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

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Table of Contents

1. Introduction: 3
2. Legal Provisions 5
3. Scope 5
4. General considerations....6
5. Abbreviations: 8
6. Definitions: 9
7. Objective....17
8. Clinical Trials Regulatory Oversight:....18
8.1 GCP Principles....18
8.2 Submission and Evaluation of Preclinical Results before (FIH)....23
8.3 Submission & Evaluation of Clinical Trials' Protocol through routine/ non-routine/ or Reliance pathways.....25
8.4 Initiation of the Study and Reporting from the Applicant....35
8.5 Safety Reporting....39
8.6 End of Clinical Medical Research....44
8.7 Post-Trial benefit.....45
8.8 Early Termination or Withdrawal of the Study by the Sponsor 45
8.9 Suspension or Termination of the Study by EDA 46
8.10 Inspection of Clinical Medical Research....46
8.11 Technical Support for Preclinical and Clinical Trials....49
8.12 The Principal Investigator Criteria and Responsibilities 51
8.13 Responsibilities of the Sponsor/CRO....53
9. References: 55
10. Template forms:....56
11. Annex I 57
12. Annex II....60
13. Annex III....61
14. Annex IV 62
15. Annex V....63
16. Annex VI 64
17. Document History 65

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 (927/2022) 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)

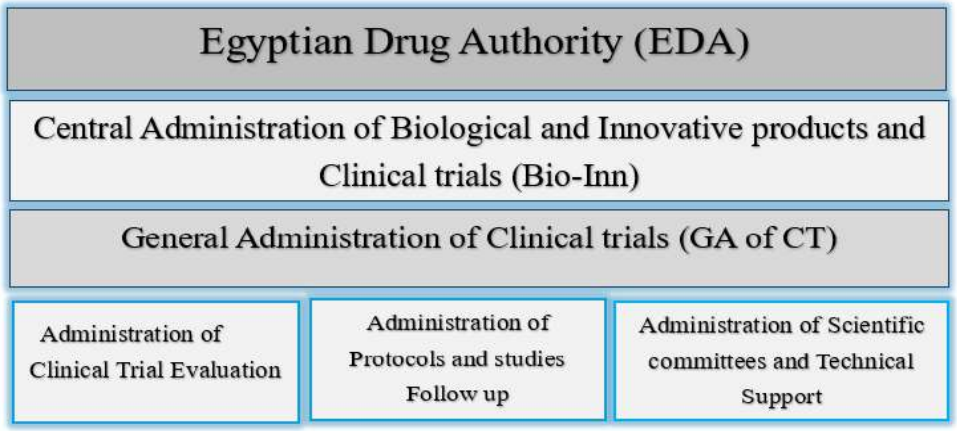

Figure (1) GA of CT organizational diagram

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 for the purpose of registration, re-registration, or variations submitted to EDA. Evidence is requested to be presented in the Common technical document (CTD) format.

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.

2.6. Prime Minister's Resolution No. 746 of 2024 for the construction of the Supreme Council for Review of Ethics Clinical Medical Research.

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. General Considerations:

4.1. The CT Submissions to EDA as per the Egyptian Clinical Trials Law no. 214/2020:

- 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 all 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. The applicant should submit an appeal to EDA, justifying the request to conduct the phase II study in Egypt, subject to EDA's review and decision.
    - For interventional medical research involving medical devices:
        - For locally manufactured medical devices, 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.
        - For imported medical devices with/without international quality certification, Applicant shall proceed directly to "Submission & Evaluation of Clinical Trials' Protocol" see section 8.3
- 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-IEC approval
- Sites' activation date.

4.2. Post-licensure Phase IV Studies:

4.2.1. For interventional studies: please follow this guideline.

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

4.3. Other Authorities Involved in CT Authorization in Egypt:

- IRB approval should be obtained before submission to EDA except in case of parallel submission (see Section 8.3.2).
- 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 the Supreme Council's final approval.
- Any change in the CT package after EDA's approval (due to any concerned entity's opinion) should be reported to EDA.

4.4. Importation of Investigational products should follow EDA regulations:

- See References 9.14, 9.15

5. 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
- **GMP:** Good Manufacturing 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.

6. Definitions:

Adverse Drug Reaction (ADR): concern noxious and unintended responses to a medicinal product. 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. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected.

Adverse Event (AE): An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

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

Applicant: The person or entity who submits any application to EDA. The applicant could be the PI, the researcher, the CRO, or the Sponsor.

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.

Blind Review: The checking and assessment of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind, for the purpose of finalizing the planned analysis.

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 drug development: Studying the drug in humans, is conducted in a sequence that builds on knowledge accumulated from non-clinical and previous clinical studies. The structure of the drug development programme will be shaped by many considerations and comprised of studies with different objectives, different designs, and different dependencies.

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 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

Clinical Trial/Study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

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

Control Group: A group of research subjects who do not receive the medical intervention under research; but rather receive what is called a "Placebo" or receive a standard treatment for the purpose of comparison and measurement of the effect of the new intervention. (Law No. 214 for Year 2020 Promulgating the law to regulate Clinical Medical Research)

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.

Remarks: 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 of 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.

Data base lock: is the point at which the trial data is finalized and "locked" to prevent any further unauthorized changes, it indicates the completion of data collection and the point at which no further changes can be made to the study database.

Dropout: A subject in a clinical trial who for any reason fails to continue in the trial until the last visit required of him/her by the study protocol record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

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

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.

Remarks: observations classified as major, may include a pattern of deviations and/or numerous minor observations.

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.

Remarks: many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

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.

Protocol deviation: Any change, divergence, or departure from the study design or procedures defined in the protocol that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

Preliminary report: A report prepared by the sponsor after the end of clinical medical research which contains the outcome, all information, data, and related reports to the Clinical Medical Research. This report is submitted to EDA till the issuance of the final clinical study report (CSR).

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

7. 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 to EDA during conduction of clinical medical research:

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.

8. Clinical Trials Regulatory Oversight:

8.1. GCP Principles

EDA is adopting the Principles of GCP according to ICH E6. The overarching principles provide a flexible framework for clinical trial conduct. They are structured to provide guidance throughout the life cycle of the clinical trial. These principles are applicable to trials involving human participants. The principles are interdependent and should be considered in their totality to assure ethical trial conduct and reliable results. These principles 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 applicable regulatory requirement(s). Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.

- The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.
- The safety of the participants should be reviewed in a timely manner as new safety information becomes available, which could have an impact on participant safety, their willingness to continue in the trial or the conduct of the trial.
- Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the anticipated benefits justify the known and anticipated risks.
- When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the population groups that the investigational product is intended to benefit, once authorized, to allow for generalizing the results across the broader population. Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require such a heterogeneous population.
- A qualified physician or, when appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) should have the overall responsibility for the trial-related medical care given to and medical decisions made on behalf of participants; however, the practical

interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals in accordance with applicable regulatory requirements.

- The confidentiality of information that could identify participants should be protected in accordance with applicable privacy and data protection requirements.

b) Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants (or their legally acceptable representatives, where applicable) are well-informed.

- Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation. For potential participants unable to provide informed consent, their legally acceptable representatives, acting in the participants' best interest, should provide consent prior to clinical trial participation. These potential participants should be informed about the trial in a manner that facilitates their understanding. In the event that a minor is a participant, assent should be collected from that minor, as appropriate, and in accordance with local regulatory requirements (see ICH E11(R1) Clinical Investigation of Medicinal Products in the Pediatric Population).
- The process and information provided should be designed to achieve the primary objective of enabling potential trial participants to evaluate the benefits, risks and burden of participating in the trial and to make an informed decision on whether or not to participate in the trial. The information provided during the informed consent process should be clear and concise so as to be understandable by potential participants or legally acceptable representatives.
- The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefits and risks of medical intervention(s), the setting and context in which the trial will be conducted (e.g., trials in emergency situations), and the potential use of technology to inform participants (or their legally acceptable representatives) and obtain informed consent.
- In emergency situations, where consent cannot be obtained prior to trial participation, consent should be obtained from the participant or their legally acceptable representative as soon as possible in accordance with applicable regulatory requirements and the processes approved by the institutional review board/independent ethics committee (IRB/IEC).

c) Clinical trials should be subject to an independent review by an IRB/IEC.

- A trial should be conducted in compliance with the protocol that received prior IRB/IEC approval/favorable opinion.
- Periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements.

D) Clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches.

- The available nonclinical and clinical information on an investigational product(s) should be adequate to support the proposed clinical trial.
- Clinical trials should be scientifically sound and reflect the state of knowledge and experience with the investigational product(s), including, if applicable, the condition to be treated, diagnosed or prevented; the current understanding of the underlying biological mechanism (of both the condition and the investigational product); and the population for which the investigational product is intended.
- There should be periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun.

e) Clinical trials should be designed and conducted by qualified individuals.

- Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, nurses, pharmacists, scientists, ethicists, technology experts, trial coordinators, monitors, auditors, and biostatisticians. Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s).

f) Quality should be built into the scientific and operational design and conduct of clinical trials.

- Quality of a clinical trial is considered in this guideline as fitness for purpose.
- Factors critical to the quality of the trial should be identified prospectively. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results, and the decisions made based on those trial results. Quality by design involves focusing on critical to quality factors of the trial in order to maximise the likelihood of the trial meeting its objectives.
- Strategies should be implemented to avoid, detect, address, and prevent recurrence of serious noncompliance with GCP, the trial protocol, and applicable

regulatory requirements.

g) Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.

- Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results.
- The focus should be on the risks associated with trial participation. For clinical trials involving patients, the focus should be on risks that go beyond those associated with usual medical care. The risks relating to investigational products that have a marketing authorization when used in the clinical trial context may differ from the usual care of patients and should be taken into consideration.
- Risks to critical to quality factors should be managed proactively and adjusted when new or unanticipated issues arise once the trial has begun.
- Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection. Trial processes should support the key trial objectives. The sponsor should not place unnecessary burden on participants and investigators.

h) Clinical trials should be described in a clear, concise, scientifically sound and operationally feasible protocol.

- A well-designed trial protocol is fundamental to the protection of participants and for the generation of reliable results.
- The scientific objectives of any trial should be clear and explicitly stated in the protocol.
- The clinical trial protocol as well as the plans or documents for the protocol execution (e.g., statistical analysis plan, data management plan, monitoring plan) should be clear, concise and operationally feasible.

i) Clinical trials should generate reliable results.

- The quality and amount of the information generated in a clinical trial should be fit for purpose and sufficient to provide confidence in the trial's results and support good decision making.
- Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the

trial, should be fit for purpose, should capture the data required by the protocol and should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data.

- Computerized systems used in clinical trials should be fit for purpose (e.g., through risk-based validation, if appropriate), and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes to ensure the integrity of relevant trial data.
- Clinical trials should incorporate efficient and robust processes for managing records (including data) to help ensure that record integrity and traceability are maintained and that personal information is protected, thereby allowing the accurate reporting, interpretation and verification of the relevant clinical trial-related information.
- Essential records should be retained securely by sponsors and investigators for the required period in accordance with applicable regulatory requirements. These essential records should be available to regulatory authorities, monitors, auditors and IRBs/IECs (as appropriate) upon request to enable appropriate evaluation of the trial conduct in order to ensure the reliability of trial results.
- The transparency of clinical trials includes timely registration on publicly accessible and recognized databases and the public posting of clinical trial results. Communicating trial results to participants should be considered. Such communication should be objective and non-promotional.

j) Roles and responsibilities in clinical trials should be clear and documented appropriately.

- The sponsor may transfer or the investigator may delegate their tasks, duties or functions (hereafter referred to as activities), but they retain overall responsibility for their respective activities.
- Agreements should clearly define the roles, activities, and responsibilities for the clinical trial and be documented appropriately. Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively.
- The sponsor or investigator should maintain appropriate oversight of the aforementioned activities.

k) Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be managed in accordance with the product specifications and the trial

protocol.

- Investigational products used in a clinical trial should be manufactured in accordance with applicable GMP standards.
- Measures should be in place to ensure that the investigational product provided to trial participants retains its quality.
- Investigational products should be used in accordance with the protocol and relevant trial documents.
- Manufacturing, handling and labelling of investigational products should be undertaken in a manner that aligns with treatment assignment and maintains blinding, where applicable.
- Investigational product labelling should follow applicable regulatory requirements.
- Appropriate processes should be implemented for the handling, shipping, storage, dispensing, returning and destroying or alternatively disposing of the investigational product.

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

Preclinical data is required to be submitted prior to initiating Phase I clinical trials for investigational products originating within the Arab Republic of Egypt, in order to demonstrate adequate safety and scientific justification for first-in-human studies.

8.2.1. Screening:

- The applicant should submit the preclinical package data to Bio-Inn, according to the list of required documents (See Template Forms 10.1), via e-mail (bio.ct@edaegypt.gov.eg) with proof of payment of the determined fees for screening.
- The clock of the process will start from date of package submission or fees payment whichever is latest.
- The submitted documents will be screened and reviewed within 5 days.
, the quality dossier (IMPD) will be screened by the relevant administration.
- 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. However, the applicant may submit an appeal to EDA requesting to shorten this one-month period, subject to EDA's review and approval.

- The applicant's reply to the requirements will be screened within 7 days. In case all requirements are fulfilled, the applicant will be notified of acceptance of the preclinical package via e-mail.

8.2.2. Submission:

- In order to proceed to official submission, the applicant should submit the proof of payment of the determined fees and the hard copy of certain documents as specified in the List of Required Documents (See Template Forms 10.1). This should be done within 10 days from the acceptance email; otherwise, the screening will be canceled (This period can be extended once based on the applicant's request if the reasons and justifications are accepted by EDA).

- The clock of the official submission evaluation process (60 days) will start from the submission of proof of payment.

8.2.3. Evaluation:

- The submitted preclinical data and results 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 scientific 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.
- This decision will be sent to the applicant via email, in case of EDA requirements are still not fulfilled within 15 days from this email, two consecutive reminders will be sent to the applicant with 5 days' interval, if still

no response, the application shall be considered null, and void and the applicant will be notified via e-mail. However, if the applicant intends to resubmit the package for evaluation, an appeal should be submitted to EDA requesting approval to proceed, subject to EDA's review and decision.

