Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority

2022

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1. Introduction:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The Arab Republic of Egypt has adopted the ICH GCP guidelines since 2006 by the effect of ministerial decree No. 436/2006 for biological products followed by ministerial decree No. 734/2016 for pharmaceutical products. In addition, ministerial decree No. 399/2010 for biological products and ministerial decree No. 132/2017 for pharmaceutical products were regulating the evaluation of clinical trials and were implemented by the National Organization for Research and Control of Biological Products (NORCB) and the National Organization for Drug Control and Research (NODCAR) respectively.

Egyptian Drug Authority (EDA) has replaced NORCB and NODCAR through Law No. (151) for year (2019). EDA is engaged in a close collaborative effort with other regulatory authorities where there is strong coordination between all bodies responsible for enforcing laws and regulations relating to biological products, pharmaceutical products, innovative products, medical devices, and herbal medicines to ensure that the principles of GCP are applied.

This guideline was developed with consideration of the current good clinical practices and international regulations regarding the clinical trial data that are intended to be submitted to the Egyptian Drug Authority.

This guideline should be read in conjunction with Clinical Trials Law 214/2020 and its executive regulation and international GCP Guidelines according to ICH E6 and WHO guidelines and their updates.

This guideline outlines clinical trial package application of all types of IMP, any further specific guidance will rely on this guideline and must be read in conjunction with it.

The General Administration of Clinical trials (GA of CT) is the body responsible for the regulatory oversight of clinical trials through review & evaluation of the submitted preclinical

and clinical data, conducting scientific committee(s), and providing technical support to those who request it and is responsible for conducting GCP inspections. See figure (1)

Figure (1) GA of CT organizational diagram

The administration of Clinical Trials Evaluation in GA of CT is responsible for all tasks related to the review and the evaluation of clinical and pre-clinical studies through the purpose of registration, re-registration, or variations submitted to EDA in the Common technical document (CTD).

The administration of Protocols & Studies Follow-up in GA of CT is responsible for all tasks related to the supervision and follow-up of clinical medical research that is conducted in the Arab Republic of Egypt. The administration implements its responsibilities through the evaluation of preclinical and/or previous clinical studies results for biological, pharmaceutical, herbal medicine, and innovative investigational medicinal products as well as medical devices; evaluation of the submitted research plan (protocol) for clinical medical research in all its phases and/or its amendments, in order to issue a decision (approval or refusal) to conduct the clinical medical research. Furthermore, the administration receives periodic progress follow-up and safety reports during the study and conducts GCP inspections on all entities related to the clinical medical research to ensure adherence to the principles of Good Clinical Practice. In addition, the administration is responsible for receiving and evaluating the interim and the final clinical study reports and overseeing that the study is completed within the clinical research sites.

The administration of Scientific Committees and Technical Support in GA of CT is responsible for all tasks related to EDA's advisory scientific committee for preclinical and clinical studies evaluation, technical support assistance through receiving technical support requests for evaluation, organizing and conducting the required support, and follow-up and update EDA decisions (regulations) and guidelines that regulate clinical medical research in accordance with the international standards of GCP.

For all general inquiries, please contact us at *Ct.scts@edaegypt.gov.eg*

2. Legal Provisions:

2.1. EDA Establishment Law No. 151 for year 2019.

2.2. Executive regulation No.777/2020 of Law no. 151 for year 2019.

2.3. The Egyptian Clinical Trials Law No. 214/2020.

2.4. Executive regulation no.927/2022 of Law No. 214 for year 2020.

2.5. EDA Chairman Decree No 111 for year 2022.

3. Scope:

This Guideline demonstrates for applicants how the national GCP regulations are carried out in Egypt with clear application submission steps at different developmental phases of the investigational medicinal product.

This guideline applies to all interventional medical research conducted in Egypt that are involving human participants, i.e., healthy volunteers or patients. Including all interventional medical research that uses new investigational pharmaceutical or biological medicinal products, new indications, new dosage forms, new medical devices, and herbal medicinal products –that have never been used before in the human body and that have not been accredited by international bodies.

For other interventional medical research and non-interventional clinical trials, the relevant IRB approval is considered final and EDA should only be notified.

4. Abbreviations:

- **ADR:** Adverse Drug Reaction
- **AE:** Adverse Event
- **Bio-Inn:** CA of Biological and Innovative Products and Clinical Studies.
- **CAPA:** Corrective Action and Preventative Action
- **CIOMS:** The Council for International Organizations of Medical Sciences.
- **CMC:** Chemistry, manufacturing and controls
- **Co-PI:** Co-Principal Investigator
- **CRF:** Case Report Form
- **CRO:** Contract Research Organization.
- **CSR:** Clinical Study Report
- **CT:** Clinical Trial
- **CTA:** Clinical Trial Authorization.
- **DSMB:** Data & Safety Monitoring Board.
- **DSUR:** Development Safety Update Report
- **EDA:** Egyptian Drug Authority
- **FIH:** First in Human.
- **GA of CT:** General Administration of Clinical trials
- **GCP:** Good Clinical Practice
- **IB:** Investigator's Brochure
- **ICH:** International Council of Harmonization
- **IEC:** Independent Ethics Committee
- **IMP/IP:** Investigational Medicinal Product.
- **IMPD:** Investigational Medicinal Product Dossier
- **IRB:** Institutional Review Board.
- **MD:** Ministerial Decree.
- **MOH**: Ministry of Health
- **NODCAR:** National Organization for Drug Control and Research.
- **NORCB:** National Organization for Research and Control of Biologicals.
- **NRA:** National Regulatory Authority
- **PASS/PAES:** Post-Authorization Safety and Efficacy Studies
- **PI:** Principal Investigator.
- **REC:** Research Ethics Committee.
- **SAE:** Serious Adverse Event.
- **SOP:** Standard Operating Procedure
- **SUSAR:** Suspected Unexpected Serious Adverse Reaction
- **WHO:** World Health Organization.

5. Definitions:

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 product" 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.

Adverse Event (AE): any minor and medically unwanted effects that are recently experienced by the research subject during the administration of the research intervention on the research subject.

Amendment: A written description of a change(s) to or formal clarification of a clinical trial package.

Applicant: Researcher, Principal Investigator (PI), Study Sponsor or Contract Research Organization (CRO)

Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit report: A written evaluation by the sponsor's auditor of the results of the audit.

Blinding/Masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), the investigator(s), the monitor(s), and, in some cases the data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

Clinical Medical Research: Studies or experiments conducted on human volunteers to evaluate the safety and efficacy of any therapeutic, medicinal, surgical, nutritional, preventive, or diagnostic interventions with the aim of arriving at scientific preventive,

diagnostic, or therapeutic discoveries for diseases, as well as, studies conducted for medical data mining for volunteers to survey the feedback of the effect of a medicine, behavior, or surgical intervention in accordance with internationally recognized research ethical standards.

Clinical Trial Site / Research Entity: The entity that conducts the medical research, which is registered with the supreme council (once established).

Clinical Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted on human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator: An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Contract Research Organization (CRO): A Body corporate that assumes the form of an organization, office, or company, that is registered with the supreme council (once established) and licensed to conduct medical research. The sponsor executes contracts with CRO to perform any of the duties or tasks of the medical research assigned to the research sponsor. In this regard; CROs are subject to periodic and regular supervision of the supreme council (once established).

Control Group: A group of research subjects who do not receive the medical intervention researched; but rather receive what is called a "Placebo" or standard treatment for the purpose of comparison and measurement of the effect of the new intervention.

Co-Principal Investigator (Co-PI): A person with the same qualification as the principal investigator assigned by the latter to carry out some of his duties under his supervision. The co-principal investigator replaces the principal investigator in case of the latter's absence or inability to continue performing the research duties.

Critical GCP Finding(s): Conditions, practices, or processes that adversely affect the rights, safety, or well-being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or

record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Good Clinical Practice (GCP): A set of internationally and domestically recognized principles and standards that apply to planning, management, execution, monitoring, auditing, recording, analysis, and reporting on medical research for the purpose of providing assurances that research declared data and results are precise and credible and ensure the safety of research subjects and their rights and confidentiality of their information against any harm.

Human Samples: include all biological materials from human origin; including organs, tissues, body fluids, teeth, hair, fingernails, as well as, tissues regenerated from the cells extracted from human bodies, and materials isolated from a cell such as nucleic acids, ribosomes, etc.

Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing a favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

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

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

Institutional Review Board (IRB): A group of persons with medical and non-medical specializations tasked with the duty of reviewing research plans (Protocols) and applying the necessary ethical principles in this regard. The institutional Review Board shall have its headquarters at the research entity and must be registered with the supreme council (once established).

