Notice to applicant

Off-site Nursing in Clinical Trials

2024

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1. Abbreviations:

- **CRF/eCRF:** Case report form/electronic case report form
- **DCT:** Decentralized Clinical Trial
- **ECG:** Electrocardiogram
- **EDA:** Egyptian Drug Authority
- **EMA:** European Medicines Agency
- **FDA:** Food and Drug Administration
- **GCP:** Good Clinical Practice
- **ICH:** International Council for Harmonization
- **IMP:** Investigational Medicinal Product
- **IRB:** Institutional Review Board
- **IRTS:** Interactive Response Technology system
- **P1:** Principal investigator

2. Definitions

Decentralized Clinical Trial (DCT): A clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites using technology to communicate with study participants and collect data.

Investigational Product (IP): Human drugs, biological products, or devices that are being investigated in a clinical trial

Off-site research nursing: (also called mobile or decentralized or remote nursing) This element of DCTs involves the provision of nursing services of simple tasks outside of traditional clinical settings either at participant home or an appropriate facility equipped for the requested activities, as per EDA regulations on a case-by-case basis

Healthcare professional: Health professionals maintain health in humans through the application of the principles and procedures of evidence-based medicine and caring. It includes medical doctors, nursing professionals, midwifery professionals, dentists, and pharmacists or who perform services in allied health professions.

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”.

Telemedicine: The use of electronic information and telecommunications technologies to support and promote long-distance clinical health care

3. Scope

This guidance addresses off-site nursing concept in interventional clinical trials conducted in the Arab Republic of Egypt under the oversight of the Egyptian Drug Authority (EDA) including investigational medicinal products, biologics and medical devices. In conjunction with this guidance, Clinical Trials Law 214/2020 92 and its executive regulation and international GCP Guidelines according to ICH E6 as well as the latest Guideline for

Good Regulatory Oversight of Clinical Trials (EDREX.GL.Bioinn.006) should be applied to off-site nursing aspects of DCTs.

4. Introduction

As evident during the COVID-19 pandemic, the utilization of decentralized solutions in clinical trials was essential and has shown to be quite helpful. Decentralized clinical trials are clinical trials where some (hybrid DCTs) or all (fully DCTs) trial-related activities are conducted at trial participants' home or another appropriate location. In a fully decentralized trial, all activities are conducted away from traditional sites, taking place at participants' homes or local healthcare facilities that offer convenience to the participants. In a hybrid DCT, certain activities require participants to visit traditional clinical trial sites, while other components are conducted at alternative locations, such as participants' homes. The choice of fully or hybrid decentralized trials depends on the clinical trial and IMP characteristics. Fully decentralized trials may be appropriate for IMPs that are simple to administer or use, have well characterized safety profiles, and do not require complex medical assessments.

DCTs involve patient-centric and innovative approaches in the design and conduct of clinical trials. They provide flexibility and enhance efficiency, addressing challenges faced in traditional clinical trials such as patients traveling long distances to study sites, which can be costly, time consuming and inconvenient.

This guidance will specifically address off-site nursing (also called mobile or decentralized or remote nursing) demonstrating the benefits along with the challenges of utilizing off-site nursing in clinical trials. Off-site research nursing involves the provision of nursing services of some simple tasks outside of traditional clinical settings either at participants' homes or at a local healthcare facility. In addition, qualifications of off-site nurses and examples of acceptable responsibilities are mentioned as well.

Overall, EDA regulations and recommendations regarding mobile nursing is illustrated throughout the document. It is important to take into consideration that general regulations and relevant laws to protect trial participant's safety, rights and well-being should be sustained in addition to this guidance. Approval by all stakeholders including ethics

committees, EDA and Supreme council is required. EDA will periodically perform inspections on clinical trial sites to ensure that Good Clinical Practice (GCP) is maintained as indicated in details in the Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority (EDREX.GL.Bioinn.006). Regarding DCTs, EDA will also ensure that off-site activities are conducted in accordance to applicable laws and regulations and in compliance with regulatory requirements and ethical standards through review of source documents and off-site nurse interview, if applicable.

