Report of Classification, Analysis, and Trending of GCP Inspection Data and Findings.

Metrics Period: From 01/01/2023 to 31/12/2023
Report Date: 07 Feb 2024

This report provides information about inspections conducted during the period from 1 Jan 2023 to 31 Dec 2023, and about deficiencies identified during these inspections. The report focuses on areas of non-compliance to help clinical trial sites, investigators, and sponsors to improve their adherence to GCP and local regulations and to be well prepared for inspections conducted by the Egyptian Drug Authority. Observed deficiencies are grouped under 8 main categories and graded as critical, major, or minor consistent with the inspection programs of the European Medicines Agency (EMA) and other international guidelines.

I- Inspections Metrics:

During the period covered by this report, EDA conducted a total of 25 GCP inspections classified by Type of Inspection, Type of IMP, Study Phase, Inspection Timing, Type of Inspected Facility, Type of Clinical Trial Site, Study Sponsorship, and Geographical Region as described in Table 1 and Figures 1-7.

Table 1: Numbers of Conducted GCP Inspections Classified by different Indicators.

Type of Inspection	**Routine (%)**	**Triggered (%)**	**Follow up (%)**			**Total number**
	22 (88%)	3 (12%)	0			25
Type of IMP	**Biological**	**Pharmaceutical**	**Innovative**	**Medical Device**		
	10 (40%)	11 (44%)	3 (12%)	1 (4%)		25
Study Phase	**Pre-clinical**	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	
	0	5 (20%)	2 (8%)	10 (40%)	8 (32%)	25
Inspection Timing	**Pre-initiation**	**During the conduction**	**After the end of the trial**			
	0	21 (84%)	4 (16%)			25
Inspected Facility	**Clinical Trial Site**	**Laboratory**	**CRO**	**Vendor**	**Sponsor**	

	25 (100%)	0	0	0	0	25
Type of Clinical Trial Site	**Academic Institution**	**MoH public Hospital**	**Private Hospital/Research Center**	**NGO**		
	19 (76%)	2 (8%)	3 (12%)	1 (4%)		25
Study Sponsorship	**Pharmaceutical Company**	**Investigator Initiated Trial**				
	22 (88%)	3 (12%)				25
Geographical Region	**Inside Cairo**	**Outside Cairo**	**Inside Egypt**	**Outside Egypt**		
	12 (48%)	10 (40%)	22 (88%)	3 (12%)		25

Figure 1: Number of Conducted Inspections Classified by Inspection Type.

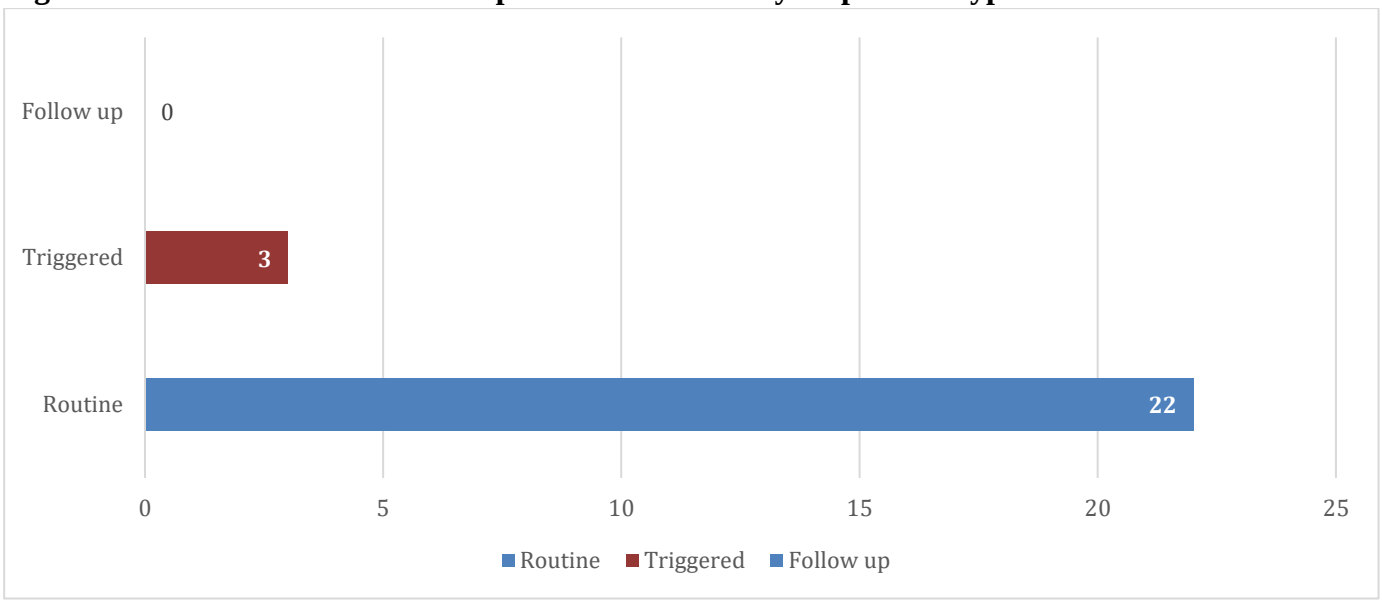


Figure 2: Number of Conducted Inspections Classified by Type of IMP.