Interim Clinical Study Report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Interventional Medical Research: a study in which the research subject is incorporated to receive medical intervention for the purpose of evaluating the effect of such intervention on medical results in terms of effectiveness and safety.

Investigational Medicinal Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigational Medicinal Product Dossier (Quality Dossier): The file which includes information concerning methods of formulation, manufacturing, and developing medical intervention under study in accordance with Good Manufacturing Practice, alongside the information concerning raw materials used, quality control tests, stability and potency of batches used in the clinical medical research.

Investigator's Brochure: A compilation of the clinical and pre-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Major GCP Finding(s): Conditions, practices, or processes that might adversely affect the rights, safety, or well-being of the subjects and/or the quality and integrity of data. Major observations are serious findings and are direct violations of GCP principles.

Minor GCP Finding (s): Conditions, practices, or processes that would not be expected to adversely affect the right, safety, or well-being of the subjects and/or the quality and integrity of data.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Nonclinical Study/Pre-clinical Research: Research conducted at an early experimental stage prior to trials on humans, which aims to specify the degrees of safety and effectiveness of the medical intervention to be studied. Pre-clinical research is conducted through in vitro tests or using experimental animals in accordance with the prescribed international standards in pre-clinical research.

Non-Interventional Medical Research: a study in which the research subjects record their remarks for the purpose of gathering information on an approved medical intervention or health history of the research subject.

Placebo: An inert product that has no therapeutic effect and completely resembles the product subject of research in form but does not contain the active substance.

Principal Investigator: A person qualified in the field of clinical medical research and responsible for the research plan and the execution and funding thereof in case there was no sponsor available for the medical research

Protocol: A document that includes a detailed explanation of the research plan for conducting medical research and relevant information that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial.

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities: Bodies having the power to review submitted clinical data, giving the decision of approval or refusal on conducting clinical trials, and those that conduct inspections.

Reliance: The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution or to any other authorities' information in reaching its own decision. The relying authority remains independent, responsible, and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

Research or Medical Intervention: The core of the clinical medical study, which includes medical interventions such as medications, medical devices, vaccines, interferential procedures to the human body, and other products that may be scope for testing or already available. Research intervention may also include ways that don't interfere with the human body such as health surveys, education, and questionnaires.

Research Group: a group of qualified researchers working in the field of medical research and taking part in the research works based on their qualifications and expertise.

Research Sponsor: A party that assumes responsibility for initiating, management, funding, and supervision of medical research; whether this party is an actual person such as the principal investigator or a body corporate such as a company, institution, domestic, regional, or international organization, provided, however, it is legally represented in the Arab Republic of Egypt.

Research Subject: A person subject of medical research who participates in the research whether that person is a patient or a healthy person and whether they are subject to medical intervention or part of the control group. In all cases; on the condition of obtaining the informed consent of the research subject before conducting the research pursuant to the provision of this law.

Serious Adverse Events : Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect or important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require

intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Serious Adverse Drug Reaction: Serious Adverse Events if suspected to be medicinal product-related.

Serious Breach: Any deviation from the approved protocol version or from the principles of GCP that is likely to affect the safety, rights of trial participants, and/or data reliability and robustness to a significant degree in a clinical trial.

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Supreme Council for Review of the Ethics of Medical Clinical Research (The Supreme Council): The council comprises a group of persons with medical and non-medical specializations who are entrusted with the duty of establishing and following up on the general policies applicable to conducting medical research. It is referred to hereinafter as "The Supreme Council".

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 product or package insert/summary of product characteristics for an approved product)

Vulnerable Subjects: research subjects who are most vulnerable to coercion or exploitation due to limitations on their will to give knowledgeable consent due to complete or partial incapacitation, poor cognitive power, or health condition.

6. Objective:

This guideline is intended to fulfill the roles assigned to the Egyptian Drug Authority in Clinical Trials Law no. 214/2020 and its Executive regulation no.927/2022 and to provide advice for the applicants on the format, submission steps, timelines, and content of the information to be submitted in the following roles:

a) Evaluating the results of pre-clinical and clinical medical research

b) Carrying out the scientific review of the medicinal or biological product prior to the clinical medical research.

c) Evaluating the Research Plan (Protocol) and amendments conducted thereto, and review the documents of the investigational product subject of the medical research in an endeavor to ensure the accomplishment of the GCP, proper manufacturing, marketing, and storage.

d) Conducting inspection of the clinical medical research site(s) and other relevant entities in which clinical medical research is carried out for the purpose of verifying GCP.

This guideline also describes the responsibilities of the Sponsor and the Principal Investigator according to Egyptian Clinical trials Law no. 214/2020 and Good Clinical Practice (GCP).

Also, this guideline outlines the information required by the Egyptian Drug Authority from applicants wishing to conduct clinical medical research and defines the evaluation and follow-up process of clinical medical research in Egypt.

7. Clinical Trials Regulatory Oversight:

7.1 GCP Principles

EDA is adopting the Principles of GCP according to ICH E6 and WHO Guidelines and all their Updates that are described as follows:

a) Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

b) Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

c) The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

d) The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

e) Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

f) A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

g) The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

h) Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

i) Freely given informed consent should be obtained from every subject prior to clinical trial participation.

j) All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

k) The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

l) Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

m) Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

7.2. Submission and Evaluation of Preclinical Results before First in Human Clinical Trial (FIH)

7.2.1 Screening:

- The applicant should submit the preclinical package data to Bio-Inn, according to the list of required documents (See Template Forms 9.1), via e-mail (bio.ct@edaegypt.gov.eg) with proof of payment of the determined fees for screening.
- The submitted documents will be screened and reviewed within 5 days.
- Any missed documents &/or required clarifications will be sent to the applicant via e-mail.
- The applicant shall fulfill the requirements within 15 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, the submission shall be cancelled and the applicant will be informed via email. In this case, the applicant can resubmit the package for re-screening with new fees after at least one month from the date of cancelation email.
- The applicant's reply to the requirements will be screened within 5 days. In case all requirements are fulfilled, the applicant will be notified of acceptance of the preclinical package via e-mail.

7.2.2. Submission:

- In order to proceed to official submission, the applicant should submit the complete screened package with proof of payment of the determined fees. This should be done within 10 days from the acceptance email; otherwise, the screening will be canceled.
- The clock of the process will start from the official submission of proof of payment.

7.2.3. Evaluation:

- The submitted preclinical data and results will be scientifically evaluated according to national and international guidelines. Any requirements and/or clarifications, raised during

the in-depth scientific evaluation or after peer review by EDA's advisory scientific committee, will be sent to the applicant.

- The applicant should respond to the requirements within 15 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, a decision will be taken regarding this issue according to EDA's regulations.

7.2.4. EDA Final Decision:

EDA's final decision of refusal or approval (final approval or conditional approval in case of further requirements) will be issued within 60 days with considering stopping the clock in case of requirements raised during the evaluation process. EDA's decision in case of refusal should be reasoned. EDA is committed to inform the applicant of its decision within 30 days of its issuance.

7.3. Submission & Evaluation of Clinical Trials' Protocol &/or Amendments

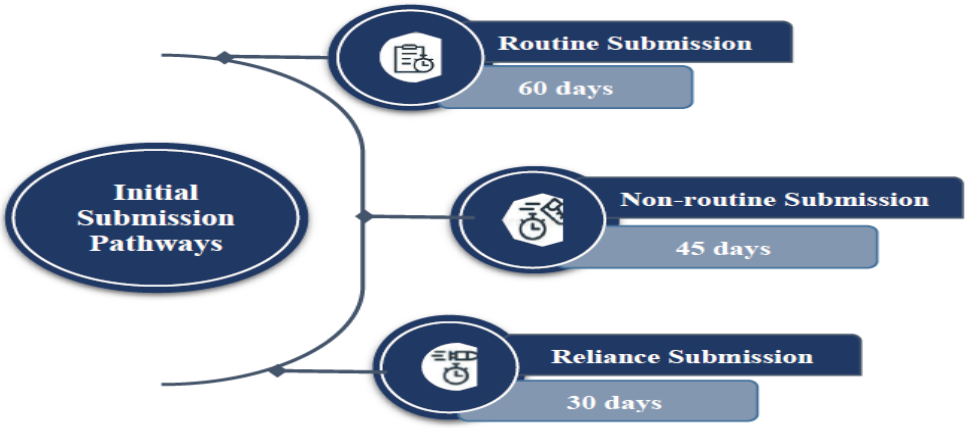


Figure (2) Different submission pathways timelines

For more clarification of different timelines of each submission pathway see (Annex III)

7.3.1. Routine Submission of Clinical Trials' Protocol:

7.3.1.1 Screening:

- The applicant should fill the Application form (See Template Forms 9.2.) and submit the clinical trial package, according to the list of required documents (See Template Forms 9.3.) to Bio-Inn as a soft copy via e-mail (bio.ct@edaegypt.gov.eg) with proof of payment of screening fees.