5. Benefits and Challenges of Decentralized Clinical Trials

5.1. Benefits of DCTs:

5.1.1 Reduce the need for travel and improve engagement, recruitment, and retention amongst potential participants with challenges accessing traditional clinical trial sites such as immobile or elderly subjects

5.1.2 More diverse participant populations

5.1.3 Flexibility and more comprehensive understanding of participants' daily lives

5.1.4 Higher reachability for the patients to ask about any safety issues/events in between the traditional site visits

5.1.5 Ensuring the proper handling of the study IMP through continuous drug accountability

5.1.6 Reduced trial costs

Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine, may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations and risks of such methods and the requirements for data protection should be taken into account and such alternative arrangements need to be adequately documented.

5.2. Challenges of DCTs:

5.2.1 Maintaining data security and privacy

5.2.2 Preserving data integrity and reliability

5.2.3 The need for robust technology infrastructures

5.2.4 A major challenge facing principal investigators is to maintain clinical trial oversight for trial-related activities performed at locations other than the clinical trial site.

5.2.5 Coordination of trial activities with individuals and facilities in multiple locations that are not traditional clinical trial sites.

5.2.6 The decentralized features of the trial may necessitate additional training, coordination, and standard operating procedures to ensure consistent implementation.

Sponsor responsibilities are the same for DCTs and traditional site-based clinical trials. Challenges must be carefully mitigated in order to ensure the success of decentralized clinical trials. Actions should be proportionate and based on benefit-risk considerations and contingency provisions taken nationally and locally by the authorities, with priority given to the impact on the health and safety of the trial participant. EDA encourages risk based monitoring approaches of DCTs to identify, follow up and apply corrective and preventive actions with regards to missing data, inconsistent data, and potential protocol deviations.

6. PI and Sponsor Responsibilities

Concerning DCTs, the below-mentioned responsibilities in addition to the responsibilities of PI and sponsor in traditional site-based clinical trials are applicable.

6.1. Principal Investigator (PI)

6.1.1 Maintaining clinical trial oversight for all trial-related activities performed at locations other than the clinical trial site and ensuring that the remote visits are conducted appropriately and in a timely manner within the permitted visit window as specified in the study protocol

6.1.2 Responsible for the decision of suitability of IMP remote administration which should be documented (for example in source documents)

6.1.3 Follow-up, at regular intervals, with participants to ensure the IMP is taken appropriately and in accordance with the approved protocol

6.1.4 Ensuring data of off-site visits are entered into the CRF/eCRF and documented in source documents with accuracy, completeness, legibility and timeliness of the data

6.1.5 Approving delegated research off-site nurses

6.1.6 Discontinuation of remote administration or use of IMP and immediately notifying EDA, Supreme council , the IRB, and the sponsor if any significant safety risks are identified as a result of the remote administration or use of an IMP

6.2. Sponsor

6.2.1 Maintaining clinical trial oversight and describing in the trial protocol how operational aspects of the DCT will be implemented.

6.2.2 Approving the protocol if applicable to be offsite nursing

6.2.3 Considering whether the IMP is suitable for administration at home

6.2.4 Discontinuation of remote administration or use of IMP and immediately notifying EDA and all investigators participating in the trial if any significant safety risks are identified as a result of the remote administration or use of an IMP

6.2.5 Reviewing and approving in advance the quantity of the trial medicine to be shipped

6.2.6 Providing alternatives in case subjects prefer site visits

6.2.7 Ensuring that the remote visits are conducted appropriately and in a timely manner within the permitted visit window as specified in the study protocol

6.2.8 Monitoring the accuracy of information that will be logged into source documents

6.2.9 Protecting participant's personal information confidentiality

7. Off-site Nurse Criteria and Qualifications

Off-site nurses should be qualified, experienced and well-trained to follow the study protocol, good clinical practice (GCP) principles, all the applicable local laws and regulations, international and national guidelines as well as strictly following the principal investigator’s instructions.