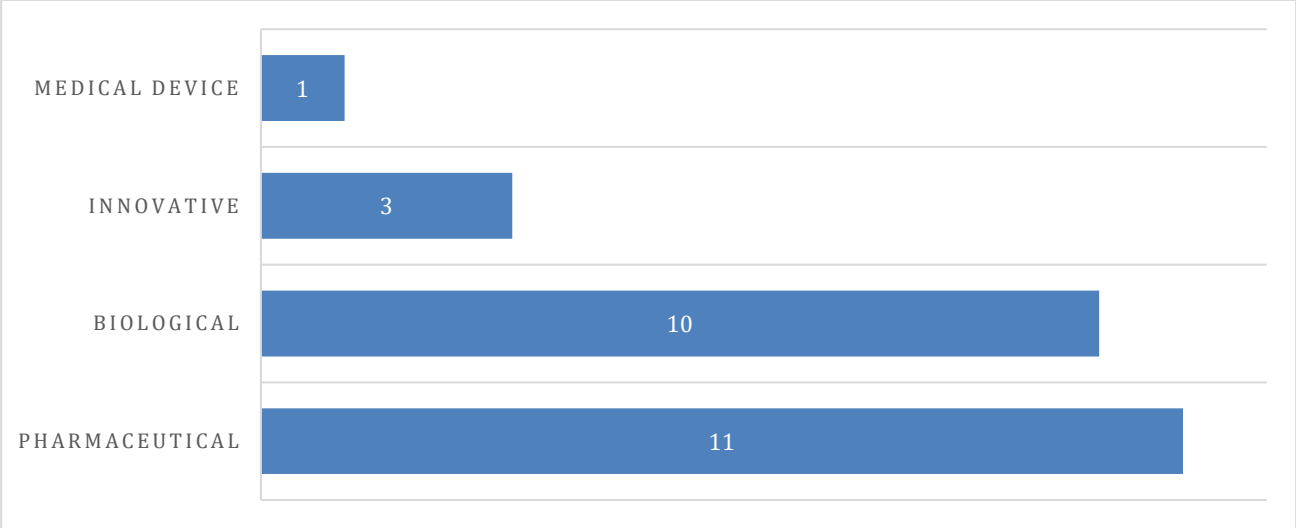


Figure 3: Number of Conducted Inspections Classified by Study Phase.

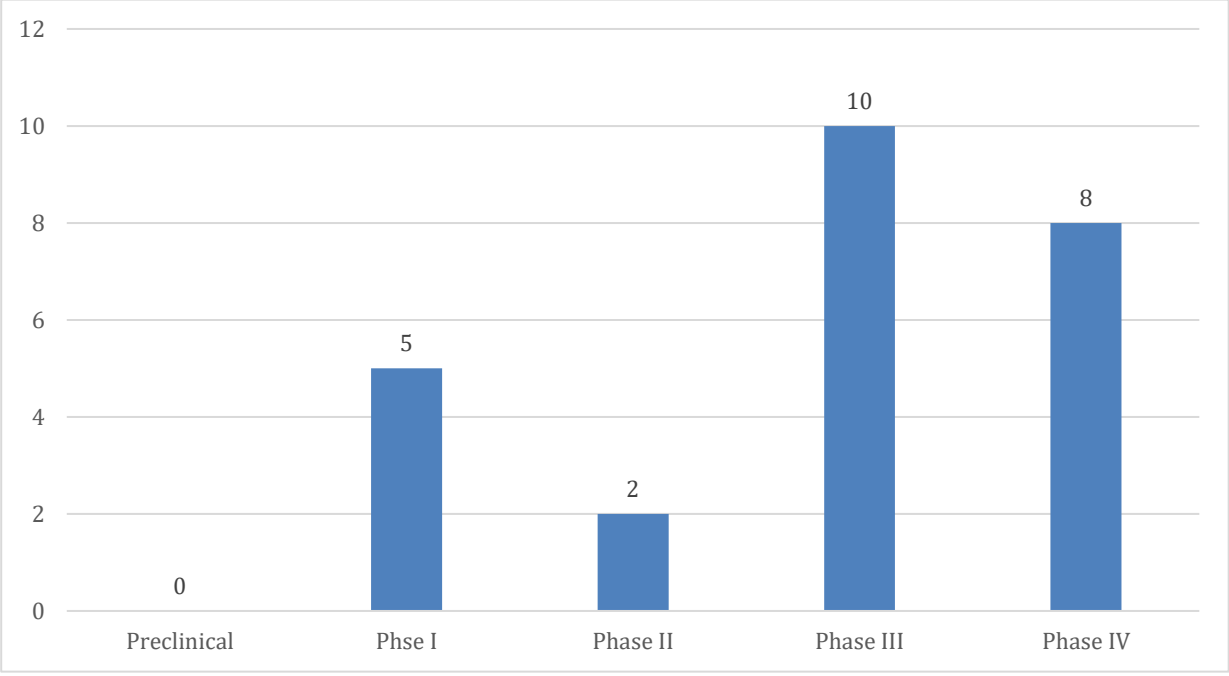


Figure 4: Number of Inspections Classified by Timing related to Study Conduction.

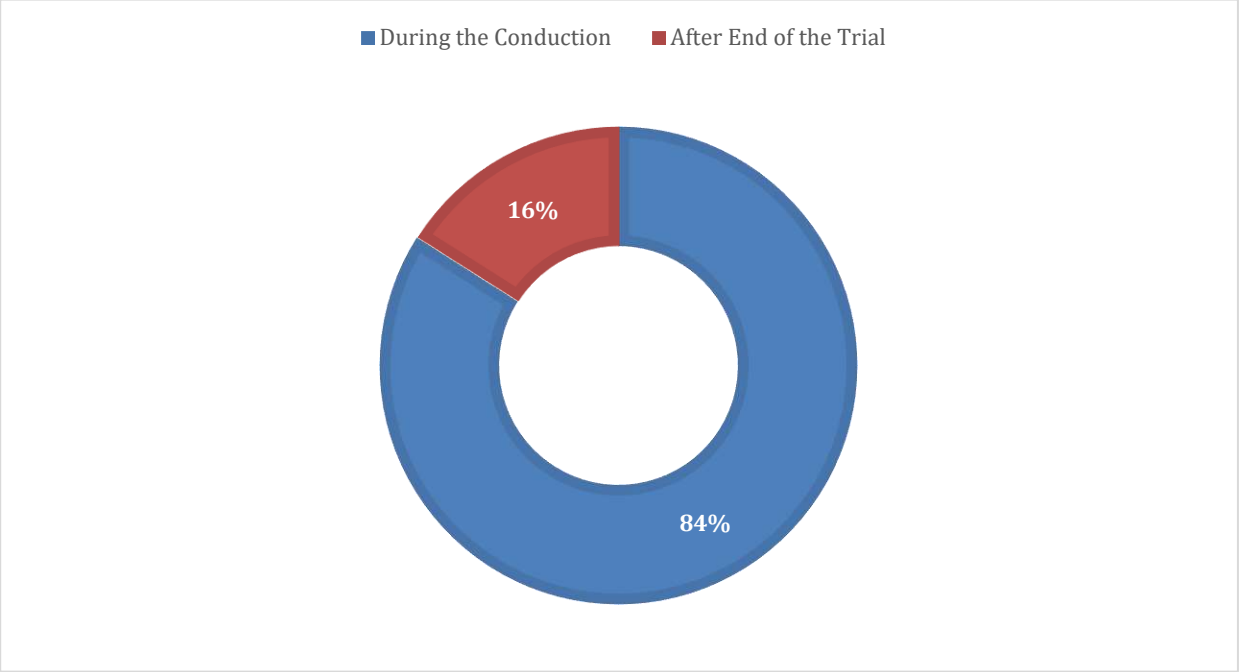


Figure 5: Number of Inspections Classified by Type of Clinical Trial Site.

