specific information sheets and ICFs when a new trial site is added to an approved trial.

Also, there may be substantial changes to the information sheets and ICFs resulting from changes to the protocol or IB.

The amended versions of these study documents shall be submitted as notification with track changes and relevant ethics approvals.

### **3.6 Urgent safety measures**

Occasions may arise to take urgent safety measures to protect clinical trial participants against any immediate hazards where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the participants.

Safety measures such as temporarily halting the clinical trial may be taken without prior approval of NMRA but must be reported to NMRA and the relevant ERC. The sponsor should notify NMRA in writing no later than three days after the measure was taken. The notification should specify the measures taken, reasons, and plan for future actions. An application for amendment detailing changes to clinical trial documents should be submitted to NMRA as soon as possible.

The restart of the trial should be treated as a substantial amendment with evidence provided that it is safe to restart the trial.

In cases of high risks to participants, review of a substantial amendment may be expedited by NMRA for safety reasons. The full committee of the CTEC shall assess the decision taken under expedited review at its next scheduled meeting.

### **3.7 Timelines for submission of amendments**

All amendments requested by sponsor should be submitted through eNMRA, or where applicable may be handed over manually or emailed to CTRD as described previously.

Maximum number of days to review an amendment: 30 days

Maximum number of days to inform decision given by CTEC to principal investigator: 07 working days

Urgent Safety measures such as temporarily halting the clinical trial may be taken without prior approval of NMRA but must be reported to NMRA. The principal investigator should notify NMRA in writing no later than three days after the measure was taken.

## **4 DEFINITIONS**

### **Amendment**

A change to any term of an application for certification to conduct a clinical trial; or any particulars or documents (including a protocol) accompanying that application

### **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

### **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.

### **Good Clinical Practices (GCP) Guidelines**

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;

### **Investigational Medicinal Product (IMP)**

Any pharmaceutical product including medicine, pharmaceutical device, borderline product or placebo being tested or used as a reference in a clinical trial.

### **Investigator’s 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.

### **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.

**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.

**Protocol Amendment**

A written description of a change(s) to or formal clarification of a protocol

**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.



## 5 ANNEX

### Submission form

#### Annex I

##### Application for amendments to a clinical trial

###### 1 Details of the trial

- I. NMRA reference number of the clinical trial [Click here to enter text.](#)
- II. Title of the Trial  
[Click here to enter text.](#)

###### 2 Details of holder of letter of authorization

- I. Name [Click here to enter text.](#)
- II. Designation [Click here to enter text.](#)
- III. Address [Click here to enter text.](#)
- IV. Contact Number [Click here to enter text.](#)
- V. Email [Click here to enter text.](#)

###### 3 Details of contact person

- I. Name [Click here to enter text.](#)
- II. Address [Click here to enter text.](#)
- III. Contact Number [Click here to enter text.](#)
- IV. Email [Click here to enter text.](#)

###### 4 Purpose of Submission *(Please tick a box)*

- Submission of a notification
- Submission of a substantial amendment
- Submission of urgent safety measure
- Answer to NMRA's request dated [Click here to enter a date.](#)

###### 5 Information regarding the submission

Regarding  
[Click here to enter text.](#)

Rationale/ Information

[Click here to enter text.](#)

###### 6 List of documents appended to the form

*Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es)*

- Cover letter

- Extract from amended document
- Entire new version of the document (Title, version & Date)
- Summary of Changes in tabulated form
- Entire document with track changes (Colour print out)
- Supporting information/Documents

**7 Mandatory additional information regarding the submission of an investigator’s brochure**  
*(Only filled if an investigator’s brochure is submitted)*

**I. Risk/Benefit statement**

Click here to enter text.

**II. The IB update has impact on study documents**

- Yes (If yes list documents)
- No

The following documents will be updated  
 Click here to enter text.

**8 Signature of the applicant**

I hereby confirm on behalf of the sponsor that,

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

.....  
 Signature

.....  
 Date

**6 RELATED LEGISLATION AND REFERENCES**

- National Medicine Regulatory Authority Act No. 05 of 2015
- National Medicine (Clinical Trials) Regulations 2145/2, 14th October 2019
- Guide to clinical trial applications, Health Products Regulatory Agency, Ireland, 21 October 2019
- Substantial protocol amendments, MHRA, United Kingdom
- Guidance on determining whether an amendment to a clinical trial is a substantial amendment, HSA Singapore, 02 May 2017