- The submitted documents will be screened and reviewed within 5 days.
- Any missed documents and/or required clarifications will be sent to the applicant via e-mail.
- The applicant shall fulfill the requirements within 15 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, the submission shall be canceled and the applicant will be informed via email. In this case, the applicant can resubmit the package for re-screening with new fees after at least one month from the date of cancelation email.
- The applicant's reply to the requirements will be screened within 5 days. In case all requirements are fulfilled, the applicant will be notified of acceptance of the clinical trial package via e-mail.

7.3.1.2. Submission:

- In order to proceed to official submission, the applicant should submit the screened complete CT package with the proof of payment of the determined fees. This should be done within 10 days from the acceptance, otherwise, the screening will be canceled.
- The clock of the process will start from the official submission of proof of payment.

7.3.1.3. Evaluation:

- The submitted previous studies' results (if any) and the clinical trial package will be scientifically evaluated according to national and international guidelines.
- The quality dossier (IMPD) will be evaluated by the relevant administration.
- Any requirements and/or clarifications, raised during the in-depth scientific evaluation or after peer review by EDA's advisory scientific committee, will be sent to the applicant.
- The applicant shall respond to the requirements within 15 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, a decision will be taken regarding this issue according to EDA's regulations.
- In the case of locally manufactured products or products imported from non-reference countries, the GMP certificates and the quality module (CMC) will be sent from Bio-Inn to the Central Administration of Operations to carry out GMP inspection (if required).
- If the IMP is authorized in Egypt, a commitment letter from the sponsor, that there is no difference between the IMP used in the clinical trial and the authorized one regarding the quality specifications of the drug product, drug substance, and packaging will be required. If

there is a difference between the IMP used in the clinical trial and the authorized one, a table of changes should be submitted.

- If the IMP is authorized in a reference country, in addition to the full quality dossier (IMPD), it is required to submit a commitment from the sponsor that there is no difference between the IMP used in the clinical trial and the authorized one regarding the quality specifications of the drug product, drug substance, and the packaging. If there is a difference between the IMP used in the clinical trial and the authorized one, a table of changes should be submitted along with the full-quality dossier.

7.3.1.4. EDA Final Decision:

- EDA's decision regarding the previous studies' results (if any) will be issued before the decision regarding the clinical medical research protocol.
- EDA's final decision of refusal or approval (final approval or conditional approval in case of further requirements), regarding the clinical trial package, will be issued within 60 days with considering stopping the clock in case of requirements raised during the evaluation process. EDA's decision in case of refusal should be reasoned.
- Bio-Inn's decision will be sent to the Central Administration of Pharmaceutical Policies and Market Access in case of imported products.
- In all cases EDA's final decision will be sent to the applicant via email and the applicant can receive the original document from Bio-Inn.
- After EDA's final approval, any change in the clinical trial package from the IRB-approved one, due to EDA requirements and regulations, all concerned IRB(s) should be notified by the applicant.

7.3.2. <u>Non-Routine Submission Pathway:</u>

- Exceptional procedures and measures other than the routine procedures of assessment and evaluation of a clinical trial package could be taken by EDA to support the expedited authorization of a clinical trial (such as parallel submission or any other measures accepted by EDA).
- Parallel submission means the submission of the clinical trial package to EDA in parallel with its submission to the IRB.

- If the clinical trial application requires the non-routine submission, this should be stated in an appeal with a rationale for the parallel submission. The appeal should be sent to Bio-Inn via email (bio.ct@edaegypt.gov.eg)
- In case the appeal is accepted, the applicant will be notified via e-mail to proceed to the parallel submission for screening and evaluation as described in section 7.3.1
- The involved IRB(s) approval(s) should be submitted to EDA before the issuance of EDA's final decision.

7.3.2.1. Cases of non-routine submission may be:

a. In case of pandemic spread or public health emergencies "internationally or domestically"
b. Unmet Medical Need
c. Drug Intended to Treat a Serious Condition such as:

- A diagnostic product intended to improve the diagnosis or detection of a serious condition in a way that would lead to improved outcomes
- A product intended to mitigate or prevent a serious treatment-related side effect (e.g. serious infections in patients receiving immunosuppressive therapy)
- A product intended to avoid or diminish a serious adverse event associated with available therapy for a serious condition (e.g., a product that is less cardiotoxic than available cancer therapy)
- A product intended to prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition or a more advanced stage of the disease

d. Any other cases that EDA deems eligible based on updated current situation. (In such cases the Non-Routine Submission appeal will be raised to the head of Bio-Inn.)

7.3.2.2. EDA Final Decision:

- EDA's final decision of refusal or approval (final approval or conditional approval in case of further requirements), regarding the clinical trial package, will be issued within 45 days with considering stopping the clock in case of requirements raised during the evaluation process. EDA's decision in case of refusal should be reasoned.
- In all cases EDA's final decision will be sent to the applicant via email and the applicant can receive the original document from Bio-Inn.

7.3.3. Reliance Submission Pathway:

- EDA has the right to rely on rules, reports, and data of regulatory authorities in reference countries "List of reference countries" (see References 8.10) through the reliance pathway in order to adopt a decision concerning the assessment and approval of the submitted clinical medical research to be conducted in Egypt. Reliance on the aforementioned bodies' decisions will neither diminish EDA's independency nor its responsibility for the issued decision.
- Any clinical trial cannot be considered for reliance assessment if this clinical trial at any stage, has already been rejected, suspended, or put on hold due to any reason, by any of the reference countries' authorities and it shall be rejected during the screening process.
- For safety, efficacy, or quality concerns, EDA reserves the right to transfer the application to the regular pathway during screening or evaluation processes. However, EDA commits to clarify the decisions for such cases.
- EDA reserves the right to subject the reliance submission of a certain part of the application for further assessment (according to local conditions) such as product quality data in relation to climatic conditions, distribution infrastructure, and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.

7.3.3.1. Screening:

- The applicant should fill the Application form (see Template Forms 9.2) and submit the clinical trial package, according to the list of required documents (see Template Forms 9.4), to Bio-Inn as a soft copy via e-mail (bio.ct@edaegypt.gov.eg) with proof of payment of the relevant screening fees.
- The submitted documents will be screened and reviewed within 5 days.
- Any missed documents and/or required clarifications will be sent to the applicant via e-mail.
- The applicant shall fulfill the requirements within 15 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, the submission shall be considered null and void and the applicant will be informed via email. In this case, the applicant can resubmit the package for re-screening with new fees after at least one month from the date of screening rejection.

- The applicant's reply to the requirements will be screened within 3 days. In case all requirements are fulfilled, the applicant will be notified of acceptance of the clinical trial package via e-mail.

7.3.3.2. Submission:

- In order to proceed to official submission, the applicant should submit the screened complete CT package with proof of payment of the determined fees. This should be done within 10 days from the acceptance, otherwise, the screening will be canceled.
- The clock of the process will start from the official submission of proof of payment.

7.3.3.3. Evaluation:

- The submitted previous studies' results and the clinical trial package will be scientifically evaluated according to national and international guidelines.
- In case of IMP(s) that are not authorized in Egypt, the applicant should submit the quality data (IMPD) to be sent to the concerned administration as per the reliance requirements of this administration. Any raised requirements during the quality data evaluation will be sent to the applicant.
- Any requirements and/or clarifications, raised during the scientific evaluation or after peer review by EDA's advisory scientific committee, will be sent to the applicant.
- The applicant shall respond to the requirements within 15 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, a decision will be taken regarding this issue according to EDA's regulations.
- In case of products imported from non-reference countries, the GMP certificates and the quality module (CMC) will be sent from Bio-Inn to the Central Administration of Operations to carry out GMP inspection (if required).
- If the IMP is authorized in a reference country, in addition to the full quality dossier (IMPD), it is required to submit a commitment from the sponsor that there is no difference between the IMP used in the clinical trial and the authorized one regarding the quality specifications of the drug product, drug substance, and the packaging. If there is a difference between the IMP used in the clinical trial and the authorized one, a table of changes should be submitted along with the full-quality dossier.