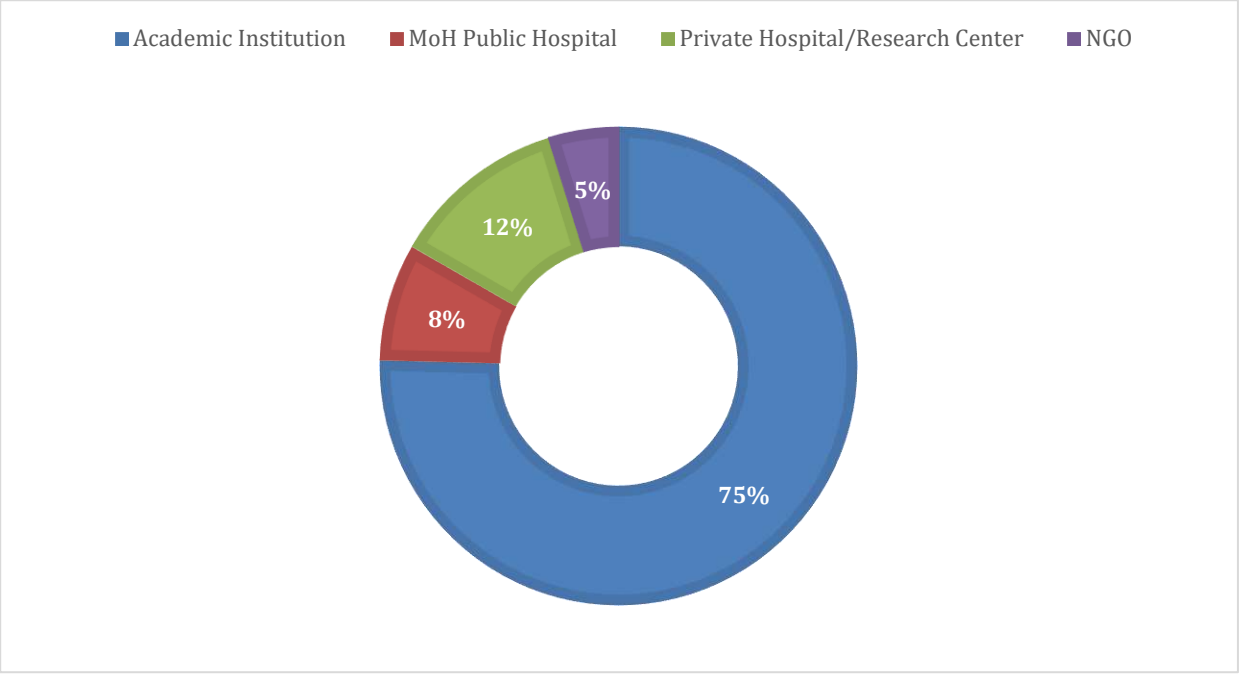


Figure 6: Number of Inspections Classified by Study Sponsorship.

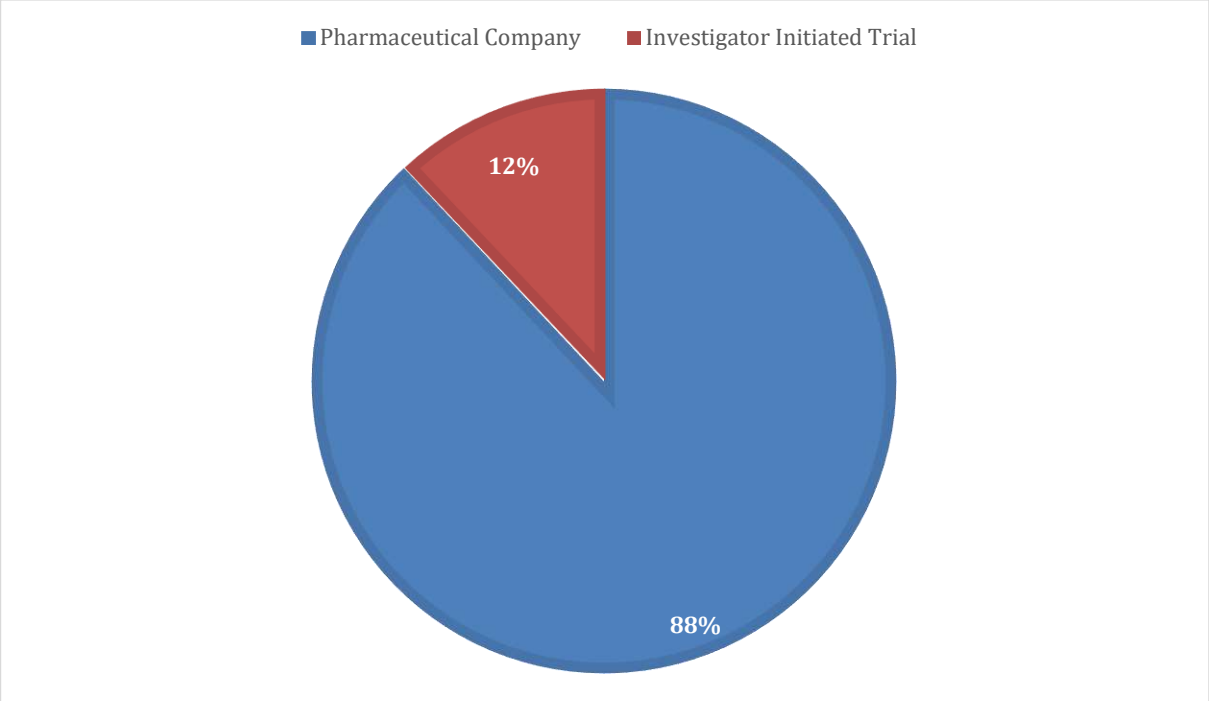
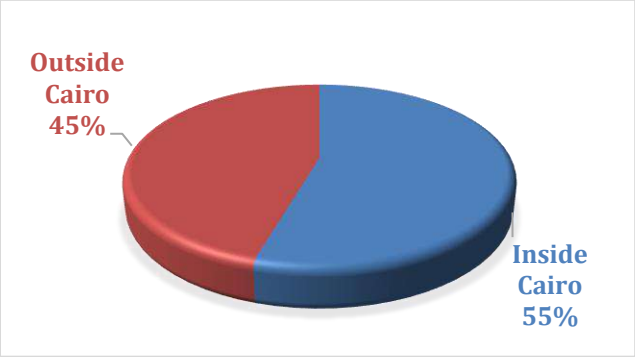
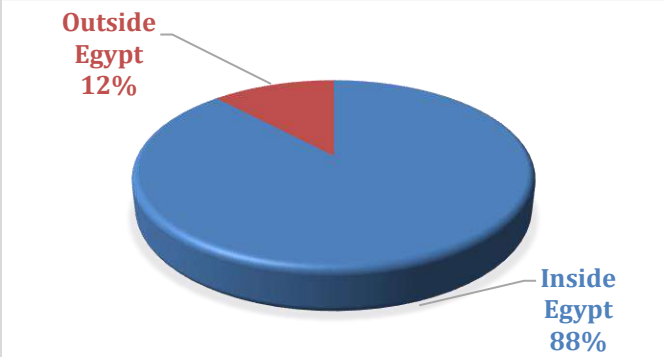