8.2.4. EDA Final Decision:

- EDA's regulatory decision (approval / conditional approval in case of further requirements or recommendations)/ refusal, 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.

8.3. Submission & Evaluation of Clinical Trials' Protocol (Through Routine/Non-Routine, or Reliance Pathways)

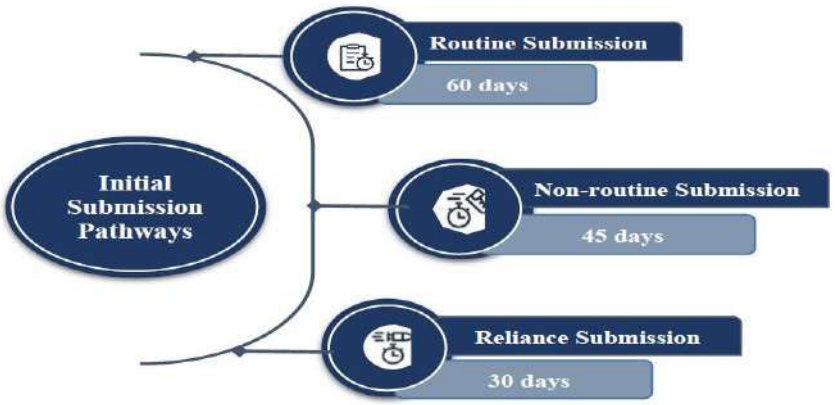

Figure (2) Different submission pathways timelines

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

8.3.1 Routine Submission of Clinical Trials' Protocol:

8.3.1.1 Screening:

The applicant should fill the Applicant Request and submit it with the whole clinical trial package, according to the list of required documents (See Template Forms 10.3/10.4 as applicable)* to Bio-Inn through EDA Clinical Trial Platform with proof of payment of screening fees.

- The clock of the screening process will start from the date of package

submission or fees payment, whichever is later.

- The submitted documents will be screened and reviewed within 5 days.
- The quality dossier (IMPD) will be screened by the relevant administration.
- Any missed documents and/or required clarifications will be sent to the applicant through EDA Clinical Trial Platform.
- 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 through EDA Clinical Trial Platform. In this case, the applicant can resubmit the package for re-screening with new fees after at least one month from the date of the cancellation email. However, the applicant may submit an appeal to EDA requesting to shorten this one-month period, subject to EDA's review and approval.
- The applicant's reply to the requirements will be screened within 7 days. In case all requirements are fulfilled, the applicant will be notified of acceptance of the clinical trial package through EDA Clinical Trial Platform.

8.3.1.2 Submission:

- In order to proceed to official submission, the applicant should submit the proof of payment of the determined fees in addition to hard copy of specific documents as listed in "List of the required documents (See Template Forms 10.3/10.4 as applicable). This should be done within 10 days from the acceptance; otherwise, the screening will be canceled (This period can be extended once, based on the applicant's request, if the reasons and justifications are accepted by EDA).
- The clock of the official submission evaluation process ~~(60 days)~~ will start from the submission of proof of payment.

8.3.1.3 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 scientific review by EDA's advisory scientific committee, will be sent to the applicant through EDA Clinical Trial Platform.
- 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.
- This decision will be sent to the applicant through EDA Clinical Trial Platform., in case of EDA requirements are still not fulfilled within 15 days from this email, two consecutive reminders will be sent to the applicant with 5 days interval, if still no response, the application shall be considered null and void, and the applicant will be notified through EDA Clinical Trial Platform. However, if the applicant intends to resubmit the package for evaluation, an appeal should be submitted to EDA requesting approval to proceed, subject to EDA's review and decision.

8.3.1.4 EDA Final Decision:

- EDA's regulatory decision regarding the previous studies' results (if any) will be issued along with EDA's regulatory decision (approval / conditional approval in case of further requirements or recommendations / refusal), regarding the clinical trial package, will be issued within the specified timelines according to the submission type, 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 final decision will be sent to the applicant through the EDA Clinical Trial Platform, and the applicant may obtain the original document from Bio-Inn. Moreover, the decision will be sent to the Supreme Council, and to the Central Administration of Pharmaceutical Policies and Market Access in the case of imported IMP(s)."
- In case of any change in the clinical trial package from the IRB-approved one, or from that submitted to the IRB (In case of non-routine parallel submission), due

to EDA requirements and regulations a conditional approval will be issued by EDA till all concerned IRB(s) are notified by the applicant.

- In case of issuance of a conditional approval by EDA, a final approval shall be granted once the applicant fulfills all requirements and conditions upon which the conditional approval was based.

* **List of Required Documents**:

- Template Form 10.3 for Routine and Non-Routine Submission Pathways
- Template Form 10.4 for Reliance Submission Pathway

** **Final Decision Timelines**:

- 60 Days for the Routine Submission Pathway
- 45 days for the Non-Routine Submission Pathway
- 30 Days for the Reliance Submission Pathway

8.3.2 Non-Routine Submission Pathway:

- 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 a non-routine submission, this should be stated in an appeal with a rationale supporting the request. The appeal should be sent to Bio-Inn through EDA Clinical Trial Platform before submission of CT package data for screening.
- In case the appeal is accepted, the applicant will be notified through EDA Clinical Trial Platform to proceed to the parallel submission for screening and evaluation as described in section 8.3.1
- The EDA final decision will not be issued until the submission of the involved IRB(s) approval(s).

8.3.2.1 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.)

- In case all EDA requirements have been fulfilled but the IRB approval(s) have not yet been submitted, the applicant shall be notified that the evaluation clock has been stopped on the applicant’s side.

8.3.3 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.
- The CT package submitted through the reliance pathway will be screened and evaluated as clarified in section 8.3.

8.3.4 Amendment Submission:

- It is mandatory to obtain EDA approval before implementing any amendment to the approved clinical trial package except when it is necessary to eliminate an immediate hazard to human participants.

- The applicant should notify EDA of any changes to the approved protocol or its related documents through EDA Clinical Trial Platform including a "notification letter" till official submission of the changed document(s) as amendment.

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 change(s)/amendment(s).

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

I. Notified; no need for official submission of the amendment unless specific documents requested from the applicant.

II. Notified and could be implemented till the official submission of the amendment.

III. Notified and should be submitted officially to be approved before

implementation.

IV. In case the amendment is implemented to eliminate immediate hazards to human participants, EDA should be notified with a written full explanation within 24 hours of the implementation then it should be officially submitted.

- The amendment official submission should be within 30 days from the notification date. 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 according to EDA's regulations.

- The applicant can submit an amendment only after obtaining EDA's approval for the initial protocol submission.

- In case of any change in the submitted CT package before obtaining EDA's approval. EDA should be consulted on case-by-case basis 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.

- Annex I is a non-exhaustive list of examples for substantial and non-substantial amendments.