- If the IMP is authorized in Egypt, only commitment from the sponsor, that there is no difference between the IMP used in the clinical trial and the authorized one regarding the quality specifications of the drug product, drug substance, and packaging, will be required. If there is a difference between the IMP used in the clinical trial and the authorized one, a table of changes should be submitted.

7.3.3.4. EDA Final Decision:

- EDA's decision regarding the previous studies' results will be issued before the decision regarding the clinical medical research protocol.
- EDA's final decision of refusal or approval (final approval or conditional approval in case of further requirements), regarding the clinical trial package, will be issued within 30 days with considering stopping the clock in case of requirements raised during the evaluation process. EDA's decision in case of refusal should be reasoned.
- EDA's decision will be sent to the Central Administration of Pharmaceutical Policies and Market Access.
- In all cases EDA's final decision will be sent to the applicant via email and the applicant can receive the original document from Bio-Inn.
- After EDA's final approval, any change in the clinical trial package from the IRB-approved one, due to EDA requirements and regulations, all concerned IRB(s) should be notified by the applicant**.**

7.3.4. Amendment submission:

- It is mandatory to obtain EDA approval before implementing any amendment to the approved clinical trial protocol except when it is necessary to eliminate an immediate hazard to human subjects.
- Annex I is a non-exhaustive list of examples for substantial and non-substantial amendments.
- The applicant should notify EDA of any changes to the approved protocol or its related documents by an official e-mail to (bio.ct@edaegypt.gov.eg) including a "notification letter".

The notification letter should include the following information:

- The applicant's name,
- The protocol title,
- The protocol number,

- The public registry identification number,
- Description of the amendment.

- A reply will be sent to the applicant regarding the submitted notification within 5 days to be either;

I. Notified; no need to be submitted, or
II. Notified and could be implemented till the submission of the amendment.
III. Notified and should be submitted as an amendment to be approved before implementation.
IV. In case the amendment is implemented to eliminate immediate hazards to human subjects, EDA should be notified with a written full explanation within 24 hours of the implementation then it should be submitted as an amendment.

- The amendment submission should be within 30 days from the notification date.
- The applicant can submit an amendment only after obtaining EDA's approval for the initial protocol submission except when the required changes/modifications are requested by EDA during the evaluation of the submitted clinical trial package.
- In case of any change in the submitted CT package before obtaining EDA's approval. EDA should be consulted on case-by-case bases for how to proceed with these changes.
- Amendments are classified as substantial or non-substantial on a case-by-case basis:
  - Cases to be considered as substantial amendments: Modifications to the clinical trial protocol, objective(s), location, and others that are likely to have a significant impact on the safety, physical or mental integrity of the subjects, the scientific value of the trial, the conduct or the management of the trial, the quality or safety of the IMP.
  - Otherwise, are considered non-substantial.
- For amendment official submission, the applicant should submit the amendment package with proof of payment of the determined fees via email (bio.ct@edaegypt.gov.eg) according to the amendment list of requirements (see Template Forms 9.5)
- For amendment official submission in case of reliance, the applicant should submit the amendment package with proof of payment of the determined fees and via email (bio.ct@edaegypt.gov.eg) according to the amendment list of requirements in case of reliance (see Template Forms 9.6)

- The submitted amendment will be scientifically evaluated according to national and international guidelines. Any requirements and/or clarifications, raised during the in-depth scientific evaluation or after peer review by EDA's advisory scientific committee, will be sent to the applicant.
- The applicant should respond to the requirements within 15 days (10 days in case of reliance). This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, a decision will be taken regarding this issue according to EDA's regulations.
- EDA's final decision of refusal or approval (final approval or conditional approval in case of further requirements) will be issued within 60 days for substantial amendment(s) and within 15 days for non-substantial ones, with considering stopping the clock in case of requirements raised during the evaluation process. EDA's decision in case of refusal should be reasoned.
- In case of the amendment through the reliance pathway, EDA's final decision will be issued within 30 days for substantial amendment(s) and within 15 days for non-substantial ones.
- After EDA's final approval, any change in the clinical trial package from the IRB-approved one, due to EDA requirements and regulations, all concerned IRB(s) should be notified by the applicant.

7.3.5. Annual EDA's Approval Renewal:

- EDA's Approval of the CT package is valid for one year through which the applicant shall initiate the study (or else delay should be justified).
- A renewal request should be submitted to EDA at least one month before the end of validity.
- The Applicant should send a renewal request to Bio-Inn according to the list of the required documents (See Template Forms 9.7) & submit it as a hard and soft copy via official e-mail (bio.ct@edaegypt.gov.eg) with proof of payment of the determined fees.
- EDA's approval renewal will be issued within 30 days with considering stopping the clock in case of requirements raised during the evaluation process.
- N.B.: The 30 days starts from date of payment.

7.4. Initiation of the Study and Reporting from the Applicant

7.4.1. Clinical Medical Research Site Activation:

The applicant shall notify Bio-Inn via e-mail (bio.ct@edaegypt.gov.eg) by the dates of the involved sites' activation in advance.

If the study sites were activated without notifying Bio-Inn/EDA, a decision will be taken regarding this issue according to EDA's regulations which may lead to study suspension.

7.4.2. Periodic Reports/Progress Reports:

The applicant shall submit progress follow-up reports, to Bio-Inn via email (bio.ct@edaegypt.gov.eg), using the template "Follow up template" (see Template Forms 9.8)

• Every 4 months (from EDA approval date)

• Annual progress reports. (Third progress report every year)

It is allowed to have a maximum of 30 calendar days after the data lock point (The date (month and day) designated as the cut-off for data to be included in the progress report) of the reporting interval to prepare and submit the progress reports.

7.4.3. Interim Clinical Study Report:

The applicant shall submit an interim clinical study report if applicable as per protocol including interim results of the clinical medical research conducted in Egypt.

7.4.4. Destruction of IMP and Surplus Human Samples:

7.4.4.1.Destruction inside Egypt:

• The applicant should notify Bio-Inn upon planning for IMP or surplus human samples' destruction by submitting all required documents via e-mail (bio.ct@edaegypt.gov.eg) see (Figure (2))

• The required documents are:

- The IMP accountability and reason for destruction,
- The records of IMP quantities and batches that will be destructed,
- The Ministry of Environment accreditation certificate for the vendor or the site at which the destruction will take place (in case of IMP and/or human samples destruction)
- The contract with the vendor at which the destruction will take place (in case of IMP and/or human samples destruction)

• The Central Administration for Operations will contact the applicant for the arrangement of the destruction process in the presence of one of EDA's inspectors.

• After completion of the destruction process, the applicant should send the destruction documented evidences and certificate of destruction via e-mail (bio.ct@edaegypt.gov.eg).

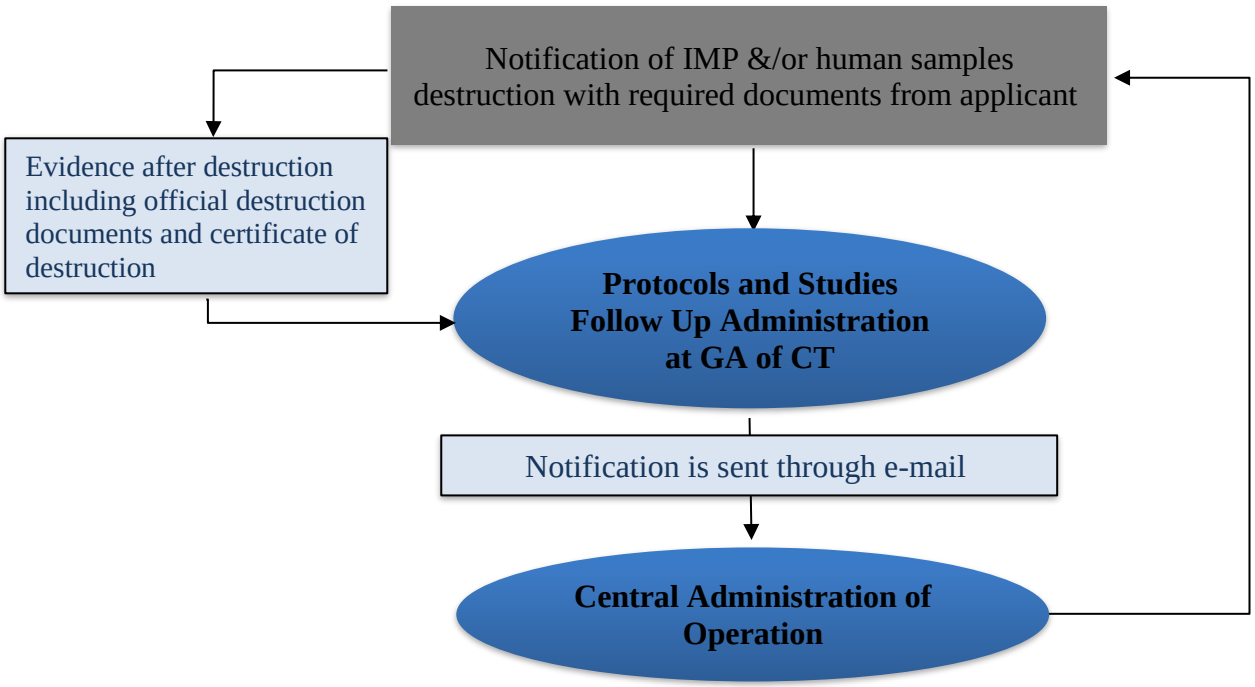


Figure (3) Flow chart for IMP & Human samples destruction process

N.B: The IMP destruction involves all kinds of IMP packages (Used, Unused, Expired, and Empty packages).