Figure 7: Number of Inspections Classified by Geographical Region.





Deficiencies addressed during the conducted inspections were identified in 7 main categories and were graded as critical, major, or minor according to their effect on the rights, safety or well-being of the subjects and/or the quality and integrity of data. All the identified deficiencies were appropriately addressed by the clinical trial sites through the development of Corrective and Preventive Action Plans submitted by applicants to EDA, and all deficiencies within this reporting period have been rectified.
The number and percentage of findings categorized by main category, as well as the number and percentage of different grades in total and in each category are identified in Table 2 and presented in Figure 8.
The most frequently observed finding category from all conducted inspections was Quality of Data/Records and Reports (Documentation) representing 39% of all findings.
Critical findings accounted for 6% of the total findings, major findings accounted for 20% and the majority (74%) were graded as minor.

The modes of the finding categories for each grade (Critical, Major, Minor);

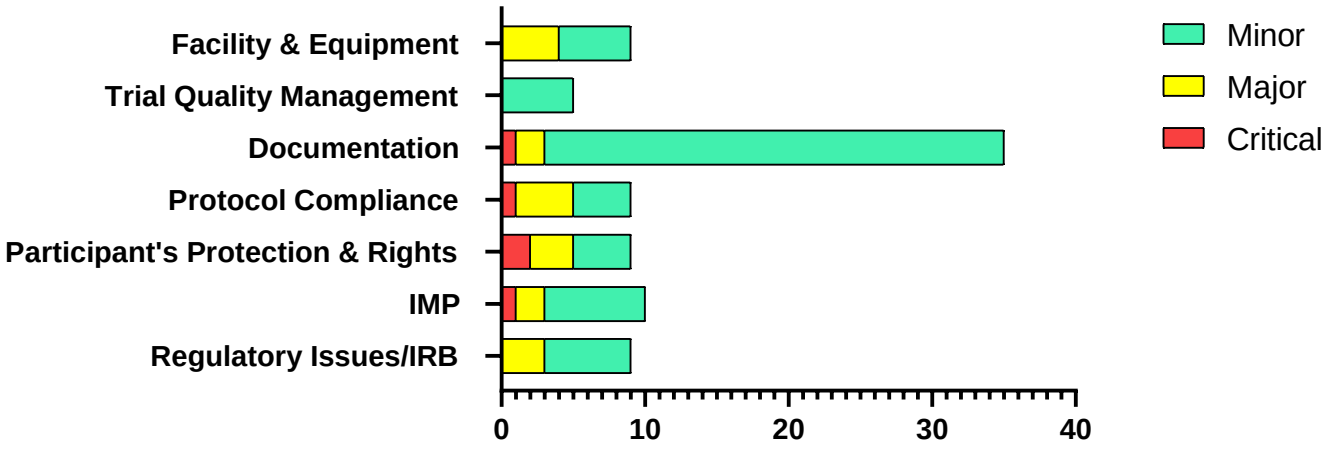
- The most frequently observed finding category for critical grade was Participant's Protection and Rights representing 40% (2 out of 5) of all critical findings.
- The most frequently observed finding category for major grade were both Protocol Compliance and Facility/Equipment/Laboratories/Technical Facilities representing 22% (4 out of 18 each) of all major findings.
- The most frequently observed finding category for minor grade was Quality of Data/Records and Reports (Documentation) representing 48% (32 out of 66) of all minor findings.

Table 2: Number and Grading of identified Deficiencies by Main Category

Main Category	Critical (%)	Major (%)	Minor (%)	Total by Main Category (%)
Regulatory issues/Ethics Committee (IRB)	0 (0%)	3 (17%)	6 (9%)	9 (10%)
Investigational Medicinal Product (IMP)	1 (20%)	2 (11%)	7 (11%)	10 (11%)
Participants' Protection and Rights	2 (40%)	3 (17%)	7 (11%)	12 (14%)
Protocol Compliance	1 (20%)	4 (22%)	4 (6%)	9 (10%)
Quality of Data/Records and Reports (Documentation)	1 (20%)	2 (11%)	32 (48%)	35 (39%)

Trial Quality Management	0	0	5 (7.5%)	5 (6%)
Facility and Equipment /Laboratories/Technical Facilities	0	4 (22 %)	5 (7.5%)	9 (10%)
General and Others not listed above	0	0	0	0
Total	5 (6%)	18 (20%)	66 (74%)	89

