GUIDELINE ON NON-ROUTINE PROCESSING OF CLINICAL TRIAL APPLICATIONS AND CONDUCT OF CLINICAL TRIALS DURING EMERGENCY SITUATIONS

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NATIONAL MEDICINE REGULATORY AUTHORITY
Norris Canal Rd, Colombo 01000, Sri Lanka

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1. INTRODUCTION

A new medicine must be proven to be therapeutically effective and safe before being licensed for human use. In general, it takes about 12 years for a new drug to progress from laboratory discovery to get approval for marketing authorization. A significant portion of this drug development timeline is spent on clinical phases in order to gather extensive efficacy and safety data.

There may be particular (desperate) situations where rapid access to new therapies need to be made faster than routine timelines. In such situations, NMRA may process clinical trial applications in an expedited manner, in order to ensure medicines that could save or dramatically improve patients' lives are available as soon as possible. Similarly, NMRA may apply the non-routine process for clinical trials involving medical devices or borderline products with claims of breakthrough therapies

Regulation 10 in part I of Clinical Trials Regulations No. 2145/2 of 2019.10.14 provides NMRA the authority for expedited processing of clinical trial applications for therapies with potential to address unmet medical needs, especially during a national epidemic, a global pandemic or other similar emergency situations.

2. PURPOSE

This guideline describes the categories of non-routine processing relevant to clinical trial application, applicable eligible criteria, and procedure of review process by NMRA. This procedure also aims to reduce clinical trial authorisation application processing times.

3. SCOPE

The non-routine route of processing targets medicines that are intended to treat a serious condition or which data demonstrate potential clinical benefits and presents no more than minimal risk to study participants.

There are two methodologies used by NMRA for non - routine processing of clinical trial applications.

i. Expedite review procedure
ii. Conduct of clinical trials in emergency situations

If a clinical trial fulfils eligible criteria for non-routine processing, NMRA may proceed with expedited review of the relevant clinical trial application. The process will include pre-review of the submission on priority basis and fast-track review of the application by one or two assigned specialist reviewers instead of convened CTEC review, in order to achieve shortened timelines.

Conducting clinical trials for life- threatening situations may be possible determining whether a condition is serious and whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, and if left untreated, will progress from a less severe condition to a more serious one. This guideline also provides guidance for life-threatening situations, during which the study subjects are unable to give consent due to their medical conditions, to follow consenting procedure as described in 'clinical trials in emergency situations' in order to protect the rights, safety and well-being of the subjects.

4. PROCEDURE

The procedure for expedited review is optional, based on voluntary approach by applicants and will be considered on a case by case basis based on the benefit – risk consideration. The applicant may make a written request to NMRA to consider the clinical trial application for expedited review with supporting data.
It is the responsibility of the principal investigator / sponsor to maintain appropriate records, in a timely manner, of all changes described in the trial master file.

4.1 Qualifying criteria

A clinical trial will qualify for expedited review under non-routine procedures if the following criteria are fulfilled;

1) The investigational medicinal product (IMP) is intended to treat a serious or life-threatening condition
2) Available data on the IMP demonstrate the potential to address an unmet medical need especially during a national epidemic, a global pandemic or other similar emergency situations.
3) Available treatments for the indication are unproven or unsatisfactory
4) Risks associated with the clinical trial are reasonable in relation to expected clinical benefits.

The IMP of the clinical trial may be an Investigational New Drug (IND) or a medicine already approved for a different indication(s). Also, the same criteria shall be applied to all applications irrespective of them being local or multinational trials or whether they are conducted by the government or the private sector.

4.2 Submission requirements

- The applicant must meet the qualifications and requirements of principal investigator or in the case of multicentre studies, coordinating principal investigator or national coordinator as defined in Clinical Trials Regulations.
- The clinical trial application shall contain complete and accurate information of all required particulars and shall furnish all applicable materials specified for submission with each application.
- If applicable, the application shall be accompanied by a fee specified in Fees Regulations.
- Ethics approval for the trial by a NMRA recognized ERC shall be submitted prior to issue of letter of authorization.

4.3 Expedited review procedure

- Upon receipt of the application with a request from the applicant for expedite review, CTRD will assess the eligibly of the application for expedited review. Also, pre-review or screening of the submission to assess completeness will be done on priority basis.
- The CTRD may request for more information from the applicant during the pre-review process for clarification or completeness of the application.
- Once the application is considered complete, CTRD will decide whether the submission should be subjected to expedited review or routine review by CTEC. The decision will be communicated to the applicant electronically.
- The Chairman CTEC will assign the protocol for expedited review to one or two experienced specialist reviewers in the CTEC.
- The review may be assigned to a specialist outside CTEC if appropriate expertise on the relevant medical condition is not available within the CTEC.