7.4.4.2.Destruction outside Egypt:

In case of exporting unused IMP, the following are required:

- Bill of lading for exported IMP.
- A commitment that the sponsor is responsible for the IMP destruction.

7.5. Safety Reporting

7.5.1. Intensity of Adverse Event or Adverse Drug Reaction:

The following are the most common practice unless otherwise specified in the protocol:

• **Grade 1- Mild**: Transient events, requiring no special treatment and not interfering with patient's daily activities

• **Grade 2- Moderate**: Events introducing some level of inconvenience and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures (may include drug therapy)

• **Grade 3- Severe**: Unacceptable or intolerable events, significantly interrupting patient's normal life and requiring systemic drug therapy or other treatment.

7.5.2. Serious Adverse Event or Adverse Drug Reaction:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

• Results in death,

• Is life-threatening,

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

• Requires inpatient hospitalization or prolongation of existing hospitalization,

• Results in persistent or significant disability/incapacity, or

• Is a congenital anomaly/birth defect.

• Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

7.5.3. Causality Assessment Criteria:

The following are the most common practice unless otherwise specified in the protocol:

• **Certain:** A clinical event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. Response to withdrawal plausible (pharmacologically, pathologically).

• **Probable/Likely:** a clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinical plausible response on withdrawal through de-challenge (this term is used when the suspected drug is discontinued, withdrawn, or dose reduced due to adverse event).

• **Possible:** A clinical event with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

• **Unlikely:** A clinical event with a temporal relationship to drug administration that makes a causal relationship improbable (but not impossible), and in which other drugs, chemicals, or underlying disease provide more plausible explanations.

• **Un-assessable:** A report suggesting an adverse drug reaction, which cannot be judged because the information is insufficient or contradictory and which cannot be supplemented or verified.

• **Not Related:** An adverse event, which is definitely not related causally to drug administration.

- **In case of vaccines** "Causality assessment of an adverse event following immunization (AEFI)" Should be followed.

7.5.4. Reporting Procedure:

7.5.4.1. Safety Reporting Procedure:

- The PI is responsible for reporting all Serious Adverse Events to Bio Inn within the specified timelines see (Annex IV). However, the PI can delegate this task to the sponsor or CRO. This delegation and the communication regarding safety reporting between the PI and the sponsor or CRO should be submitted to Bio-Inn via e-mail (bio.ct@edaegypt.gov.eg).

➢ Fatal or life-threatening serious adverse events, whether expected or unexpected should be notified within 24 hours starts from the site is notified of the event. The immediate notification should contain the following information:

- The study number,
- The site number and name,
- The subject's identification number,
- The investigational medicinal product
- The date of the serious adverse event occurrence,
- Description of the SAE,

- This immediate notification should be followed by an initial, as complete as possible report, using CIOMS form and XML format, within 7 calendar days starts from the site is notified of the event. The initial report should include:
  - Causality assessment,
  - A narrative about all diagnostic tests and examinations performed, treatment procedures, and medications administered to the study participant to the date of the report,
  - Expectedness of the serious adverse event,
  - The Outcome.
- The initial report should be followed by the follow-up report using CIOMS form and XML format whenever further information becomes available.

➢ Non-fatal, non-life threatening serious adverse events, whether expected or unexpected should be notified to EDA as soon as possible and not later than 7 calendar days starts from the site is notified of the event. This expedited notification should contain the following information:

- The study number,
- The site number and name,
- The subject's identification number,
- The investigational medicinal product,
- The date of the serious adverse event occurrence,
- Description of the SAE,
- The severity of the SAE,
- Causal Relationship and Expectedness of the SAE

- The notification should be followed by as complete as possible report within additional 8 calendar days using CIOMS form and XML format. This report should include:
  - Causality assessment,
  - A narrative about all diagnostic tests and examinations performed, treatment procedures, and medications administered to the study participant to the date of the report,
  - Expectedness of the serious adverse event,
  - The Outcome.
- Follow-up reports using CIOMS form and XML format should be submitted whenever further information becomes available.

- In the case of a serious adverse event that was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, it should be reported within 24 hours after the PI became aware of the event being fatal or life-threatening.
- Follow-up reports of serious adverse events should be submitted until the resolution of the event and the recovery of the study participant.
- For local non-serious adverse events, Line Listing should be submitted along with the progress follow-up report.
- 6 Months Line listing of global SUSARs should be reported as long the clinical medical research is authorized in Egypt even if it is not started yet.
- The annual Development Safety Update Report (DSUR) should be submitted.
- **N.B: Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial, for instance:**

  a) New events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects, such as:

  - A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
  - A major safety finding from a newly completed animal study (such as carcinogenicity)
  - Any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same sponsor, this should be notified within 7 days.

  b) Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects,

  c) Post-study SUSARs that occur after the patient has completed a clinical trial if reported to the investigator by the subject.

7.5.4.2. Serious Breaches Reporting Procedure:

- Serious breaches of the approved protocol and/or the GCP principles should be notified by the sponsor or the delegated party (CRO), to Bio-Inn, via email (bio.ct@edaegypt.gov.eg), without undue delay and at the latest within 7 days of the sponsor becoming aware of a serious breach. Updates to the serious breach can be made whenever further information becomes available.
- Serious breaches of the approved protocol and/or the GCP principles as well as protocol deviations shall be submitted in the progress follow-up reports and the annual reports as well.

7.6. End of Clinical Medical Research

- The definition of the End of Clinical Medical Research should be clearly described in the protocol.
- Any change to the End of Clinical Medical Research definition, after EDA's approval has been issued, should be notified as an amendment.
- The applicant should notify Bio-inn by the end of clinical medical research at local sites and global sites (in case of international studies) via e-mail (bio.ct@edaegypt.gov.eg).
- A summary of the Clinical Medical Research's outcome, all information, data, and related reports should be submitted, as a preliminary report, to Bio-Inn via e-mail (bio.ct@edaegypt.gov.eg), within 60 days from the end of the clinical medical research till the issuance of the final CSR.
- The final CSR should be submitted to Bio-Inn, within 12 months of the study completion, for reviewing and evaluation along with the payment of the relevant evaluation fees and a notification with EDA`s decision will be sent to the applicant within 60 days.
- Any retained human samples are not allowed to be used for possible future research without granting approval from the concerned bodies. In this case, the use of the retained human samples should be within the terms of separate consent from the participant or the participant's legal representative.
- The research sponsor is committed to provide the medical intervention to the participants after the medical research completion if the following apply:

- it is reasonable to expect that it will be possible to give the study intervention safely after the study;
- it is reasonable to expect a clinical benefit;

•The research findings, whether positive, negative, neutral, or inconclusive should be published and made accessible after the End of Clinical Medical Research.

7.7. Early Termination or Withdrawal of the Study by the Sponsor

- In case of trial premature termination or suspension for any reason by the sponsor, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and as per applicable regulatory requirement(s), should inform Bio-Inn in a formal letter via email (bio.ct@edaegypt.gov.eg) within 15 days**.**
- The applicant may request the withdrawal of his protocol/ amendment before/after EDA's approval is issued, then a formal letter of withdrawal providing a brief description of the reasons must be submitted to Bio-Inn via email (bio.ct@edaegypt.gov.eg).
- The applicant may re-submit the application, in this case, it must be identified as a resubmission in the Application Form (see Template Forms 9.2) and the changes as compared to the original submission should be marked.