Figure 8: Summary of Identified Deficiencies by Main Categories and Grades



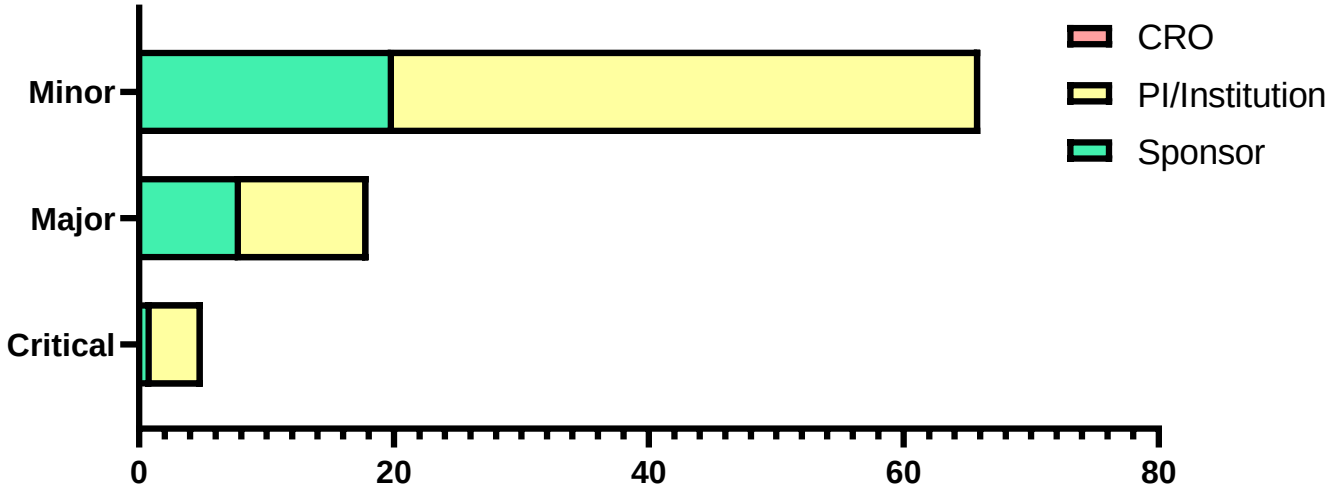
Most of the findings (67%) rest with the responsibility of the PI/Institution, the same mode of responsibility was observed for critical as well as major findings. The numbers and percentages of finding responsibilities in different grades are identified in Table 3 and Figure 9.

Table 3: Number and Percentage of Responsibility of Different Grades of Findings

Finding Responsibility	Critical	Major	Minor	Total
Sponsor	1 (20%)	8 (44%)	20 (30%)	**29 (33%)**
PI/Institution	4 (80%)	10 (56%)	46 (70%)	**60 (67%)**
CRO	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**

Total	5	18	66	**89**

Figure 9: Responsibility of Different Entities at Different Grades of Findings



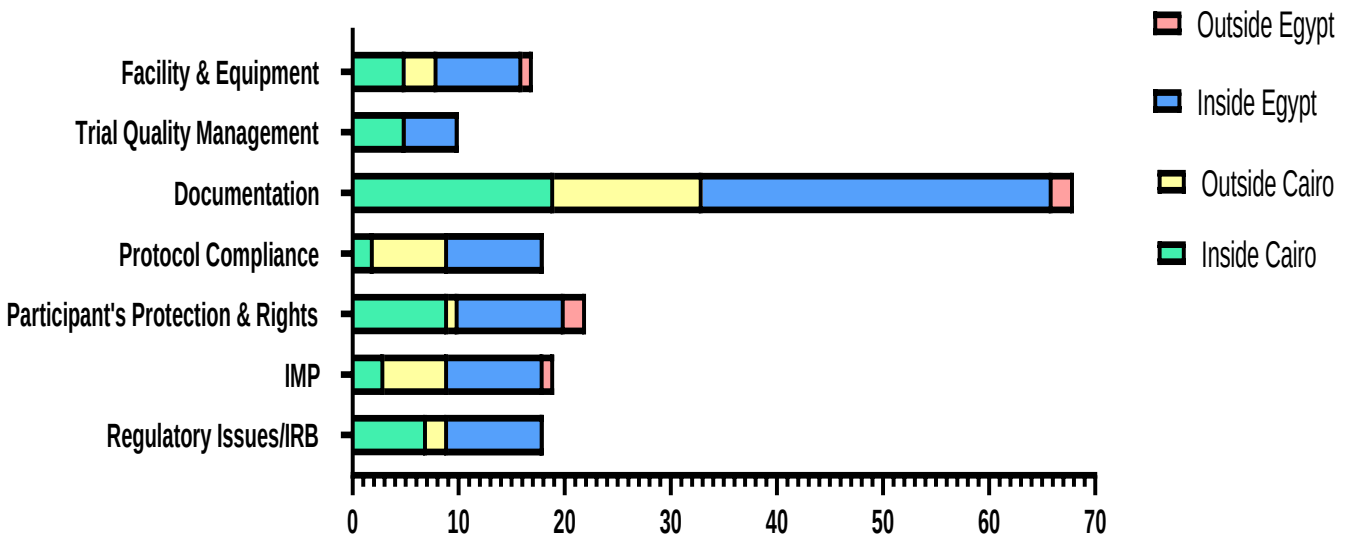
Conducted inspections covered several sites inside Cairo and various Governorates outside Cairo. In addition, 3 GCP inspections were conducted outside Egypt. This part of metrics report identifies the most frequently observed deficiency category in relation to the geographical region. The number of identified deficiencies categorized by main category and classified by geographical regions are identified in Table 4 and presented in Figure 10.

- For inspections conducted inside Cairo, the most frequently observed finding category was Quality of Data/Records and Reports (Documentation) representing 38% (19 out of 50) of all findings inside Cairo.
- For inspections conducted outside Cairo, the most frequently observed finding category was Quality of Data/Records and Reports (Documentation) representing 42% (14 out of 33) of all findings outside Cairo.
- For inspections conducted inside Egypt, the most frequently observed finding category was Quality of Data/Records and Reports (Documentation) representing 40% (33 out of 83) of all findings inside Egypt.
- For inspections conducted outside Egypt, the most frequently observed finding category were Quality of Data/Records and Reports (Documentation) and Participants' Protection and Rights representing 33% each (2 out of 6 each) of all findings outside Egypt.

Table 4: Number of Identified Deficiencies by Main Categories in Different Geographical Regions

Main Category	Inside Cairo	Outside Cairo	Inside Egypt	Outside Egypt
Regulatory issues/Ethics Committee (IRB)	7 (14%)	2 (6%)	9 (11%)	0
Investigational Medicinal Product (IMP)	3 (6%)	6 (18%)	9 (11%)	1 (17%))
Participants' Protection and Rights	9 (18%)	1 (3%)	10 (12%)	2 (33%)
Protocol Compliance	2 (4%)	7 (21%)	9 (11%)	0
Quality of Data/Records and Reports (Documentation)	19 (38%)	14 (42%)	33 (40%)	2 (33%)
Trial Quality Management	5 (10%)	0	5 (6%)	0
Facility and Equipment /Laboratories/Technical Facilities	5 (10%)	3 (9%)	8 (10%)	1 (17%)
General and Others not listed above	---	---	---	---
Total	**50**	**33**	**83**	**6**

Figure 10: Identified Deficiencies by Main Category in Different Geographical Regions



The number and percentage of findings' grades in each geographical region are identified in Table 5 and presented in Figure 11.