- The reviewer(s) may request for more information or require modification to the submitted material during this initial review process.
- The applicant may respond to reviewer's recommendations within specified timelines by complying or by providing justification for not doing so. The time taken to respond will be considered as stop-clocks.
- The responses will be reviewed by the designated reviewer and will communicate his recommendation to the CTRD.
- CTRD will communicate the final decision on the application to the applicant. NMRA will issue the letter of authorization, if the reviewer has recommended the trial to proceed and ethics approval for the trial has been granted by a recognized ERC.
- CTEC will be informed of the decisions taken relevant to applications processed or under processing via expedited review route, at its ensuing meetings. The CTEC may recommend for further review of the application if it is not in agreement with the preceding decision.
- In such an eventuality, CTEC may request for further information or modifications to the proposal from the applicant.
- NMRA has the authority to suspend a letter of authorization issued via expedited review process pending conclusion of the CTEC review or to cancel the letter of authorization based on CTEC recommendation, in terms of regulations 12 and 13 of the Clinical Trials Regulations.
- All communications between CTRD, the reviewers, the applicant, and if necessary, with the ERC will be done electronically, in order to expedite relevant processes.

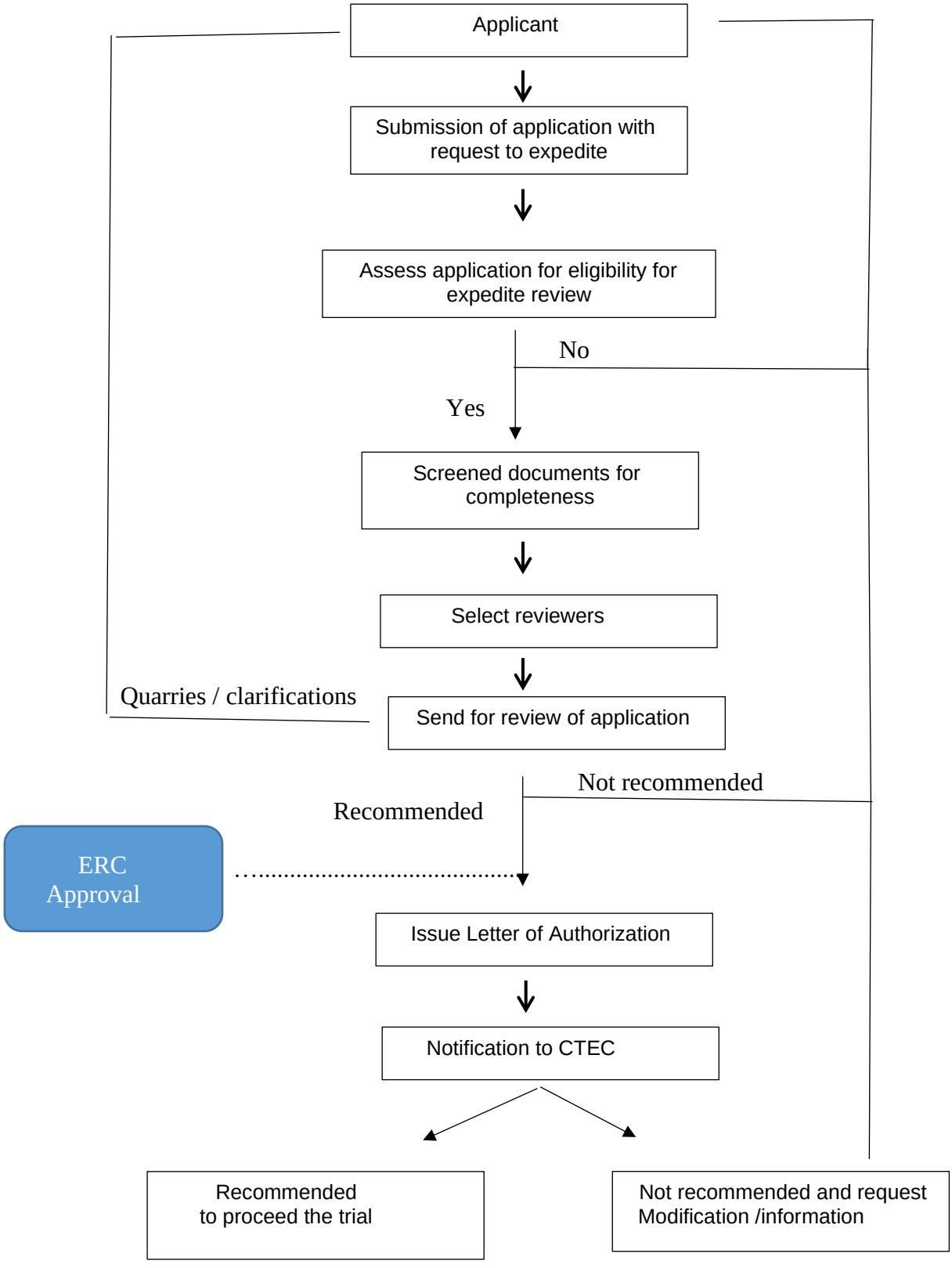

Figure 1: Flow chart for expedite review

4.4 Conduct of clinical trials in emergency situations

In emergency situations, when prior informed consent or assent in children of the study subject is not possible, and the subject's legally acceptable representative is not available, enrolment of subjects should follow procedures described in the protocol and/or elsewhere, with approval by NMRA and ERC.