7.8. Suspension or Termination of the Study by EDA

EDA has the right to suspend or terminate clinical medical research that has been granted approval to be conducted in Egypt for any reasons concerning GCP non-compliance, GMP non-compliance, non-compliance with the protocol, or SUSARs.

The decision of suspension or termination will be issued after holding a scientific committee (if needed) and will be raised to the head of Bio-Inn for final approval.

The applicant will receive an email to be informed of EDA's decision.

7.9. Inspection of Clinical Medical Research

The Egyptian Drug Authority is responsible for inspecting research sites in which the clinical medical research is conducted as well as other related entities with a view to verify compliance with GCP. For this purpose, EDA has the right to accomplish the following:

1- Preparing an inspection plan on the research sites in which the research is conducted as well as other related entities
2- Examining and reviewing the documents, installations, records, and other sources related to clinical medical research.
3- Ensuring the research protocol implementation and verifying GCP compliance.
4- Ensuring the application of the domestically and internationally recognized standards of GCP.
5- Monitoring any observations or violations, and preparing a report of the inspection findings.
6- Following up and assessing the periodic reports concerning the clinical medical research under study.

The inspection plan for clinical medical research is prepared according to risk based approach. EDA may conduct an inspection at any stage of the clinical medical research whether **before study initiation**, **during study conduction** or **after the end of the study** to ensure compliance with GCP guidelines.

7.9.1. Inspection Plan Notification:

7.9.1.1. For Routine Inspection:

- The applicant will be notified within two weeks before the proposed date of inspection.
- The applicant should confirm the availability of the PI and/or Co-PI(s) and other study personnel (required as per the scope of inspection) at the proposed date.
- Upon affirmation, the inspection agenda and confirmation letter will be sent to the PI through the applicant.

7.9.1.2. For Triggered Inspection:

In the case of triggered inspection, the applicant may be notified within 24 hours before the inspection date.

7.9.1.3. For Follow up Inspection:

Follow-up inspection can be carried out either to ensure the corrective action(s) &/or preventive action(s) implementation or after any applied amendments approved by EDA.

The applicant will be notified within one week before the proposed date of inspection.

7.9.2. Inspection Report:

The inspection report will be sent to the applicant within 15 days after the inspection.

The findings in the inspection report are classified into critical, major, or minor.

• **Critical GCP findings**, Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data, and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

• **Major GCP findings**, Observations classified as major may include a pattern of deviations and/or numerous minor observations.

• **Minor GCP findings**, Observations classified as minor indicate the need for improvement of conditions, practices, and processes. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences

7.9.3. Corrective Action and Preventive Action (CAPA) Plan:

The applicant shall prepare the corrective and preventive actions plan (See Template Forms 9.9) within 20 days from receiving the inspection report from EDA then, in case of delay two acceleration letters of 5 days interval will be sent to the applicant. Otherwise, the issue will be raised to the Head of Bio-Inn.

7.10. Technical Support for Preclinical and Clinical Trials

- Technical support of preclinical and clinical data can make the evaluation easier and quicker because the evidence is likely to be more robust, appropriate, and complete, but it does not affect the stringent assessment of safety and efficacy.
- Applicants are advised to comply with the technical support approach see (Annex V), therefore, enhancing the chances of submission of preclinical results and clinical trial(s) application but it does not guarantee it.

7.10.1. Submission:

The applicant shall fill the Application form (See Template Forms 9.10) and send it with the technical support data and proof of payment to Bio-Inn as hard and soft copy via e-mail (ct.scts@edaegypt.gov.eg), preliminary screening is done within 10 days. In case any document is missing after reviewing the whole submitted technical support dossier, the applicant is notified to complete it. The applicant should respond to the letter within 15 days, this period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, a decision will be taken regarding this issue according to EDA's regulations.

7.10.2. Technical Support file evaluation:

The whole dossier of the technical support is reviewed according to international and national guidelines.

Data of technical support may be presented to the scientific committee for reviewing some of the critical issues (if necessary) to aid in the final decision concerning the submitted technical support data.

In case of any requirements &/or clarification(s) are raised they will be sent to the applicant through an official letter &/or through a meeting held with the applicant at Bio-Inn. The applicant should respond within 10 days. This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA. Otherwise, a decision will be taken regarding this issue according to EDA's regulations.

7.10.3. EDA Technical Support Report:

A report of technical support assistance is issued within 60 days from the date of submission with considering stopping the clock in case of any requirements raised by the administration.

7.11. The Principal Investigator Criteria and Responsibilities

7.11.1. The Principal Investigator Criteria

a) The Principal Investigator should meet all academic qualifications, training, and experience criteria to be able to assume the responsibility of administering medical research and to be fully acquainted with the rules and ethics of scientific research, and possess the skills deemed inevitable and necessary to deal with patients.

b) To be of good reputation.

c) Not to have been sentenced in a penal punishment or incarceration for a crime of honor or honesty unless otherwise exonerated.

d) To be free from any personal conflict of interest against conducting or completing the research or protecting the safety of any of the research subjects.

7.11.2 Responsibilities before Starting the Study

a) To obtain the approvals required for conducting the medical research as per Clinical Trials Law 214/2020.

b) To obtain the approved informed consent of research subjects or their legal representatives and document it, which shall be signed and dated by the research subject and reviewed and approved by the institutional committee.

c) To obtain approval on the research plan (protocol) of the medical research.

d) To register the research plan (protocol) in the designated database.

e) To obtain the other permits and approvals as stipulated under the law.

f) To choose an assistant to the principal investigator and members of the research team in accordance with the criteria of scientific competence.

g) To choose the research subject with complete impartiality and to specify the appropriate number to conduct the medical research in accordance with the approved research plan (protocol).

7.11.3 Responsibilities during Conduction of the Study

a) To conduct the medical research at the clinical trial site and attend and supervise the research on a regular basis; in accordance with recognized practices and standards.

b) To conform with the relevant laws and regulations and to apply the principles of good clinical practices, as well as, recognized and relevant local and international standards.

c) To manage the medical research in accordance with the research plan (Protocol) as approved by all concerned entities, on a case-by-case basis.

d) The principal investigator may not cause any amendments to the research plan (Protocol) except after obtaining the approval of all concerned entities.

e) To inform research subjects of any amendments to the research plan that may affect their safety and of any unexpected risks that they or other research subjects may become exposed to, in the process of conducting the medical research.

f) To take necessary measures to protect the life, physical, psychological health, and dignity of research subjects, as well as, minimize the side effects of the medical research; including the introduction of amendments to the research plan in event of the emergence of serious side effects that may place the safety of the research subjects at risk. In such case; the principal investigator shall notify the research sponsor, institutional review board, EDA, and the Supreme Council (once established); each in their jurisdiction of the adverse events and the procedures taken to protect the research subjects within no more than 24 hours.

g) To keep the documents of the medical research at the research facility and the premises of the research sponsor (if any) and take sufficient precautions to protect the same from any loss or damage.

h) To publish the results of the medical research in a peer-reviewed scientific journal after completion of the research based on publication policy of the sponsor.

i) To provide the necessary medical care to research subjects after completion of the medical research on a case-by-case basis whenever the principal investigator concludes the occurrence of adverse events or serious adverse events, and to notify research subjects of their need for such medical care; all for the purpose of mitigation of the harmful effects.

7.12. Responsibilities of the Sponsor/CRO

a) The Sponsor should obtain all the required approvals depending on the nature and type of the medical research.

b) To supervise the completion of the medical research and fund the research from its beginning until its completion.

c) To establish the mechanisms required for monitoring performance and quality of performance and assurance to obtaining, documenting, and publication of the results of the medical research in accordance with the approved study protocol and good clinical practices.

d) To serve the competent institutional review board and the Supreme Council (once established) with periodical reports on the progress of the medical research and the funding made by the sponsor, as the case may be.

e) To enter into agreements with all parties concerned with the medical research and include these agreements in the medical research file.

f) To safe-keep with self, and in the Supreme Council's medical research database inside the Arab Republic of Egypt (once established) all the main documents and dates related to the medical research after publication of the results.

g) To provide research subjects with medical intervention during and after the completion of the medical research on a case-by-case basis and as required.

h) To immediately notify the research subjects of any modifications to the medical research, of any results that may adversely affect their safety, and of any unexpected adverse events of the medical research.

i) To conclude an insurance contract with the research subjects named as beneficiaries, and with an insurance company chartered in the Arab Republic of Egypt against any damages sustained by the research subject due to their participation in the medical research.

j) The insurance contract stated herein shall cover the entire period of the medical research and the follow-up period provided however that it shall be valid for one year after the completion of the medical research, and the insurance value shall be approved by the Supreme Council (once established).

k) Indemnification and treatment of research subjects in case of injuries related to medical research.

l) To complete the treatment of research subjects proven to need treatment after the completion of the medical research.

