Supplementary Temporary Guidance to Conduct Clinical Trial of Medicinal products on COVID-19 Pandemic

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1. INTRODUCTION

In Ethiopia, Clinical trial conducted on human participants are under the mandate of Ethiopian Food and Drug Authority (EFDA) as indicated in the proclamation No. 1112/2019 and Regulation No. 299/2013. These activities include evaluation of protocols; authorize the trial to be conducted and oversight clinical trial once the trial is initiated. To implement such mandate the authority has developed using "Clinical Trial Authorization Guideline, 2nd edition, 2017" and "Good Clinical Practice Guidelines, 2nd edition, 2018".

The World Health Organization (WHO) has declared a devastating pandemic disease called COVID-19 which spreads with an alarming speed which challenges the stable supply of medicines. Currently, there is no specific vaccines and medicines used for prevention and treatment of COVID-19, respectively. However, clinical trials are being conducted on immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab, and traditional Chinese medicines (TCM). In addition, WHO is currently advocating "Solidarity" clinical trial for COVID-19 treatments so as to save the life of the public.

Despite the need for the simplified and coordinated approach, there are various challenges regarding how to conduct the clinical trials considering the current COVID-19 pandemic situation. These includes restrictions of visits to healthcare facilities, increased demands on the health service, existence of complex requirements across countries and requirement of trial participants to self-isolate, which create difficulties for Investigators to maintain their medical oversight.

In Ethiopia, the available guidelines and legislations are for conducting normal clinical trials which are not suitable for clinical trials to be commenced for emergency situations such as COVID-19. Hence, with the objective to support, promote, and accelerate trials of vaccines and/or medicinal products against COVID-19, the Authority publishes this supplementary guidance for clinical trials to be conducted in Ethiopia. This supplementary guidance document clearly outlines the requirement for facilitated protocol reviews and authorization of clinical trial conducted in country.

2. REQUIREMENTS TO SUPPORT CLINICAL TRIALS FOR COVID 19

2.1. General Requirements

All clinical trials involving investigational products carried out in the territory of the country must be reviewed by the EFDA for use of the investigational products or intervention in human subjects to ensure that the protocol is appropriately designed to meet its stated objectives. The general requirements for clinical trial authorization are indicated in the Clinical Trial Authorization Guideline, 2nd edition, 2017 of the Authority. However, the below specific modifications and/supplements are outlined to facilitate the rapid response for the conduct of the clinical trial in this supplemental guideline Ethiopia. Therefore, the requirements indicated below are intended to encourage the investigator/Sponsor/CRO who conducts clinical trial on investigational products for treatment and prevention of COVID-19 disease.

2.2. Fast-track procedure for review of application for the conduct COVID-19 clinical trial

EFDA supports the submission of clinical trial protocols (including multi-centered trials) on the investigation products intended for treatments and prevention of COVID-19. Sponsors are encouraged to consider the submission of such applications for a fast-track (accelerated) assessment. The Authority will provide absolute priority for applicationsto conduct clinical trials for the prevention or treatment of COVID-19 and COVID19- related illnesses.To facilitate the review process, the investigator/sponsors/CRO is required to submit high quality, clear, complete well structured dossiers to the Authority as per the Clinical Trial Authorization Guideline of the Authority. This will allow most efficient review by the Authority and National Research Ethical Review Committee (NREC).

2.3. Parallel Review Process

Clinical trial studies will be reviewed parallelly by the National Research Ethical Review Committee of Ethiopia (NRERC) and Institutional Review Board as well as the regulatory authorityApproval letters will be no more a prerequisite forregulatory submission part of clinical trial application. This abbreviated procedure is devised to avoid the delay of the approval process

of clinical trials aiming for research on prevention or treatment of COVID-19 and COVID-19 related illness. Hence, he Authority encourages simultaneous or parallel submissionof applicationsto the ethical committees and authority. Efforts will also be made for joint review with the ethical committees.

2.4. Review process

Normally the review process of clinical trial application was conducted by the clinical team of Authority staff in a way that first come first serve fashion, rarely need engagement of external experts and partnership with other organization (such as academia, research institutes, NGO etc). This has its own impact on time to the approval of the clinical trial conducted in country. However, in response to the current situation of COVID-19 pandemic, the Authority will provide maximum efforts to shorten timeframe and ensure a time-sensitive response for review of clinical trial applications.