The following procedure shall be followed:

- As defined in ICH GCP guidelines, a clinical trial in an emergency situation should not be conducted except with the prior approval of the NMRA.
- In order for NMRA to approve a clinical trial to be conducted in emergency situations, the principal investigator and two specialists who are not involved in the trial should certify in writing that:
  a) The clinical trial needs to be conducted on a person who is in a life-threatening situation to determine the safety and efficacy of the IMP;
  b) Available treatments are unproven or unsatisfactory;
  c) There is a reasonable prospect that participation in the clinical trial will directly benefit the person because –
     the person is facing a life-threatening situation that necessitates intervention, appropriate pre-clinical studies have been conducted and there is evidence to support the potential for the proposed use of the IMP to provide a direct benefit to the individual subjects, and risks associated with the clinical trial is reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of the standard therapy if any, and what is known about the risks and benefits of the proposed use of the IMP;
  d) The person is unable to give consent as a result of his medical condition;
  e) It is not feasible to request consent from the person or to contact his legal representative with the window period in which the treatment must be administered;
  f) Neither the person or his legal representatives nor members of his family has informed the principal investigator of his objection to that person being used as a study participant in the clinical trial;
  g) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical trial; and
  h) The clinical trial could not practically be carried out if the consent referred to in part III of the Clinical Trials Regulation must be obtained

At the earliest feasible opportunity, the study participant or his legally acceptable representative should be given a full and reasonable explanation and consent to continue and other consents as appropriate should be requested.

Procedure described in 4.3 under expedite review shall be applied for the processing of applications.

4.5 Timelines for processing via expedited procedure

The objective is to make a decision in a maximum of 30 days (including time for stop-clocks) after receipt of a complete clinical trial application, and payment of the processing fee if applicable. These timelines are purely administrative targets of the NMRA and may deviate especially for advance therapy medicinal products such as products derived from cell or tissue engineering and gene therapy products.

Step	Target timelines	Deliverables
Pre-review by CTRD	02 days	Notification of the acceptability to the applicant via Email
Initial review	10 days	Sending review comments (if any) to the applicant via Email
Applicant's response	07 days	Submission of answers/clarifications to CTRD via Email
Final evaluation	07days	Notification of the final decision to the applicant via Email

5. ABBREVIATIONS

CTEC – Clinical Trials Evaluation Committee
CTRD – Clinical Trials Regulatory Division
ERC – Ethics Review Committee
ICH – International Conference on Harmonisation
IMP – Investigational Medicinal Product
IND – Investigational New Drug
GCP – Good Clinical Practices
NMRA – National Medicines Regulatory Authority

6. DEFINITIONS

Expedite review
A process where the approval time taken to review a clinical trial have been shortened where rapid access to new therapies need to be made faster than routine timelines to save or dramatically improve patients' lives are necessary.

Informed Consent
A process by which a subject voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Investigational Medicinal Product (IMP)
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.

Legal Representative
An individual or juridical or other body authorized under law to grant consent on behalf of that person, to the participation of such person in the clinical trial.

Protocol
A document that describes the study design, methodology, objectives, statistical considerations, and organization of a clinical trial. It also usually gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Study Participant/Subject
An individual who participates in a clinical trial either as a recipient of the IMP or as a control.

Vulnerable Subjects
A category of study participants whose willingness to participate in a trial are likely inclined to coercion or undue influence. Examples include children, mentally disabled persons, prisoners, groups with hierarchy structures such as medical and pharmacy students, subordinate hospital and laboratory staff, and members of armed forces.

Well-being (of the trial subjects)
The physical and mental integrity of the subjects participating in a clinical trial.

7. RELATED LEGISLATION AND DOCUMENTS

- National Medicine (Clinical Trials) Regulations 2145/2, 14th October 2019
- Guideline for Expedited Review of Research, University Rochester, 15th March 2019
- Singapore Guideline for Good Clinical Practice, Ministry of Health, Singapore
- Medicines (Clinical Trials) Regulations, HSA Singapore
- Medicinal Product & ATMP CT-FAST-TRACK procedure guide, ANSM France

8. FEEDBACK

Staff and stakeholders may provide feedback about this document by emailing pathmaperuma.a@nmra.gov.lk

Next Review Date	09/08/2022