- For amendment official submission, the applicant should submit the amendment package through EDA Clinical Trial Platform hard copy of specified documents with proof of payment of the determined fees according to the amendment list of requirements (see Template Forms 10.5)

- "In cases where the initial submission was made under reliance, the applicant may

submit subsequent amendments either as a reliance submission—if the applicant intends to maintain the reliance pathway and all required reliance-related documents are applicable and fulfilled—or as a routine submission if the applicant does not wish the amendment to proceed under reliance. The reliance pathway doesn't apply to amendments that do not include reliance documents such as Principal Investigator (PI) changes or site additions and these should be submitted through the routine pathway."

- The submitted amendment will be evaluated according to national and international guidelines. Any requirements and/or clarifications, raised during the evaluation or after scientific review by EDA's advisory scientific committee, will be sent to the applicant through EDA Clinical Trial Platform.
- 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.
- This decision will be sent to the applicant , through EDA Clinical Trial Platform, in case of EDA requirements are still not fulfilled within 15 days from the decision date ,two consecutive reminders will be sent to the applicant with 5 days' interval, if still no response, Action will be taken according to EDA regulation and the applicant will be notified through EDA Clinical Trial Platform
- EDA's regulatory decision (approval / conditional approval in case of further requirements / refusal) 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.
- In case of the amendment through the non-routine pathway, EDA's final decision

will be issued within 45 days for substantial amendment(s).

- EDA's final decision will be sent to the applicant through the EDA Clinical Trial Platform, and the applicant may obtain the original document from Bio-Inn. Moreover, the decision will be sent to the Supreme Council, and to the Central Administration of Pharmaceutical Policies and Market Access in the case of imported IMP(s)."

- In case of any change in the clinical trial package from the IRB-approved one, due to EDA requirements and regulations. A conditional approval will be issued by EDA till all concerned IRB(s) are notified by the applicant.

- In case of issuance of a conditional approval by EDA, a final approval shall be granted once the applicant fulfills all requirements and conditions upon which the conditional approval was based.

8.3.5. Investigational Medicinal Product (IMP) Quality Requirements

- 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.
- In 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 for Inspection of Pharmaceutical Institutes carry out GMP inspection (if required).
- The submitted quality dossier (IMPD) will be screened and evaluated by the

relevant administration.

8.3.6. Annual EDA's Approval Renewal:

- EDA's Approval of the CT package is valid for one year.
- A renewal request should be submitted to EDA at least one month before the end of validity in order to obtain the EDA approval renewal before end of validity of initial issued EDA approval. Otherwise, delay should be justified or a decision will be taken according to EDA regulation which may lead to suspension/termination of trial conduction. The decision will be notified to The Supreme Council.
- The Applicant should send a renewal request to Bio-Inn according to the list of the required documents attached with Investigational medicinal product (IMP) Identification form (See Template Forms 10.6 and 10.10) & submit it as through EDA Clinical Trial Platform with proof of payment of the determined fees.
- The IMP Identification Form should specify the quantity of IMP requested for approval by the Central Administration of Pharmaceutical Policies and Market Access for the upcoming year. The requested quantity should be justified with a clear calculation based on the number of participants (planned &/or ongoing), the dosing regimen, and the duration.
- 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 the date of package submission or fees payment, whichever is latest.

- EDA's approval renewal will be sent to the Supreme Council via email
- In case of imported IMP(s), EDA's approval renewal will be sent to the EDA Central Administration of Pharmaceutical Policies and Market Access via email
- Renewal submissions shall continue to be made until the close-out of every involved site in Egypt. Each renewal request shall include only those sites that remain active and have not yet been closed."

8.4. Initiation of the Study and Reporting from the Applicant

8.4.1. Clinical Medical Research Site Activation:

-The applicant shall initiate the study within the validity period of the initial approval (or else delay should be justified).

-The applicant shall notify Bio-Inn through EDA Clinical Trial Platform of the planned activation date of the involved sites (which is the time-point at which a selected clinical trial site has completed all required preparatory tasks—including regulatory/ethics approvals, contracts, training, supplies, availability of the Investigational Medicinal Product (IMP), and completion of the Investigator Site File (ISF)—and is formally permitted by the trial sponsor and EDA to begin enrolling participants in the study) at least two weeks in advance. Any changes to the planned activation dates shall also be communicated accordingly. Sites shall not proceed with activation until receiving the formal green light from EDA

- 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.

8.4.2. Periodic Reports/Progress Reports:

- The applicant should fill and submit progress follow-up reports to Bio-Inn-EDA via e-mail (bio.ct@edaegypt.gov.eg) and the Supreme Council simultaneously by adding both entities as recipients in the same email and through EDA Clinical Trial Platform, using the template "Follow up template" (see Template Forms 10.7)
  - Every 4 months (from EDA approval date).
  - The progress report shall continue to be submitted every 4 months until the close-out of all sites in Egypt.
- The following data in the progress report should be cumulative:
  - Section 3. Recruitment Information.
  - Other sections of the progress report should cover only data during the reporting period.

- It is allowed to have a maximum of 15 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.

8.4.3. Interim Clinical Study Report:

The applicant shall submit through EDA Clinical Trial Platform an interim clinical study report if applicable as per protocol including interim results of the clinical medical research conducted in Egypt in compliance with ICH E3 Structure And Content of Clinical Study Reports.

8.4.4. IMP(s) Shipment Unlock After Release from Egyptian Customs:

- In case of imported IMP(s), the sealed IMP(s) shipment released from the Egyptian Customs by the Central Administration of Pharmaceutical Policies and Market Access will be transferred to clinical trial site(s) or any contracted local depot.
- The sealed IMP shipment must not be unlocked except in the presence of EDA inspector.
- Upon unlocking the sealed IMP shipment in the presence of EDA inspector(s), the applicant shall submit the unlock form to Bio-Inn through EDA Clinical Trial Platform.

8.4.5. Destruction of IMP:

8.4.5.1. Destruction Inside Egypt:

- The applicant should notify Bio-Inn upon planning for IMP destruction by submitting all required documents through EDA Clinical Trial Platform See Figure (3)
- The required documents are:
  - Detailed procedures of destruction.
  - Accreditation certificate from the Ministry of Environment for the vendor or the clinical trial site where the destruction will take place.
  - If the destruction of the IMP will take place in the clinical trial site, this should be clearly stated in the contract between the sponsor/CRO and the site.

- If the destruction of the IMP will take place through a vendor, the contract between the sponsor/CRO and the vendor will be required.

- The Central Administration for Inspection of Pharmaceutical Institutes will contact the applicant for the arrangement of the destruction process in the presence of one of the EDA's inspectors.
- After completion of the destruction process, the applicant should send the destruction documented evidence and certificate of destruction through EDA Clinical Trial Platform.

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

8.4.5.2. Destruction Outside Egypt:

- If the IMP will be returned to the sponsor outside Egypt, the following are required:

-Bill of lading for exported IMP.

-A commitment that the sponsor is responsible for the IMP destruction.

- After completion of the destruction process, the applicant should send the destruction documented evidence and certificate of destruction through EDA Clinical Trial Platform.

8.5.6. Destruction of Surplus Human Samples:

8.5.6.1. Destruction inside Egypt

- The applicant should notify Bio-Inn upon planning for surplus human samples' destruction by submitting all required documents through EDA Clinical Trial Platform.

