Notice to applicant for

Post-Trial Access in Clinical Medical Research

2025

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1. Abbreviations:

Bio Inn: Central Administration of Biological and Innovative Products and Clinical Studies

CA: Continued Access

CIOMS: Council for International Organizations of Medical Sciences

EDA: Egyptian Drug Authority

IMP: Investigational Medicinal Product

PI: Principle Investigator

PTA: Post-Trial Access in Clinical Medical

SOC: Standard of care

SUSARs: Suspected Unexpected Serious Adverse Reactions

2. Definitions

Access: Access refers to the ability, right or permission of an individual to use an object or asset, and implies the removal of barriers to allow such use.

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

Post-Trial Access/ Continued Access: The provision of investigational drugs or interventions to participants after the completion of a clinical trial. This ensures continued access to a treatment that may not be otherwise available, especially if it proves beneficial during the trial phase.

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.

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.

Roll-over study: is a clinical trial design that allows participants who have completed an initial study to continue receiving the investigational treatment or to be enrolled in an open-label extension study. This approach ensures that participants maintain access to potentially beneficial interventions, particularly when the investigational product has demonstrated significant benefit or when no suitable alternative treatments are available.

The Principle 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.

3. Introduction

According to Egyptian Law No. 214 for Year 2020 Promulgating the law to regulate Clinical Medical Research (Chapter 8): (Obligations of the Research Sponsor) ,Article (20),Clause(7): "*Provide research subjects with medical intervention during and after the completion of the medical research on case-by-case basis and as required.*"

According to The Executive Regulation of the Law No. 927 for Year 2022 on Regulating Clinical Medical Researches (Chapter 6): (Obligations of the Clinical Research Sponsor), Article (25), Clause (7): "*Providing medical intervention for the participating research human subjects during and after the clinical research completion, in accordance with each individual case and in whatever form it may be, as well as transferring, preserving and storing everything related to clinical research in the appropriate safe ways.*"

In the context of clinical trials, it is essential for researchers and sponsors to ensure that participants' health needs are appropriately addressed throughout the study, and, when necessary, to facilitate the transition of participants to ongoing care once the research is completed.

The applicant should submit post-trial benefit plan according to local regulation, in addition, the protocol must describe any post-trial provisions of whether post-trial or continued access to the investigational product according to benefit -risk assessment. (if there is sufficient

efficacy and safety data to make a reasonable assessment of potential benefits and risks for the study population and the benefit/risk balance is favorable).

In advance of a clinical trial, post-trial provisions must be arranged by applicant to be provided by themselves, for all participants who still need an intervention identified as beneficial and reasonably safe in the trial. Exceptions to this requirement must be approved by a research ethics committee of the clinical trial site and EDA. Specific information about post-trial provisions must be disclosed to participants as part of informed consent.

This is justified by the principle of beneficence, which requires applicants to safeguard the health of participants when it is in their power to do so, It is also supported by the principle of reciprocity; participants assist researchers in generating valuable data and, in return, sponsors should ensure that participants receive needed care or preventive measures to safeguard their health. Furthermore, even though the provision of care during and after the trial may be an incentive for people to enroll, it should not be considered an undue influence.

4. Types of post-trial access

If post-trial or continued access is possible, the proposal must include an explanation of how such access will occur, for example:

- In a roll-over study (Open-label extension study), OR
- Through post-trial access program (PTA) of investigational product.

Where PTA to the study medicine is possible, a smooth transition must occur between the trial and the roll-over protocols or into the post-trial access program so that no harm occurs to the participant.

The applicant should notify Bio Inn-EDA via e-mail upon shifting of the participants to the post-trial benefit (Post-trial access), Then the involved PI(s) should submit declaration letters including names of participants, stating that they are proven to need continuation (based on clinical trial results and investigator benefit risk assessment) of treatment with the IMP after the end of the clinical trial and indicating the IMP quantities for the proposed duration.

When access is provided after the research to investigational interventions that have demonstrated significant benefit (sufficient efficacy and safety data and a positive benefit-risk balance), the provision may end as soon as the study intervention is made available through the local market and reasonably accessible (covered by participant's insurance or dose not Impose financial hardship) or after a predetermined period of time that the sponsors, have agreed before the start of a trial.