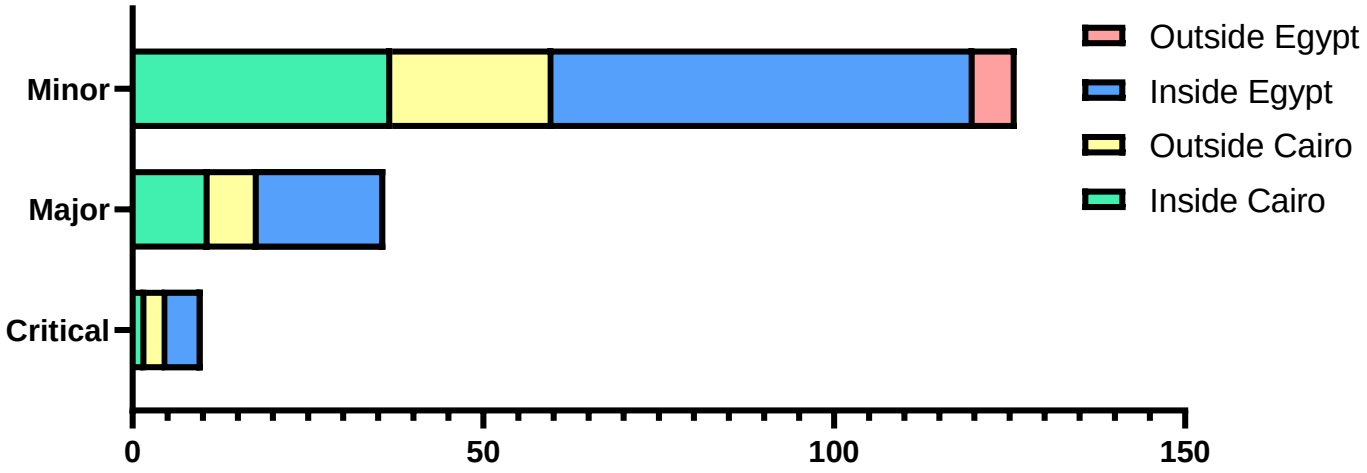
For inspections conducted inside Cairo, the critical findings represented only 4% (2 out of 50) of the total findings in this geographical region, while for inspections conducted outside Cairo, the critical findings represented 9% (3 out of 33).

Inside Egypt, critical findings represented 6% (5 out of 83) of the total findings observed, while there were no critical findings raised during inspections conducted outside Egypt and all findings were graded as minor.

Table 5: Grading of Identified Deficiencies in each Geographical Region

Geographical Region	Critical	Major	Minor	Total
Inside Cairo	2 (4%)	11 (22%)	37 (74%)	50
Outside Cairo	3 (9%)	7 (21%)	23 (70%)	33
Inside Egypt	5 (6%)	18 (22%)	60 (72%)	83
Outside Egypt	0	0	6 (100%)	6
Total	5	18	66	89

Figure 11: Grading of Identified Deficiencies in each Geographical Region



Conclusions Drawn from Identified Metrics:

- The number of conducted inspections depends on the number of initiated and ongoing clinical trials and on risk-based criteria. Most of the conducted inspections were routine and were carried out during the conduction of the clinical trial. No inspections were conducted at the pre-initiation stage during this year, however; this will be considered in future inspections especially for sites that are involved in clinical trial for the first time and for clinical trials including critical conditions and high-risk patients.
- All of the inspections were conducted on clinical trial sites in the year 2023, however; it is planned to increase the share of inspection on other related entities in next years based on risk –based approach.
- Most of inspected sites were affiliated to academic institutions indicating that the majority of sites involved in clinical trials in Egypt belongs to this type of institutions.
- Most of inspections were carried out on clinical trials sponsored by pharmaceutical companies since most of clinical trial applications submitted to the Egyptian Drug Authority are sponsored by pharmaceutical companies rather than being investigator initiated.
- Conducted inspections were almost equally distributed regarding geographical regions for sites inside and outside Cairo.
- Critical findings accounted only for 6% of the total findings, while most of the identified deficiencies (74%) were graded as minor, indicating a high level of compliance with GCP as well as local regulations and provides confidence in the quality of clinical trials conducted in the Arab Republic of Egypt.
- Critical findings were identified in the IMP, Protocol Compliance, Participants' Protection and Rights, and Documentation categories.
- While most of its findings were graded as minor, the finding category Quality of Data/Records and Reports (Documentation) represented a key area of non-compliance that requires improvement.
- The majority of findings' responsibility rests with the Principal Investigator, for this the General Administration of Clinical Trials is heading for providing a unified GCP training and certification for all involved PIs.
- Quality of Data/Records and Reports (Documentation) was the most frequently observed category both inside and outside Cairo. While for inspections conducted outside Egypt; in addition to the Quality of Data/Records and Reports (Documentation) category, the Participants' Protection and Rights category was also observed with the same frequency. However, this is inconclusive as only 3 inspections were conducted outside Egypt in only one country (Germany).
- Critical findings represented higher percentage (9%) of deficiencies raised from inspections conducted outside Cairo than those raised during inspections inside Cairo (4%), which implying more focusing in future inspection on these sites to provide proper education and awareness about GCP guideline as well as local regulations and to work with those sites to ensure there are effective procedures and systems in place to conduct clinical trials that meet all the relevant requirements.

II- Inspection Findings:

This section of the report provides details on the inspection findings within each main category, highlighting the most relevant reference sections from ICH E6 (R2), other international guidelines, and applicable local regulations. Critical findings were identified in 4 main categories: IMP, Participants' Protection and Rights, Protocol Compliance, and Documentation. Documentation category was a key area of non-compliance that represented approximately 39% of total findings.

Regulatory Issues/ Ethics Committee (IRB)

The applicant should adhere to the local regulations pertinent to clinical trials conduction in Egypt that stipulated in the Clinical Trials Law 214/2020, Executive Regulations 927/2022, and the Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority. All these regulations are published on the EDA website to be available for applicants.