- The required documents are:
  - Detailed procedures of destruction.
  - Accreditation certificate from the Ministry of Environment for the vendor or the clinical trial site where the destruction will take place
  - Destruction of the biological sample should be clearly stated in the contract with the responsible entity (e.g. the laboratory, the clinical trial

site, or the vendor)

- The Central Administration for Inspection of Pharmaceutical Institutes 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 evidence and certificate of destruction through EDA Clinical Trial Platform.

8.5.6.2. Destruction outside Egypt

In case of sample exportation, a commitment will be required that the sponsor or the lab is responsible for the destruction of surplus human samples.

After completion of the destruction process, the applicant should send the destruction documented evidence and certificate of destruction through EDA Clinical Trial Platform.

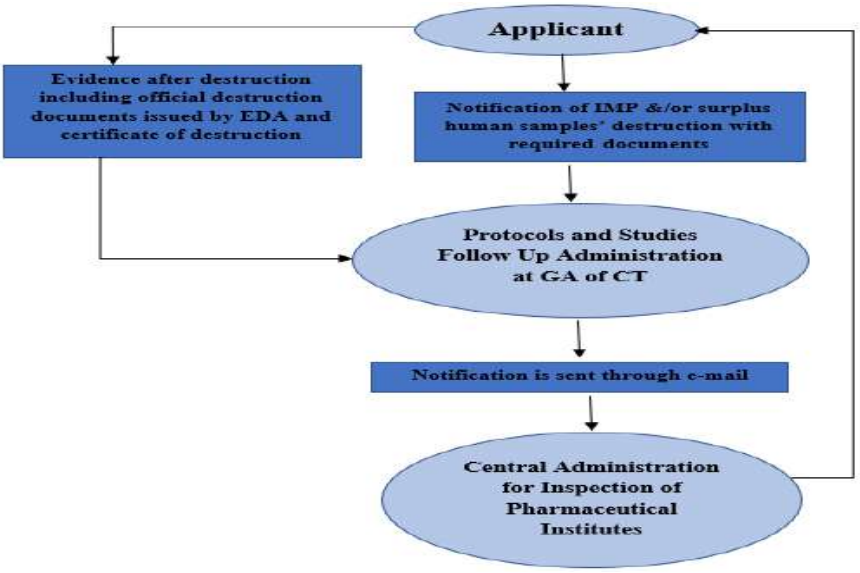

Figure (3)

Flow chart for IMP & Human samples destruction process

8.5. Safety Reporting

8.5.1. Intensity of Adverse Event or Adverse Drug Reaction:

- **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.

8.5.2. 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.

8.5.3. 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.

8.5.4. Reporting Procedure:

8.5.4.1. Safety Reporting Procedure:

The PI is responsible for reporting all Serious Adverse Events to Bio Inn and the Supreme Council simultaneously by adding both entities as recipients in the same email within the specified timelines. Reporting to Bio-Inn via the following email (bio.ct@edaegypt.gov.eg) and reporting to Supreme Council

via the official email of the Supreme Council. (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 also be submitted to EDA through EDA Clinical Trial Platform. Fatal or life-threatening serious adverse events, whether expected or unexpected, should be notified within 24 hours starting 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, (For vaccines, the WHO Guideline "Causality assessment of an adverse event following immunization (AEFI) should be followed)
- 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 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, (For vaccines, the WHO Guideline "Causality assessment of an adverse event following immunization (AEFI) should be followed)
- 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 & suspicion 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.

- Unblinded 6-month SUSAR line listing shall be submitted to EDA via e-mail (bio.ct@edaegypt.gov.eg) and the Supreme Council simultaneously by adding both entities as recipients in the same email and through EDA Clinical Trial Platform,

every six months starting from the date the clinical trial is authorized by EDA to be conducted in Egypt, even if the trial has not yet been initiated. The most recently issued line listing following EDA approval shall be submitted, and thereafter, subsequent listings shall continue to be submitted every six months until the close-out of all sites in Egypt.

-The annual Development Safety Update Report (DSUR) shall be submitted to Bio-Inn-EDA via e-mail (bio.ct@edaegypt.gov.eg) and the Supreme Council simultaneously by adding both entities as recipients in the same email and through EDA Clinical Trial Platform starting from the date the clinical trial is authorized by EDA to be conducted in Egypt, even if the trial has not yet been initiated. The most recently issued DSUR following EDA approval shall be submitted, and thereafter, subsequent DSURs shall continue to be submitted annually until the close-out of all sites in Egypt.

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 calendar 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.

8.5.4.2. 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 through EDA Clinical Trial Platform, 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.

8.6. 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 dates of the involved sites' close out, including the involved IRB acknowledgement, the end of clinical medical research in Egypt, and the global end of clinical medical research (in case of international studies) through EDA Clinical Trial Platform.
- Local sites' closeout visit reports should be submitted once finalized.
- 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 through EDA Clinical Trial Platform within 60 days from the database lock till the issuance of the final CSR in compliance with ICH E3 Structure and Content of Clinical Study Reports.
- The final CSR should be submitted to Bio-Inn through EDA Clinical Trial Platform, within 12 months of the study completion, for review and evaluation, along with the payment of the relevant evaluation fees, otherwise, a decision will be taken according to EDA's and a notification with EDA`s decision on CSR will be sent to the applicant within 60 days starting from the date of the CSR submission and/or proof of payment

submission whichever comes latest considering stopping the process clock in case of requirements &/or clarification(s) raised by EDA

- 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 providing 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.

8.7. Post-trial benefit:

The applicant should notify Bio Inn-EDA EDA through EDA Clinical Trial Platform upon shifting of the participants to the post-trial benefit. The involved PI(s) should submit declaration letters including names of participants, stating that they are proven to need continuation of treatment with the IMP after the end of the clinical trial and indicating the IMP quantities for the proposed duration. For further details regarding regulatory requirements related to post-trial benefits, see the Notice to Applicants."

8.8. Early Termination, Suspension, or Withdrawal of the Study by the Sponsor

- In case of trial premature termination or suspension for any reason by the sponsor/IRB/investigator, the applicant should inform Bio-Inn in a formal letter through EDA Clinical Trial Platform with clear explanation within 15 days.

- The investigator should promptly inform the trial participants, assure appropriate therapy and follow-up for the participants, and as per applicable regulatory requirement(s).
- The applicant may request the withdrawal of his protocol/ amendment before/after EDA's approval is issued and before trial initiation; then a formal letter of withdrawal providing a brief description of the reasons must be submitted to Bio-Inn through EDA Clinical Trial Platform.
- The applicant may re-submit the application, in this case, it must be identified as a resubmission in the Application Form (see Template Forms 10.2) and the changes as compared to the original submission should be marked.

8.9. 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, SUSARs or any other reasons related to regulatory perspective.
- EDA's decision will be notified to the Supreme Council and the applicant will be informed with the EDA's decision through EDA Clinical Trial Platform.

8.10. Inspection of Clinical Medical Research

The Egyptian Drug Authority is responsible for inspecting research sites and 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:

A) Preparing an inspection plan on the research sites in which the research is conducted as well as other related entities

B) Examining and reviewing the documents, installations, records, and other sources related to clinical medical research.