5. Cases where post-trial access is obligatory:

1. If discontinuing an intervention will deprive participants of basic capabilities, such as the ability to communicate or function independently, or significantly reduce a quality of life they had attained during the study.
2. When there are no available alternatives with clinical effectiveness similar to the intervention that has demonstrated significant benefit.
3. Continued access to interventions that have demonstrated significant benefit but await regulatory approval.
4. Immediately life-threatening disease, or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.
5. Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.
6. There may be instances when the individual has benefited, but the trial population has not. If trial data suggest benefit data are unfavorable, but individual participants have benefited, post–trial access must be evaluated on a case-by-case basis.

6. Cases where post-trial access is non-obligatory

1. A Supreme council, research ethics committee and EDA will discuss whether sponsors are under an obligation to provide participants with PTA/continued access to the investigational intervention in a non-inferiority trial. When the investigational intervention is not inferior to the standard of care (soc), there is no obligation to provide participants with the tested intervention, Unless the SOC is not reasonably accessible, in such cases, the benefit-risk assessment of the investigational product (IMP) must also be taken into account.
2. Applicants may no longer have an obligation to provide PTA/CA to a study intervention that has demonstrated significant benefit when the intervention becomes available at the local market, Except When participants are not able to access the needed care or prevention within the local market, in such cases there should be a system whereby participants in low-resource settings derive some benefits , for example PTA/CA to the investigational product or an established effective intervention that was provided as part of the standard of care or prevention to all participants during the research.

7. Context for Post-Trial Access / Continued Access

Phase I and II

PTA/CA is not applicable for Phase I and II studies. However, PTA /CA may be necessary for particular cases such as cancer and other dread or rare diseases for which no other medicines or other standard of care is available.

Phase III

PTA/CA should be considered for Phase III studies provided that data from interim or final analyses shows that post-trial access / continued access is clinically justifiable in light of the study's parameters and endpoints.

Benefit must be objective as well as significant to be clinically justifiable and be based on study endpoints and not only investigator opinion.

Where the standard of care (SOC) is registered and marketed (as applicable), PTA / CA of the investigational product should be considered only when data from an interim and/or final analysis shows safety and superior efficacy or have any benefit to individuals according to investigator as compared to the standard of care.

In the case of blinded controlled trials, it may take time to unblind the results and determine which participants received which intervention. Similarly, in open-label trials, there may be a delay before the statistical analysis of the data is completed and the efficacy and safety outcomes are known. applicants should make provisions for this transition period….to be discussed with ethics committee, Supreme council and EDA and inform participants if they will be temporarily receiving the current standard or the investigational product, based on the investigator's / sponsor assessment of the benefit-risk profile of the participant's response to the intervention until the final study results are available.

Phase IV

When participants are not able to access the needed care or prevention within the local health system, in such cases there should be a system whereby participants in low-resource settings derive some other benefit, for example continued access to the investigational product or an established effective intervention that was provided as part of the standard of care or prevention to all participants during the research.

8. Roles and Responsibilities in PTA/ CA Program

Egyptian Drug Authority (EDA):

1. If a roll-over study is proposed, the proposal and protocol must be submitted for scientific and regulatory review, if this extension study was not part of the original submission. An eligible participant would be enrolled in the roll-over study in the usual way and all the usual clinical trial regulations and standards would apply.
2. If an PTA/CA program is proposed, the plan must clearly outline the roles and responsibilities of the key health care personnel. The plan must be submitted for scientific and ethics review. The implications for allocation of responsibility for the cost of investigational product and other requirements must be evident.
3. The EDA reviews and tracks all Suspected Unexpected Serious Adverse Reactions (SUSARs) reports submitted by the PI/Sponsor, EDA will evaluate any adverse event data obtained from post-trial access recognizing that:

- Post-trial access treatment generally occurs outside a controlled clinical trial setting.
- Patients who receive a drug post-trial access may have a more advanced stage of the disease
- Patients who receive a drug through post-trial access may be receiving other therapies for their disease or condition at the same time.
- Patients who receive a drug through post-trial access may have one or more comorbidities.