7.13. General Considerations:

7.13.1. <u>The CT Submissions to EDA as per the Egyptian Clinical Trials Law no. 214/2020:</u>

For nationally originated interventions, all phases of clinical trials (I, II, III, and IV) are allowed to be conducted in Egypt on the condition that the results of each stage are reviewed and approved by EDA to move forward to the next clinical phase.

- For the medical interventions that arise outside the Arab Republic of Egypt, clinical trial phases III and IV are only allowed under the following conditions:
  - The submitted clinical medical research is concurrently conducted in any reference country "List of reference countries" (see References 8.9).
  - The pre-clinical, previous clinical phases I and II results which were conducted in the country of origin were reviewed and approved by EDA
- As an exemption from this condition; In case of medical intervention for endemic diseases that do not exist in the country of origin of the medical intervention and in case of rare diseases, in which cases medical research is allowed in the Arab Republic of Egypt starting from the clinical trial phase II and is subjected to EDA's approval.

7.13.2. This guideline applies to all interventional medical research conducted in Egypt that are involving human participants, i.e., healthy volunteers or patients. All interventional medical research that uses new investigational pharmaceutical or biological medicinal products, new indications, new dosage forms, new medical devices, and herbal medicinal products –that have never been used before in the human body and that have not been accredited by international bodies- are included.

- For other interventional medical research and non-interventional clinical trials for which the relevant IRB approval is considered final, EDA should only be notified via email (bio.ct@edaegypt.gov.eg) before study initiation. The notification should include the following:
    - The name of the study
    - Name of PI (s)
    - The involved sites
    - IRB(s) /MOH approval
    - Sites' activation date.
- In case of interventional medical research with local manufactured medical device, the applicant should get technical file approval for the intended device and its classification from Central Administration of Medical Device-EDA and then proceed to the process of protocol submission.

7.13.3. <u>Post-licensure Phase IV Studies:</u>

7.13.3.1. For interventional studies: please follow the Guideline for Good Regulatory Oversight of Clinical Trials by the Egyptian Drug Authority.

7.13.3.2. For observational, non-interventional PASS/PAES: Please follow the "PASS module" within the PV regulations by the Egyptian Drug Authority.

7.13.4. <u>Other Authorities Involved in the Decision of the CT Application:</u>

- IRB approval should be obtained before submission to EDA except in case of parallel submission (see Section 7.3.2).
- General Intelligence Agency opinion shall be obtained in case the research is being conducted with foreign entities, in case of jointly conducted international trials, and for approval of human samples exportation.

- The Supreme Council for Review of Clinical Medical Research Ethics: it is a must to acquire supreme council final approval (once established).
- Any change in CT package after EDA's approval (due to any concerned entity opinion) should be reported to EDA.

7.13.5. <u>Importation of Investigational products should follow EDA regulations:</u>

- See References 8.14, 8.15

8. References:

8.1 European Medicines Agency EMA, Committee for Medicinal Products for Human Use, ICH. ICH guideline E6 on good clinical practice Guideline for good clinical practice E6(R2)

8.2 Handbook for good clinical research practice (GCP): guidance for implementation. World Health Organization, 2005.

8.3 Medicines Agency E. Procedure for reporting of GCP inspections requested by the Committee for Medicinal Products for Human Use (CHMP) GCP Inspectors Working Group. 2016;44(March):18. Available from: www.ema.europa.eu

8.4 Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics- U.S. Department of Health and Human Services- FDA, May 2014

8.5 Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004- EMA, 25 February 2016

8.6 Causality assessment of an adverse event following immunization (AEFI), WHO, second edition 2019 update

8.7 Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments, and the declaration of the end of the trial (2010).

8.8 Causality assessment of an adverse event following immunization (AEFI) User manual for the revised WHO classification, Second edition 2019 update

8.9 Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol

8.10 List of reference countries " available on the EDA website and should be checked regularly for updates.

8.11 Clinical trials Law no. (214) of 2020.

8.12 EDA chairman Decree no (111) of (2022)

8.13 Law decree No (151) of (2019)

8.14 EDA decision No (66) of (2020) for regulations of procedures of importation and customs release of medicinal products

8.15 Importation and Customs release guidance 2021

8.16 Ministerial decree No. 399 of 2010.

8.17 Ministerial decree no.436/2006.

8.18 Ministerial decree no.132/2017.

8.19 Ministerial no.734/2016.

9. Template forms:

9.1. List of Required Documents in the Preclinical Package to be submitted to GA of CT for Scientific Opinion before First in Human Clinical Trial

9.2. "Applicant request to the Egyptian Drug Authority For Clinical Trial Authorization ".

9.3. List of the required documents from the investigator, sponsor&/or CRO to be submitted to Bio Inn-EDA for clinical trials in Egypt

9.4. List of required documents for protocol reliance submission from the investigator, sponsor &/or CRO to be submitted to Bio-Inn-EDA for clinical trials in Egypt.

9.5. List of required documents from the investigator, sponsor&/or CRO to be submitted in case of Amendment.

9.6. List of required documents for protocol amendment reliance submission from the investigator, sponsor &/or CRO to be submitted to Bio-Inn-EDA for clinical trials in Egypt.

9.7. List of documents submitted for EDA Approval Renewal of CT protocol

9.8. Progress Follow up Report Template

9.9. Corrective Action and Preventive Action (CAPA) Template

9.10. Application Form of Pre-clinical and Clinical Technical Support Request

All these forms are available on the EDA website and should be checked regularly for updates.

10. Annex I

Non-Exhaustive List of Amendment Cases

Classification	Amendment Cases	Type
1. Amendments related to protocol	• Purpose of the trial • Design of the trial including: ▪ addition of trial arm or placebo group or ▪ addition of a different set of study participants • Inclusion criteria & Exclusion criteria (Such as age range of participants) • Change number of clinic visits: (Significantly affect the safety of the study participants) • Addition or deletion of tests or measures • New monitoring procedure: (To improve monitoring or reduce the risk of side effects or adverse events) • Duration of all trial periods beyond that described in the currently approved protocol including duration of exposure of individual subjects to the drug and follow-up • New measures of the primary or secondary endpoint: (Significantly alter the scientific value of the trial) • Schedule of samples • Change the definition of the end of the trial, even if the trial has in practice already ended • Changes in the following documents: (Informed consent (ICF), participants' information sheets, Questionnaires) • Change in Insurance arrangements • New protocol version after approval • Statistical analysis • Changes in safety measures	**Substantial**
	• Change in number of participants per trial site as long as the total number of participants is the same • Minor changes in the recruitment procedure • Renewal of insurance agreements • Correction of typographic errors • Changes in documentation used for data recording during the trial (e.g.: Case Report Form "CRF"). • Adding or deleting exploratory endpoints • Additional safety measures which are not part of an urgent safety measure but are taken on a precautionary basis	**Non-Substantial**