C) Ensuring the research protocol implementation and verifying GCP compliance.

D) Ensuring the application of the domestically and internationally recognized

standards of GCP.

E) Monitoring any observations or deviations, and preparing a report of the inspection findings.

F) 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 clinical medical research whether before trial activation, during trial conduction or after trial completion/termination to ensure compliance with GCP guidelines.

8.10.1. Inspection Plan Notification:

8.10.1.1. For Routine Inspection:

- The applicant will be notified within two weeks before the proposed date of inspection in case of clinical medical research.
- 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 applicant.

8.10.1.2. For-Cause (Triggered) Inspection:

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

8.10.1.3. For Follow up Inspection:

Follow-up inspection may be carried out either to ensure the corrective action(s) &/or preventive action(s) implementation or after any applied amendments approved by EDA. In case of clinical trials, the applicant will be notified within one week before the proposed date of inspection, and in case of bioequivalence studies, the BE center will be notified within 3 days before the proposed date of inspection.

8.10.2. 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**, 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.
Possible consequences: Suspension/termination of the trial, rejection of data and/or legal action required

Remark: 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**, Conditions, practices or processes that might adversely affect the rights, safety or well-being of the participants and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: data may be rejected and/or any other regulatory &/or legal action required

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations

• **Minor GCP findings**, Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes of clinical trial conduction.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

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

The applicant/BE Center shall prepare the corrective and preventive actions plan (See Template Forms 10.8) within 20 days from receiving the inspection report from EDA.

In case of delay two acceleration Emails of 5 days interval will be sent to the applicant. Otherwise, the issue will be raised to the Head of Bio-Inn.

A notification e-mail about the decision taken will be sent to the relevant interested parties (Applicant / Supreme Council / Central Administration of Pharmaceutical Policies and Market Access)

EDA evaluation of the submitted CAPA will be sent to the applicant within 10 days from CAPA submission, if the submitted CAPA was incomplete or assessed as not accepted, additional requirements will be requested from the applicant until CAPA assessed as accepted. The applicant shall respond within seven days of receiving the requirements, and the evaluation of the response will be completed within seven days.

8.10.4. In case of Collection of IMP samples due to quality attributes:

In some cases, e.g. IMP quality issues raised during GCP inspection or during scientific evaluation of IMPD, IMP samples may be collected by EDA inspector to be sent to the concerned administration for analysis, the samples will be kept in the same storage conditions in which they were found during the inspection visit until delivered.

After the IMP Analysis report is issued, a decision will be taken according to EDA's regulations.

8.11. 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.

8.11.1. Submission:

The applicant shall fill the Application form (See Template Forms 10.9) 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 10days. 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.

8.11.2. 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.

8.11.3. 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.

8.12. The Principal Investigator Criteria and Responsibilities

8.12.1. 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.

8.12.2. 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).

8.12.3. 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; 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 at least 5 years after CSR 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.

8.13. 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 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 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.

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.

9. References:

9.1. ICH guideline E6 on good clinical practice Guideline for good clinical practice E6(R3)

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

9.3. 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

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

9.5. 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

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

9.7. 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).

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

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

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

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

9.12. EDA chairman Decree no (111) of (2022)

9.13. Law decree No (151) of (2019)

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

9.15. Importation and Customs release guidance 2021

9.16. Ministerial decree No. 399 of 2010.

9.17. Ministerial decree no.436/2006.

9.18. Ministerial decree no.132/2017.

9.19. Ministerial no.734/2016.

9.20. Clinical Trial Law Executive Regulation no. 927/2022

9.21. Prime Minister's Resolution No. (746) of 2024 for the construction of the

9.22. Supreme Council for Review of Ethics Clinical Medical Research.

10. Template forms:

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

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

10.3. List of the required documents from the Applicant to be submitted to GA of CT at EDA for clinical trials to be conducted in Egypt

10.4. List of required documents for protocol reliance submission from the Applicant to be submitted to Bio-Inn-EDA for clinical trials in Egypt.

10.5. List of required documents to be submitted to GA of CT at Bio-Inn EDA for CT package data amendment(s)

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

10.7.Progress Follow up Report Template

10.8. Corrective Action and Preventive Action (CAPA) Template

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

10.10. Investigational medicinal product (IMP) Identification Form

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

11. 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	**Non-Substantial**

	▪ 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 ▪ Other documents previously approved by EDA	
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 ▪(Where this is relevant to the ongoing trial, might alter the initial risk-to-benefit assessment)	Substantial

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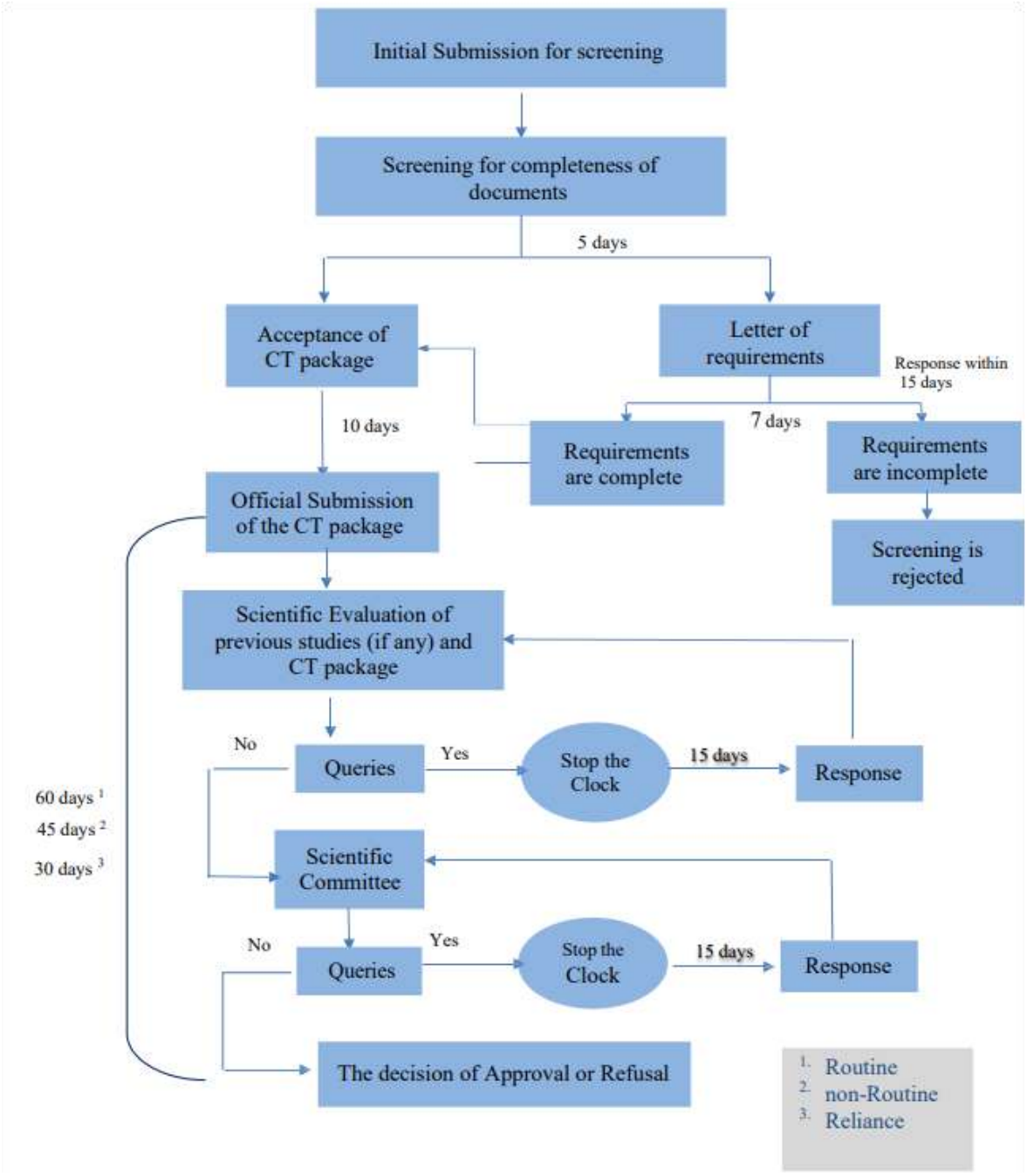
12. Annex II