4. An importation license must be obtained from EDA, which permits the smooth entry of drug supplies into Egypt and ensures that all concerned authorities are notified. For more details about, please refer to:

"الدليل التنظيمي للقواعد والإجراءات المنظمة لعملية الاستيراد والإفراج الطبي الجمركي للمستحضرات الطبية وخاماتها ومستلزمات التعبئة والتغليف"

Sponsors:

1. In advance of a clinical trial, post-trial provisions must be arranged by sponsors for all participants who still need an intervention identified as beneficial and reasonably safe in the trial.
2. Sponsor shall agree with the PTA/ CA program before a trial starts that any intervention that has demonstrated significant benefit will be provided only for a predetermined period of time.
3. The sponsor may impose conditions on providing a drug to ensure that it is used in accordance with the latest information available.

4. Provide research subjects with medical intervention during and after the completion of the medical research on case-by-case basis and as required.
5. Notify EDA upon shifting of the participants to the post-trial benefit (post-trial access).
6. Sponsor is also responsible for providing all relevant information of safety and efficacy for CA/PTA program.
7. Sponsors are responsible for ensuring that they meet the national regulatory requirements for the imported medicinal products.
8. Sponsors are responsible for complying with local safety reporting requirements.
9. The trial sponsor is responsible for ongoing monitoring throughout the clinical trial and the overall product development program to assess whether an unmet medical need persists or justifies the plans for continued access to the investigational product.
10. When new relevant information may become available (e.g., adverse events) that could impact PTA/ CA plans, the PTA/ CA plan should be updated in all relevant documents (protocol and informed consent) and communicate to all parties (investigators, ethics committees, EDA and participants). In addition to receiving new information, the sponsor should define, and the protocol should clarify, the time duration for routine review and assessment of the continued access plan (e.g., annual assessment).
11. Submitting Benefit/Risk assessment of Investigational product.
12. Discussing with IRB, EDA exceptions of PTA/ CA provisions.

Principle Investigator:

1. Ensuring that information about post-trial provisions are disclosed to participants as part of informed consent.
2. Ensuring that any PTA/ CA benefit plan was submitted according to local regulations.
3. Upon shifting of the participants to the post-trial benefit (Post-trial access Program) The involved PI(s) should submit declaration letters to EDA 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, as follows:

Principle Investigator	Patient Number	Patient Name	Scheduled completion Date.	Treatment dose allowed for proposed duration.

*For further information regarding importation, please refer to:

" الدليل التنظيمي للقواعد والإجراءات المنظمة لعملية الاستيراد والإفراج الطبي الجمركي للمستحضرات الطبية وخاماتها ومستلزمات التعبئة والتغليف."

4. Investigators are responsible for reporting adverse events to EDA during PTA/ CA according to local guidelines.
5. Discussing with IRB, EDA exceptions of PTA/ CA provisions.
6. Maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with local regulations.

7. The investigator is responsible for evaluating, determining, and communicating (to the participant and sponsor) whether the individual's benefit/risk assessment warrants continued access to the intervention(s) received during the trial in accordance with research program.
8. The investigator is ultimately responsible for determining if the ~~newly~~ available treatments are appropriate for the individual patient given the specific medical situation. Even if new treatments become available, patients for whom the alternative treatment is not appropriate may exist.

9. References

9.1 Egyptian Law No. 214 for Year 2020 Promulgating the law to regulate Clinical Medical Research.

9.2 Prime Minister's Decree No.927 of 2022 on Promulgating the Executive Regulation of Law on Regulating Clinical Medical Researches

9.3 Guideline for Good Regulatory Oversight of Trials by the Egyptian Drug Authority, Issue date: 15 Sep. 2024.

9.4 WMA declaration of Helsinki 64 WMA General Assembly, Fortaleza, Brazil, October 2013 and by the 75 WMA General Assembly, Helsinki, Finland, October 2024.

9.5 International Ethical Guidelines for Health-related Research Involving Humans, Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) 2016.

9.6 Clinical research in resource-limited settings A consensus by a CIOMS Working Group Council for International Organizations of Medical Sciences (CIOMS) 2021.

9.7 FDA Expanded Access to Investigational Drugs for Treatment Use Questions and Answers Guidance for Industry. Updated October 2017.