Examples of findings by the sub-category include:

1- Amendment Approvals:

Minor:

- The delegated study Sub-I is different from that approved by EDA and this change wasn't notified as non-substantial amendment to EDA before being implemented.
- The version of the pharmacy manual filed in the Investigator's Site File (ISF) was different from that submitted to and approved by EDA, and this updated version wasn't notified to EDA.
- The study Sub-Is were removed from the trial without notifying EDA, this is considered as non-substantial amendment and must be notified to EDA before being implemented.
- Some activities of the clinical trial are performed at different site rather than the one mentioned in EDA application without submission of these site' documents for EDA approval.

Reference: Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority 7.3.4

The applicant should notify EDA of any changes to the approved protocol or its related documents.

2- Notification to Regulatory Authority:

Minor:

- No evidence of communicating EDA for attending IMP destruction.

Reference: EDA Chairman Decree 111/2022

An Egyptian Drug Authority inspector shall be present during the destruction of the residual samples of the product under study in the Arab Republic of Egypt.

Investigational Medicinal Product

Clinical trials often involve use of the unapproved therapeutic products, which have not been registered for use in Egypt or other countries and for which there are limited information. IMP-related actions from IMP receipt to return/destruction are expected to be documented in relevant records, including shipping records, scripts, IMP accountability logs, IMP return records or destruction certificates. Management of the IMP at the site must follow strict procedures to mitigate the risks and to ensure compliance with ICH GCP E6 (R2) and local regulations.

ICH GCP E6 (R2) section 4.6 outlines the site's responsibilities relating to the management of IMP from receipt, through prescription, dispensing, accountability, treatment compliance, to return to sponsor and destruction.

Examples of findings by the sub-category include:

1- **IMP Accountability**

Minor:

- During the accountability of the IMP, it was found that there's an extra strip in the participant's kit.
- Discrepancy between the IMP accountability recorded in the source documents and the actual IMP accountability at the site.
- According to the IMP accountability, there was one empty box missing from the pharmacy.

Major:

- The accountability of the returned IMP indicated that there was IMP overdose by the participants.

Reference: ICH-GCP E6 (R2) Section 4.6.3

The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

2- **Shelf life/Expiry Date**

Critical:

- The IMP was dispensed to two participants after being expired.

Reference: ICH-GCP E6 (R2) Section 5.14.4. item C

The sponsor should

- Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaims).

3- <u>Manufacturing/Packaging/Labeling</u>

Minor:

- The label on the IMP didn't include the statement "For clinical trial use only."

Reference: EU guidelines to Good Manufacturing practice: Medicinal products for Human and veterinary use

Labelling Section-item 26 (the following information should be included on labels, unless its absence can be justified), (h-For clinical trial use only or similar wording).

4- <u>Supply/storage/retrieval/destruction.</u>

Minor:

- The IMP vials were not stored on a separate shelf in the refrigerator.
- There was no documented evidence of IMP prefilled syringes destruction.
- The temperature monitoring record during the IMP transportation wasn't found.

Major:

- Temperature excursion was recorded for the IMP and there was no evidence of communication with the sponsor about it.

Reference: ICH-GCP E6 (R2) Section 4.6.4

The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

Reference: ICH-GCP E6 (R2) Section 5.13.2

The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

Reference: ICH-GCP E6 (R2) Section 8.4.2

DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION To document destruction of unused investigational products by sponsor or at site.

<u>Participant's Protection and Rights</u>

Clinical trials are often conducted using unapproved therapeutic goods with an unknown safety profile. All parties are responsible for the protection of trial participants when conducting and overseeing a

clinical trial. Informed consent is a main element of participant protection. Informed consent is obtained following a discussion between the participant and the medically qualified site staff and is documented by the signing of the consent form by both parties.

According to ICH GCP E6(R2) section 1.28 Informed Consent is a process by which a subject voluntarily confirms their 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. Informed consent is documented by means of a written, signed and dated informed consent form.

Examples of findings by the sub-category include:

1- ICF Content

Minor:

- The signature field in the Model Parent/Legal Guardian Informed Consent Form was not filled out by the participant's parent. However, the name of the participant's parent was written.
- The ICF was signed by the participant, but the date & time of consenting was filled by PI.
- The ICF was signed by a legal representative which is not one of the participant's parents.

Major:

- The ICF was signed by the participant's son as an impartial witness as claimed by Sub-I, as the subject is illiterate, however; there was no fingerprint for the participant.

Critical:

- The ICF of one of the participants was not signed by the PI/Sub-I.
- The ICF was signed by the participant before granting IRB approval.

Reference: ICH-GCP E6 (R2) Section 4.8.8.
Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

Reference: ICH-GCP E6 (R2) Section
In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

Reference: Clinical Trials Law 214/2020 Chapter 1 Article 1, Definition of Informed Consent

Reference: Executive Regulation 927/2022 Article 3 Point 4
An informed consent shall be obtained from each one of the research subjects; if the clinical research is conducted on one of the vulnerable groups that deserve an additional protection, an informed consent shall be obtained from their parents; in the event of the death of one or both parents, an informed consent shall be obtained from the person who had the right of tutelage or guardianship or from the legal representative.

2- Informed Consent Process

Major:

- The room where the consenting process was performed was not suitable to provide the appropriate environment for such a process; the room was lacking confidentiality due to the presence of a partition for data entry not related to the trial. In addition, the surrounding area was full of patients which doesn't allow for a suitable quiet environment for the consenting process and hence affecting the participants' rights. Moreover, the Sub-I informed that the consenting process takes around 15-20 minutes which is not considered an ample time for the participant to be informed and to inquire about all aspects and details of the trial.

Reference: ICH-GCP E6 (R2) Section 4.8.7
Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

3- Personal Data Protection

Minor:

- The participants' full name (not initials) was recorded in the withdrawn samples sheet to which the access wasn't restricted which contradicts with the trial participants confidentiality.

Reference: ICH-GCP E6 (R2) Section 2.11 and Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority, Section 7.1:
The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

4- Safeguard of the safety and well-being of subjects

Minor:

- There was no complete follow up for an SAE.
- There was a reported death case, and no further investigations were performed.

Reference: ICH-GCP E6 (R2) Section 4.3.2
During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should

inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

Protocol Compliance:

Protocol compliance is expected from all parties involved in the trial conduct, and it is verified at multiple levels via clinical trial monitoring, quality management, quality assurance (e.g. audits) and regulatory inspections. Trials with multiple deviations from the approved protocol and procedures pose risks to the participants and may jeopardize the quality of the data generated in a trial.