Standard Time frames

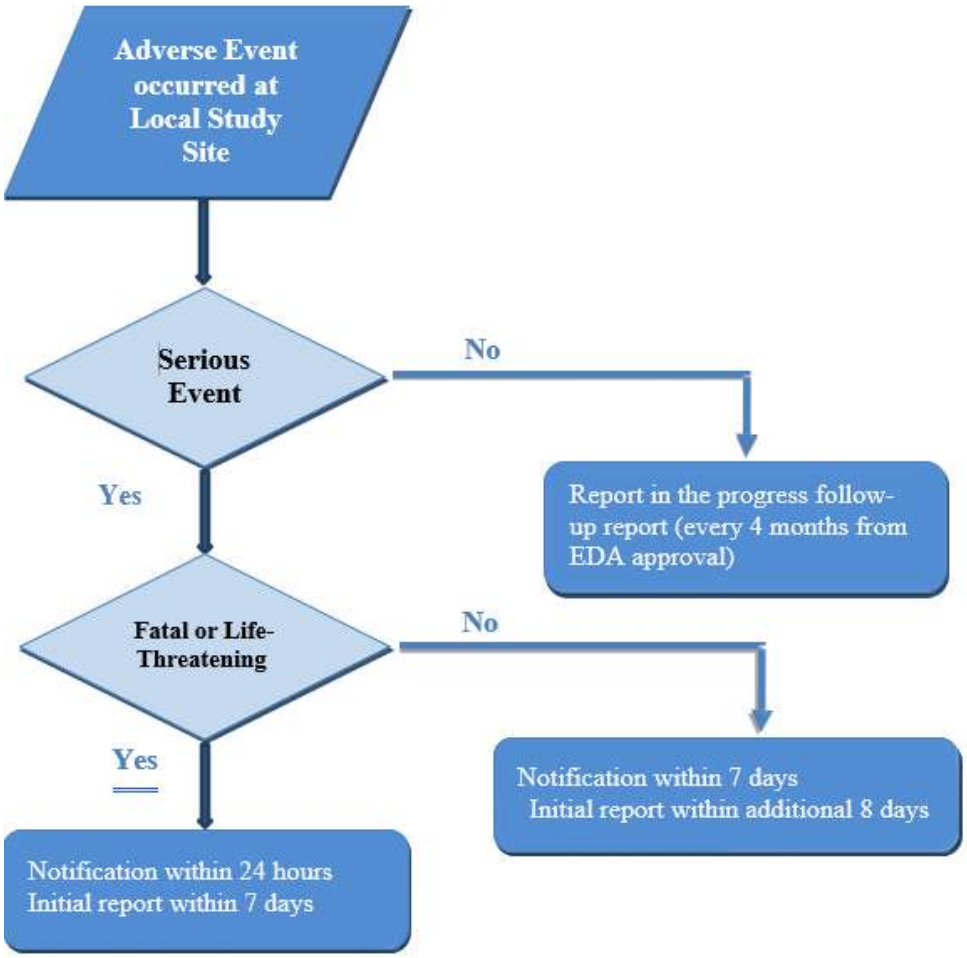
S.	Process Name	Time frame
Administration of Protocols and Studies Follow up		
1	Submission and Evaluation of Preclinical Results before First in Human Clinical Trial (FIH)	Screening: 5 days Reply assessment: 7days Final decision: 60 days Clock stopping: 15 days
2	Initial Routine Submission of Clinical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

13. Annex III


Initial Submission for screening
Screening for completeness of documents
5 days
Acceptance of CT package
Letter of requirements
Response within 15 days
10 days
7 days
Requirements are complete
Requirements are incomplete
Official Submission of the CT package
Screening is rejected
Scientific Evaluation of previous studies (if any) and CT package
No
Queries
Yes
Stop the Clock
15 days
Response
60 days [1]
45 days [2]
30 days [3]
Scientific Committee
No
Queries
Yes
Stop the Clock
15 days
Response
The decision of Approval or Refusal
1. Routine
2. non-Routine
3. Reliance