7.1. Training and Qualifications of off-site nurses must include the following:

7.1.1 Technical Institute of Nursing degree, practice license from Ministry of Health in Egypt and registration in the Egyptian Nursing Syndicate

7.1.2 Valid and up-to-date Good Clinical Practice, Good Documentation Practice, and safety reporting training

7.1.3 Protocol-specific training covering all the study details and the subjects' visits activities, covering the IP administration and handling instructions as per protocol

7.1.4 Additional training in remote monitoring, and effective communication skills with participants and other study personnel and ability to adapt to different patients' cultural backgrounds

At the start of the study, the sponsor approves if the protocol is applicable to be offsite nursing and all the delegated research nurses will need to be approved formally by the principal investigator

8. Off-site Nurse Roles and Responsibilities

8.1. Roles and responsibilities may include one or more of the following:

8.1.1 IP administration (which may be injectables, oral, topical, via nebulizer or inhaler)

8.1.2 Adverse event identification and prompt reporting to investigators for investigator assessment and safety evaluation.

8.1.3 Management procedure for any adverse effect occur to trial participant until going to a hospital if needed according to the principal investigator instructions.

8.1.4 Concomitant medication reporting

8.1.5 Collecting Vital Signs and temperature (tympanic, oral, infra-red)

8.1.6 12-lead ECG recording

Note that it is the investigator's responsibility to interpret the ECG report and personally sign and date it.

8.1.7 Blood sample (pharmacokinetic or safety lab tests) collection and preparation

8.1.8 Urine sample collection and processing

8.1.9 Attaching of monitors such as cough and spirometry monitors

8.1.10 Diary compliance and Questionnaire completion checks

8.1.11 Weight and Height measurements

8.1.12 Ensuring compliance with study protocols and conducting drug accountability

8.1.13 Documenting all off-site visits details to be shared with the principal investigator and then added by the investigator or their delegated staff to the CRF/eCRF and patient's

file in the source documents or direct completion of CRF/eCRF and source documentation.

8.1.14 Any other responsibility is assigned by sponsor and delegated by PI as per protocol and approved by national regulatory authority.

9. Considerations on IMP Administration at the Trial Participant's Home

- It is the responsibility of the sponsor to consider whether the IMP is suitable for administration at home or at an appropriately equipped facility and approved by EDA on a case-by-case basis

- IMPs that involve complex administration procedures; special preparation or handling requirements; have a high-risk safety profile, especially in the immediate post-administration period; or are in early stages of development such that the safety profile is not well defined may need in-person supervision by the investigator at a trial site. Generally, if any significant safety risks are identified as a result of the remote administration or use of an IMP, sponsors must discontinue remote administration or use and immediately notify EDA, Supreme council, the IRB, and all investigators participating in the trial.

- The investigator remains responsible for the decision of treatment which should be documented (for example in source documents, prescription or Interactive Response Technology system (IRTS)) prior to the administration of IMP at the trial participant's home.

- The investigator should follow-up, at regular intervals, with participants to ensure the IMP is taken appropriately and according to the IMP instructions.

- The used IMP should be returned by the health care professional from the trial participant's home, for accountability and destruction according to regulatory requirements. Procedures for the accountability of the IMP must be in place (among others for compliance monitoring). Accountability of the IMP should be maintained. Clear records of shipment from the trial site or from the distributor should be kept in the investigator site file, itemizing the medication being delivered and the quantity involved.

- Consideration must be given to sharps disposal, single use items disposal, transport of specimens (in case of blood sample collection by off-site nurses), and infection control.

- Ensure safe and compliance for transport of specimens and cold chain maintenance of IMP and blood samples.

- Precautions for equipment required to maintain clinical safety (gloves, goggles, hand wash).

10. Considerations on IMP delivery direct to trial participants

- If an IMP is required to be administered by a healthcare professional (nurse), shipping directly to the trial participant may not be appropriate.

- If the IMP is delivered to the participant's home by the health care professional (nurse), the nurse should be informed of, and commit to, the shipment conditions (regarding temperature) and maximum duration.

- The maintenance of the medicine's stability and the maintenance of the appropriate storage conditions during the transportation by nurse should be evidenced and recorded and these records should be kept at the site.