ICH GCP E6 (R2) section 1.44 defines protocol as a document 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.
ICH GCP E6 (R2) section 2.6 states that a trial should be conducted in compliance with the protocol that has received prior ethics committee approval.
ICH GCP E6 (R2) section 4.5 outlines the requirements of trial conduct in compliance with the protocol.

Examples of findings by the sub-category include:

1- **Randomization to study arms:**

Minor:

- It was documented that the site received equal quantity of the active IMP and placebo although the randomization is not stratified by center according to the study protocol.

2- **Protocol-specified timelines:**

Minor:

- The screening period of some participants exceeded that specified in the protocol.
- There was no evidence of communicating the participant to avoid conducting visits out of protocol-specified window, or in case of required blood resampling for missed lab results.

Major:

- Urine and serum pregnancy tests were performed out of the protocol-specified window.

3- **Eligibility Criteria**

Major:

- Some participants were enrolled and randomized but there were no screening laboratory results as required by the protocol.
- One of the participants was on NSAID at the time of screening, however it wasn't recorded whether the regimen is acute or chronic since participants on chronic NSAIDs should be excluded from the trial according to the protocol exclusion criteria.
- One of the participants was enrolled in the study although having comorbidities listed in the protocol-specified exclusion criteria.

Critical:

- Some participants were enrolled although being not-eligible according to protocol-specified eligibility criteria.

4- Assessment of Safety and/or Efficacy

Minor:

- Some laboratory blood chemistry tests were missing from one of the participant's visits.

Reference: ICH-GCP E6 (R2) Section 4.5.1.
The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies) and which was given approval/favorable opinion by the IRB/IEC

Quality of Data/Records and Reports (Documentation)

Clinical trial conduct is documented in multiple records defined by the trial sponsor and the site. The records may include source documentation such as participants' medical records, signed forms, laboratory and imaging results, logs, study files and other records. The trial documentation describes the details of the trial conduct at the site. It is maintained throughout the trial and archived for at least 5 years following the completion of a clinical trial according to EDA regulations.
The documentation allows for reconstruction of the trial conduct while it is ongoing and after its completion when the site personnel may no longer be available to answer any questions. The quality, integrity and reliability of clinical trial data is critical to the acceptability of the clinical trial outcome by regulatory authorities.

Examples of findings by the sub-category include:

1- Consistency of CRF data with source documents:

Minor:

- Inconsistency between the data documented in the source documents (e.g. Participant's blood pressure, Participant's Marital Status) and the eCRF.
- There was a discrepancy in the date of randomization between the source document and the e-CRF.

Reference: ICH-GCP E6 (R2) Section 4.9.2
Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

2- Source documents:

Minor:

- Some of participant's scheduled visits were conducted outside the protocol-specified window and the deviation wasn't documented and there was no evidence for communicating this deviation with the study sponsor.

- Records of participant's medical history were not filed in the subjects' files.
- Some of the protocol-specified laboratory results were not filed in the participant's file.
- The study-related questionnaires were not signed by the participants.
- Minor mistakes in the data recorded in the source documents.
- There was no subject reimbursement log to document that participants were reimbursed according to the approved ICF.
- The date of PI's signature on of X-ray source document (which proves evidence of verification by the PI) was after the date of the participant's enrollment.
- Overwriting and corrections were not initialized and there was missing information in the source documents of participants' files.
- The laboratory request for performing protocol-specified tests was not found in the participant's file.

Major:

- Child Pugh score was not filled in the "screening visit" item in the participant's source note, **which is mandatory for subject eligibility for enrollment as per protocol.**

Reference: ICH-GCP E6 (R2) Section 4.9.0
The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

3- <u>Essential Documents according to ICH E6 (GCP):</u>

Minor:

- Documents of the used local lab (e.g accreditation certificate, normal ranges, lab manual) were not filed in the Site Master File.
- EDA's conditional approval for the trial wasn't filed in the Site Master File.
- Trial initiation monitoring report was not found at the site.

Critical:

- The Investigator Site File (ISF) including source documents wasn't found in the clinical trial site.

Reference: ICH-GCP E6 (R2) Section 8.1
Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor

sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.
Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files. Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

Trial Quality Management

Clinical trial management is an important aspect of clinical trial conduct. Trial management includes careful planning of clinical trial sites' participation in a clinical trial to ensure compliance with the requirements, including proactive identification, assessment and monitoring of the risks associated with trial conduct.

Examples of findings by the sub-category include:

1- SOPs:

Minor:

- No procedures (SOPs) were found at the site for implementing and maintaining quality assurance e.g. SOPs for IMP handling, transportation, storage, use of study-related equipment, waste disposal, reporting of serious adverse events, etc…

Reference: ICH-GCP E6 (R2) Section 5.1.1.
The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)

2- Organization and Personnel:

Minor:

- The protocol-related ultrasound imaging was performed by a non-delegated physician.
- A former delegated pharmacist was found, as stated in the source documents, to dispense the IMP and counsel the participants although her delegation ended at an earlier date.

Reference: ICH-GCP E6 (R2) Section 4.1.5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Reference: ICH-GCP E6 (R2) Section 5.18.4
Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution and have not delegated these functions to unauthorized individuals.

Facility and Equipment/Laboratories/Technical Facilities

Examples of findings by the sub-category include:

1- Calibration:

Minor:

- The labels on the used equipment (vital monitor, data logger) didn't include calibration date or due date.

Major:

- There was no evidence for calibration of the used equipment (ECG, sphygmomanometer, and weight balance used for determining body weight-based dose of IMP). The equipment had neither a label including its Serial Number and calibration dates nor a calibration certificate in the SMF.

Reference: ICH-GCP E6 (R2) Section 5.18.4.
Monitor's responsibilities
The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:
b) Verifying that the investigator has adequate qualifications and resources and
remain adequate throughout the trial period, **that facilities, including** laboratories, **equipment,** staff, **are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.**

2- Accreditation:

Major:

- The study site used external non-accredited laboratory other than that approved by EDA.
- The laboratory used in the study for the analysis of lab results was not accredited.

Reference: ICH-GCP E6 (R2) Section 8.2.12
MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required) to document competence of facility to perform required test(s), and support reliability of results.

3- <u>Waste Disposal</u>

Minor:

- There was no safe management of waste from health-care activities used in the clinical trial and there were no waste disposal containers as per coloring coding system.
- In the procedure room, which was used for blood sampling, the disposal container was not labeled nor colored as per the international color-coding system.

Reference: Safe management of wastes from health care activities WHO/FWC/WSH/17.05 World Health Organization 2017