14. Annex IV

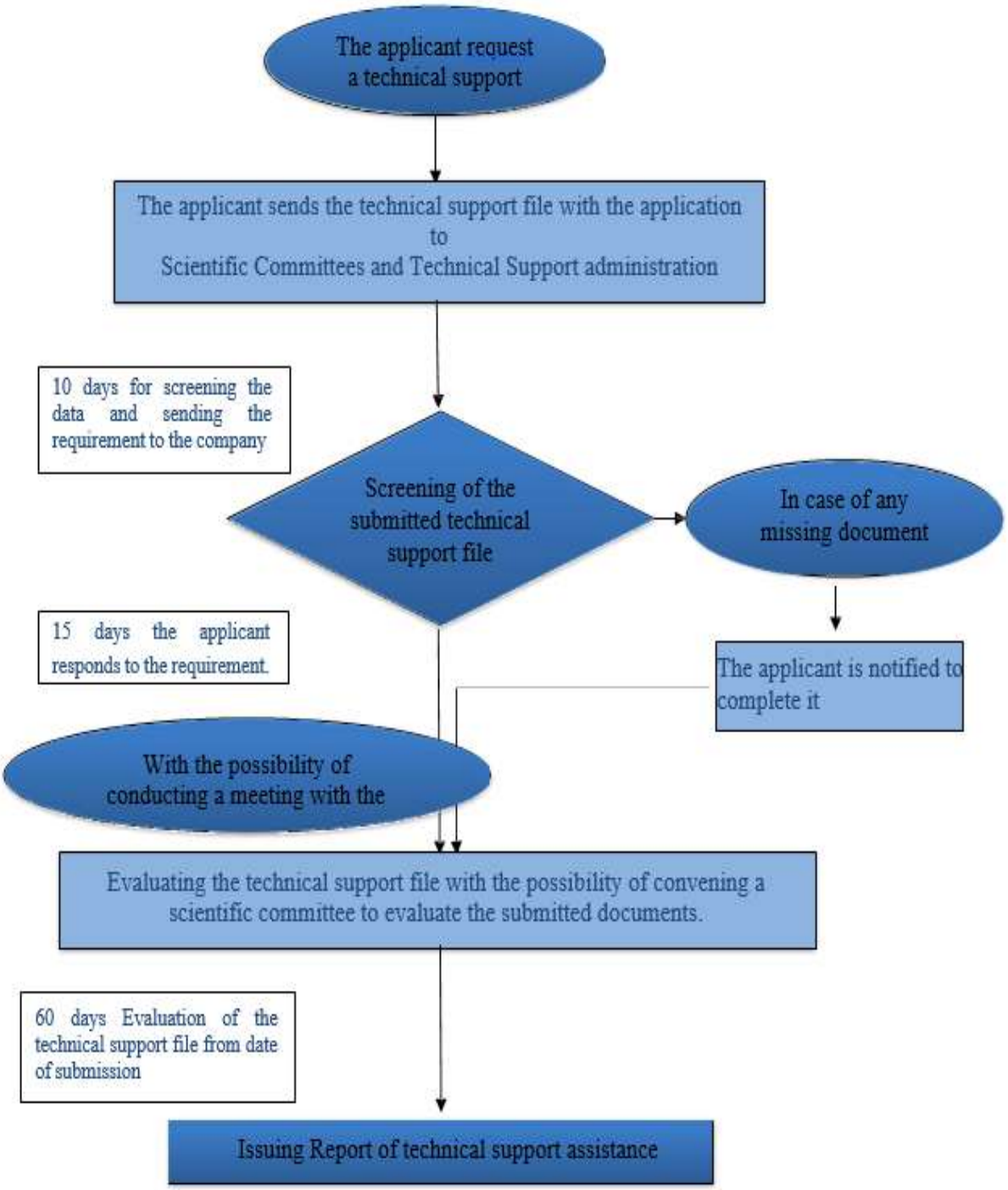
Adverse Event Reporting



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

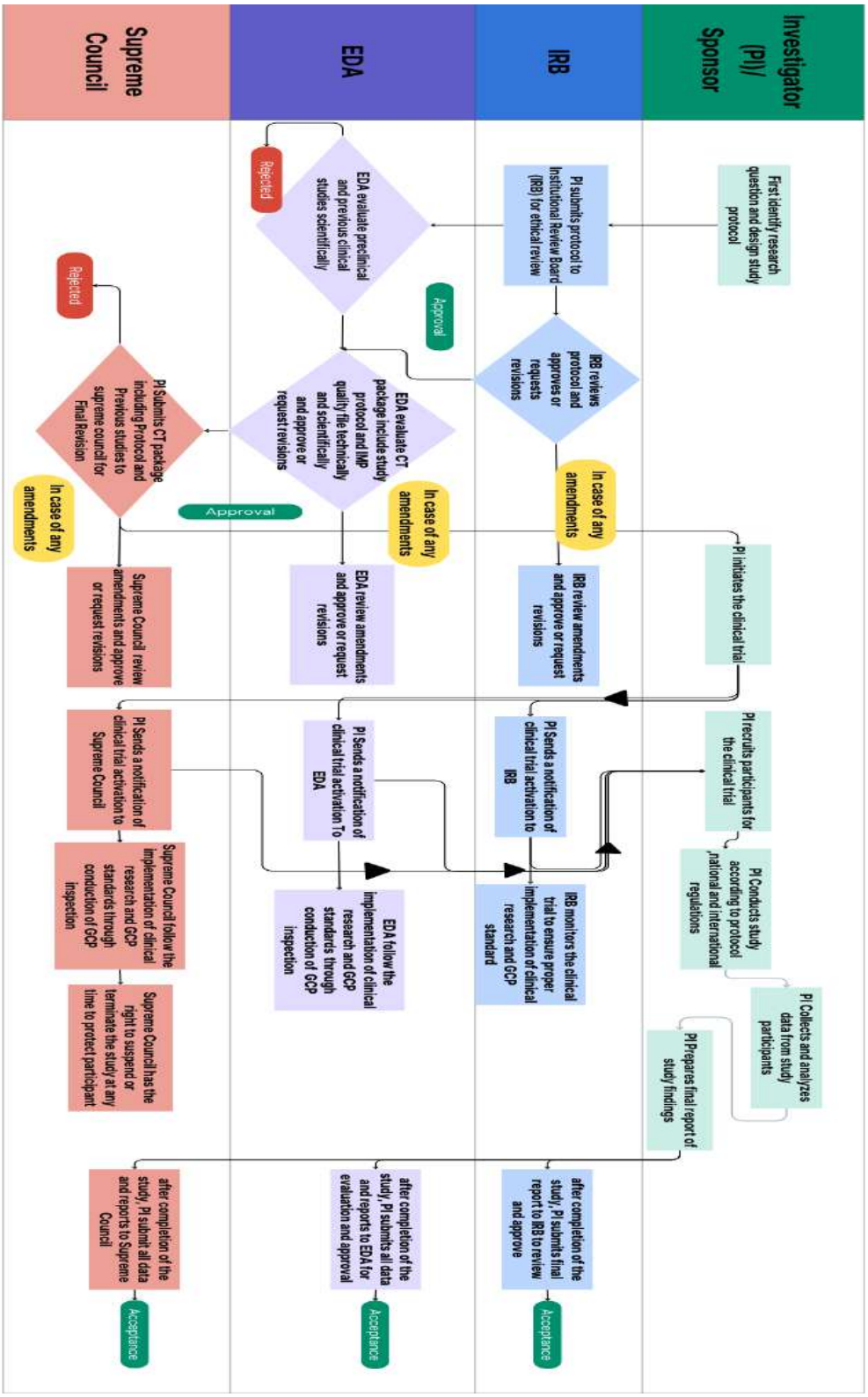
15. Annex V

Flow chart for Technical Support



16. Annex VI

Clinical Trials Oversight in Egypt



17. Document History Table:

Version Number	Issue Date	Summary of Change
1	February 2022	New version
2	January 2023	Updating to comply with Clinical Trial Law Executive Regulation no. 927/2022
3	September 2024	▪ **Add the role of supreme council** with EDA in CT oversight after issuance of "Prime Minister's Resolution No. (746) of 2024 for the construction of the Supreme Council for Review of Ethics Clinical Medical Research". ▪ **Updating the followings:** -Screening step -Evaluation step -Amendment submission pathway -Destruction of IMP and Surplus Human Samples -Interim Clinical Study Report -End of clinical medical research -Periodic reports/Progress reports -Safety reporting procedures -Suspension or Termination of the Study by EDA -Inspection of Clinical Medical Research -General Consideration -Annex I -Annex II -Annex III ▪ **The following sections are newly added:** -IMP(s) shipment unlock after release from Egyptian customs -In case of Collection of IMP samples due to quality attributes -Post-trial benefits -Investigational medicinal product (IMP) Identification Template Form -Annex VI
4	December 2025	**Updated to comply with:** ▪ **ICH E6 R3** ▪ **EDA chairman Decree no. (444/2025)**