- In the event it is required for IMP to be shipped directly to the trial participant separately, clear instructions for storage of the IMP prior to healthcare professional visit should be given, as well as a clear explanation that the IMP is not to be administrated before the visit of the healthcare professional nor before the investigator's decision. In addition, if the IMP is to be shipped directly to the trial participant separately, the IMP delivery Direct to Patient considerations should be followed.

- The participant should be consented for the direct shipment of the trial medicine. The consent should clarify that the participant's information (name, address, telephone) will be revealed to the distributor.

- IMP shipment to the trial participants should be described in a contract or other supplementary documentation between the sponsor and the distributor. The contract should identify all involved investigators/ trial sites, if applicable.

- The participant's personal information should not be used for any other purpose or disclosed to a third party by the distributor for any purpose, other than monitors, auditors, or inspectors verifying the conduct of the trial. This should be set out in the contract between the sponsor and distributor.

- The organizational measures agreed between the sponsor and the contracted distributor should protect blinding (if applicable) and ensure compliance with the randomization.

- The participant should provide acknowledgment of receipt of the trial medicine. This acknowledgment should include the date of receipt and the quantity received and should be kept in the subject's file at the site.

- The quantity of the trial medicine to be shipped should be recorded with evidence that it was reviewed and approved in advance by the sponsor or designee in agreement with the investigator.
  These records should be kept at the site.

- Return of unused trial medicine as well as empty packages should be recorded.

- Trial medicine accountability should be accurately recorded and maintained at the study site.

- A secure trackable method should be used for the direct shipment of the trial medicine to the participant.

- The maintenance of the medicine’s stability and the maintenance of the appropriate storage conditions during the transportation should be evidenced and recorded and these records should be kept at the site.

- The courier should be informed of, and commit to, the shipment conditions (regarding temperature) and maximum duration.

- Procedures should be in place for IMP return from the trial participant’s home, and destruction of the unused IMPs, in compliance with the protocol and local safety requirements. The procedure should also cover recalls during the conduct of the trial, and the

steps taken to avoid that the IMP remains at the trial participant's home beyond the foreseen treatment period.

11. Regulatory Considerations

Off-site nurses must be included in the delegation log with assignment of specific and clear tasks. Furthermore, utilization of remote nursing should be stated clearly in the study protocol with documentation of all related details including, but not limited to, pre-specification of tasks done by off-site nurses and the place at which they will be conducted, how oversight is maintained, clear communication plan between the nurses, sponsor, investigator and participants, means for documentation of notes (paper or laptop or tablet) and whether off-site nurses will be responsible to enter data directly into the CRF\eCRF, in this case the investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools completed by the investigator site (e.g., case report form (CRF)) and in all required reports, or to communicate it to the investigator who will be responsible for its entry into the appropriate CRF\eCRF. The trial protocol should specify how adverse events identified remotely will be evaluated and managed especially adverse events of special interest or adverse events that require urgent in-person medical care. Procedures for adverse event management and reporting during off-site visits should be available. Off-site nurses must sign a financial disclosure form and confidentiality agreement as well.

In case some trial related procedures are intended to be performed at the participant's home, suitability of conducting these procedures at home should be evaluated and participants must be informed during the informed consent process. Trial-related procedures at home should be done only if neither the participants are exposed to additional risk nor data reliability is affected. Also, insurance should cover any damage resulting from trial related procedures performed at home.

The sponsor should provide alternatives in case subjects prefer site visits and investigator's contact should be provided to trial participants whether off-site or site visits are chosen in case patients need support.

Since it is the responsibility of the investigator and sponsor to ensure that the remote visits are conducted appropriately and in a timely manner within the permitted visit window specified in the study protocol and to facilitate the clinical trial oversight by the principal investigator and ensure accuracy of information that will be logged into source documents, a checklist may be used by off-site nurses during remote visits.

The following is an example:

Participant ID\ Subject number	Visit number and date	Visit start time	Visit completion time	Activity/ Assessment carried out	Notes/ Observations	Investigator review

Any additional specific issues related to the feasibility, design, implementation, or analysis of a DCT should be discussed early with EDA.

12. References

12.1. EMA Recommendation Paper on Decentralized Elements in Clinical Trials, Version 01, 13 December 2022

12.2. FDA Guidance on Decentralized Clinical Trials