To achieve this and expedite the review process, the Authority will conduct the following activities:

a) Explore all options including the use of phone or online meetings to discuss on protocols with investigators or sponsor and provide informal feedback. The Authority also will respond quickly to protocol amendments as necessary.
b) The Authority will improve on collaborative work with selected local academics or local NGOs and engagement of experts with the relevant experience and expertise in reviewing clinical trial protocols.
c) Depending on the available safety and efficacy preclinical data of investigational products (IPs) during laboratory experimentations and/or animal studies as well as strong evidences and experiences from other countries and/or recommendations to initiate clinical trials on IPs from Stringent Regulatory Agencies (SRA) including WHO, the Authority may give an approval to conduct clinical trials in humans without going through the conventional stages of clinical trials.
d) Research during this pandemic often involves many organizations and countries, and multiple reviews. Multiple reviews of multi-country protocols present an opportunity to complement review process through sharing experiences of different countries, with the

potential for mutual learning. Therefore, as per the article…of proclamation 1112/2019, the authority will explore the mechanisms for regional (multi-country) ethical review consultations to support the expedited approval for clinical trials being conducted or planned to be conducted in multiple countries

2.5. Informed Consent form

To initiate a trial aiming to test new treatments or prevention for COVID-19, Sponsor or Investigator or CRO should sought advice on alternative procedures to obtain informed consent, as it is likely that getting informed consent physically may not possible for the prospective participant will not be able to leave the isolation room, and therefore will not appropriate for trial documentation.

However, the following specific aspects should be taken into account with trials involving COVID-19 patients.

a) If getting written consent from the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the trial participant in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent document and the investigator is expected to record how the impartial witness was selected. This could also be supported by audio recording of the consent giver.
b) In addition, it could be considered that the trial participant and the person obtaining consent sign and date separate informed consent forms. In either case, all relevant records should be archived in the investigator site's Trial Master File. A correctly signed and dated informed consent form should be obtained from the trial participant later, as soon as possible.
c) Where potential COVID-19 trial participants lack capacity to consent due to the severity of their medical condition, or when minors are included, proxy consent has to be obtained from the legal representative(s).
d) In case of acute life-threatening situations, where it is not possible within the therapeutic window to obtain prior informed consent from the participants (or her/his legal representatives(s)), informed consent will need to be acquired later in such cases, the

investigator is expected to record why it was not possible to obtain consent from the participant or legal representatives prior to enrollment.

2.6. Investigational Products (IPs).

In principle, the sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP. However, the authority may waive good manufacturing practice (GMP) in such emergency situation. Instead of requesting GMP compliance certificate of manufacturers of IP(s), the Authority may focus on other quality assurance system. This includes, supporting document for meeting minimum regulatory requirements of the country of origin, testing of the product in its laboratory, and/or relay on certificate of analysisfrom otheraccredited laboratories, etc which ever appropriate.

2.7. Import Permit of IP

The availability of investigational products is paramount important for timely completion of clinical trial. In these circumstances, the Authority will provide support to the sponsor and/or investigators for approval and facilitate the importation and distribution of investigator products. Applicant can refer Annex IV of Clinical Trial Authorization guideline 2017 of the Authority for required documents for import permit of investigational product.

2.8. Laboratory testing of IP

The Authority may conduct laboratory test on the IP if Good Manufacturing Practice (GMP) manufacturers is not provided. In such circumstances the applicant is requested to submit;

a) Adequate sample for the laboratory tests

b) Reference standards,

c) Test methods (part of dossier)

3. REQUIREMENTS GOOD CLINICAL PRACTICE ON CLINICAL TRIALS FOR COVID 19

The general requirements for Good Clinical Practice are indicated in the Good Clinical Practice Guidelines, 2nd edition, 2018of the Authority. However, the below specific modifications and/supplements are outlined to facilitate the rapid response during the conduct of the clinical trial on the prevention or treatment of COVID-19 and COVID-19 related illnesses in Ethiopia. To support investigator/Sponsor/CRO who conducts clinical trial on investigational products intended for treatment and prevention of COVID-19, the Authority indicated below the challenges and the specific responses (requirements):

- Participants in the trial may be required to self-isolate, which introduces difficulties for Investigators to maintain their medical oversight. Therefore, the investigators may use tele or video conversions in place of physical visits and ensure that only strictly necessary visits are performed at sites.
- Changes to informed consent: The informed consent procedure in trials needs to remain compliant with the trial protocol. During the conduct of the trial, the informed consent form procedure needs to be in consistent with "2.6 Consent form" of this supplementary document.
- Change in monitoring: Certain sponsor oversight responsibilities, such as monitoring and quality assurance activities may be modified based on specific nature of COVID-19, alternative proportionate mechanisms of oversight may be required. This may include; Implementing phone and video visits (without increasing burden to the investigator site and taking into account trial participant integrity), Adapting the on-site monitoring plan, Remote source data verification (e.g. providing sponsor with copies of medical records or remote access to electronic medical records) etc.

Reference

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- Rosa SGV and Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Rev PanamSaludPublica. 2020;44:e40. https://doi.org/10.26633/RPSP.2020.40
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- Clinical Trial Authorization Guideline, 2nd Edition, June 2017, EFDA, Addis Ababa Ethiopia.
- Good Clinical Practice Guidelines, 2nd Edition, April 2018, EFDA, Addis Ababa, Ethiopia.