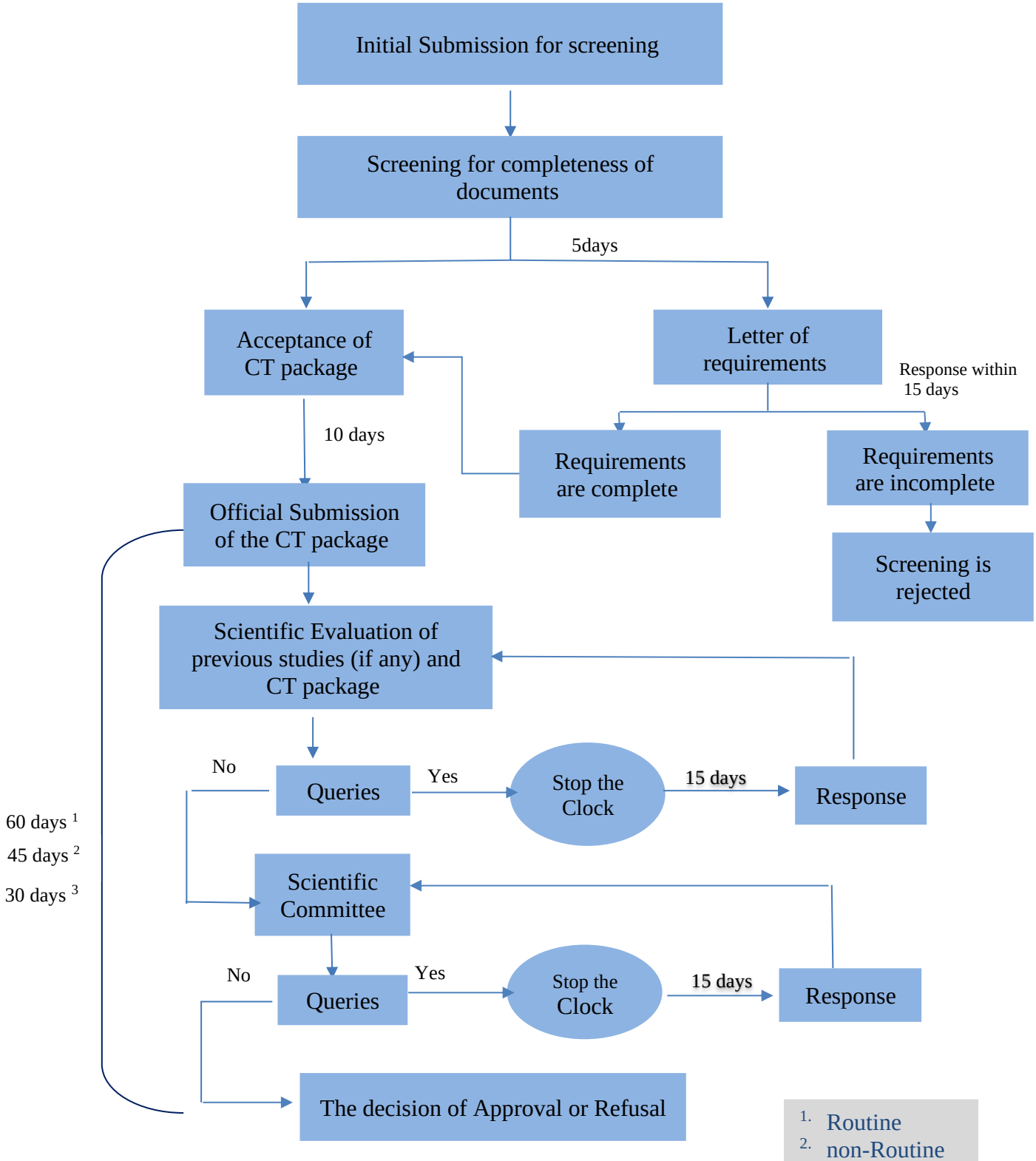
2. Amendments related to the trial arrangements	• Change of "principal investigator" "PI" or addition of new ones • Change of trial site or addition of new sites • Transfer of the sponsor responsibilities to a new organization (or change of CRO assigned significant tasks)	**Substantial**
	• Name(s) and address (es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial • Change of the coordinating investigator "Co-PI" (s) • Contacting point/person • Change in PI research team at any of the clinical trials sites	**Non-Substantial**
3. Amendments related to Investigational Medicinal Product "IMP"	• Quality of IMP (e.g.: Change of formulation, packaging material, Manufacturer(s) of active substance / medicinal product, Manufacturing process, specifications of active substance/ medicinal product, Specification of Excipients (where these may affect product performance), Stability, Storage conditions, Shelf-life) • Change to the route of administration, dosage, dosage regimen, and treatment period(s) • Suspension of the marketing authorization of IMP	**Substantial**
	• Minor changes in the labeling of IMP • Logistic arrangements (such as storage and transportation)	**Non-Substantial**
4. Amendments related to Investigator's Brochure (IB)	• Investigator's Brochure (IB): (Any changes affecting risk/benefit assessment) • A new version of IB after approval . Changes to Pre-clinical pharmacology and toxicology data, For example: ▪ Data from additional studies of pharmacology and toxicology ▪ Results of new interaction studies ii. Changes to Clinical trial and human experience data, For example: Safety-related to a clinical trial or human experience with IMP Results of new clinical pharmacology tests Results of new clinical trials New data from human experience with IMP (Where this is relevant to the ongoing trial, might alter the initial risk-to-benefit assessment)	**Substantial**

11. Annex II

Standard Time frames

S.N.	Process Name	Time frame
Administration of Protocols and Studies Follow up		
1	Submission and Evaluation of Preclinical Results before First in Human Clinical Trial (FIH)	Screening: 5 days Final decision: 60 days Clock stopping: 15 days
2	Initial Routine Submission of Clinical Trials' Protocol	Screening: 5 days Final decision: 60 days Clock stopping: 15 days
3	Non-routine submission	Screening: 5 days Final decision: 45 days Clock stopping: 15 days
4	Reliance submission	Screening: 5 days Final decision: 30 days Clock stopping: 15 days
5	Amendment (Substantial)	Final decision: 60 days Clock stopping: 15 days
6	Amendment (Non-Substantial)	Final decision: 15 days Clock stopping: 15 days
Administration of Scientific committees and Technical Support		
7	Technical Support for Preclinical and Clinical Trials	Final decision: 60 days Clock stopping: 15 days

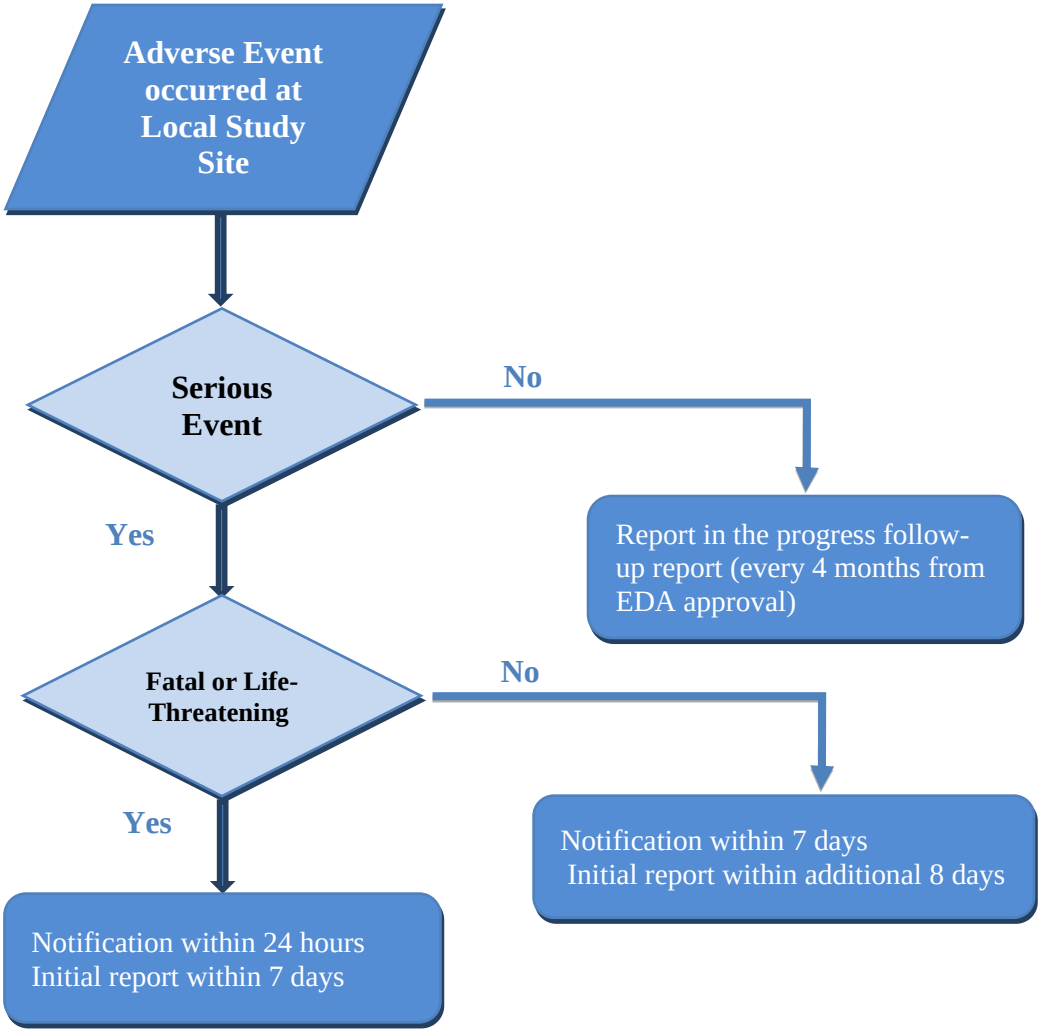
12. Annex III



1. Routine
2. non-Routine
3. Reliance

13. Annex IV

Adverse Event Reporting



N.B.: Reporting times are in calendar days and start once the site is notified of SAE

14. Annex V

Flow chart for Technical Support