الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Contract Research Organization Guideline

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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1.0	Executive Directorate of Benefit & Risk Evaluation	25 August 2022	Final

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GLOSSARY

Clinical Trials Application (CTAp)

The CTAp comprises the clinical trial application headed letter associated with the relevant documents described in Table 1 in the *Regulations and Requirements for Conducting Clinical Trials.*

Clinical Trials Registry (SCTR)

It is an electronic system with electronic database which includes official records of all drugs clinical studies in Saudi Arabia to ensure that all received information is accurate and completed along with publishing the minimum amount of information about the clinical trials, which is globally agreed, so it can be viewed by the public.

Licensed Contract Research Organizations (CRO)

A CRO organization licensed by the SFDA in accordance with the Guidance for Investor on Licensing CRO, contracted with the sponsor to perform one or more of the clinical trial-related activities and had a legal entity in Saudi Arabia

Sponsor or Sponsor with a Legal Entity in Saudi Arabia

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial located in Saudi Arabia.

Sponsor without a Legal Entity in Saudi Arabia

An individual, company, institution, or organization based outside Saudi Arabia (without a legal representative) which takes responsibility for the initiation, management, and/or financing of a clinical trial not located in Saudi Arabia.

Note: Some of the terminologies in this guideline have a detailed definition valid only in Saudi Arabia.

1. INTRODUCTION

The clinical trials team at the Saudi Food and Drug Authority (SFDA) provides this guideline for the Contract Research Organizations (CROs) who have a legal entity and licensed by SFDA to conduct clinical trials in Saudi Arabia. A new approach has been introduced to mitigate the new regulation challenges and minimize gaps between the licensed CROs clinical trial stakeholders and the international standards.

The development of new regulations was based on a robust analysis of the available data on CRO in Saudi Arabia, in addition to the collaboration with key stakeholders along the rule-making process to assist in effective implementation.

1.1. Objective

This guideline aims to regulate, support, improve and extend the collaboration between the licensed CROs, clinical trials sponsors, and regulators.

1.2. Related guidelines

This guideline should be read in conjunction with the following documents:

- SFDA Guideline for Good Clinical Practice (GCP)
- Regulations and Requirements for Conducting Clinical Trials on Drugs
- Guidance for Investors on Licensing Contract Research Organizations

2. CLINICAL TRIALS APPLICATION (CTAp)

To Initiate the CTAp in Saudi Arabia, sponsor or licensed CROs should create an account on the Saudi Clinical Trials Registry (SCTR) and apply in compliance with SFDA Regulations and Requirements for Conducting Clinical Trials, following the appropriate submission process.

2.1.Submission Process

- **Process 1**: for sponsors **without a legal entity** in Saudi Arabia

Applicant planning to conduct a clinical trial in Saudi Arabia should submit their clinical trial application through a licensed CRO by the SFDA. (See Figure 1)

- **Process 2**: for sponsors **with a legal entity** in Saudi Arabia

Sponsors with a legal entity could submit their CTAp either directly to the SFDA through their official local office in Saudi Arabia or via a licensed CRO. (See Figure 1)

Subsequently, the applicant should submit required documents for the CTAp in accordance with Regulations and Requirements for Conducting Clinical Trials on Drugs.

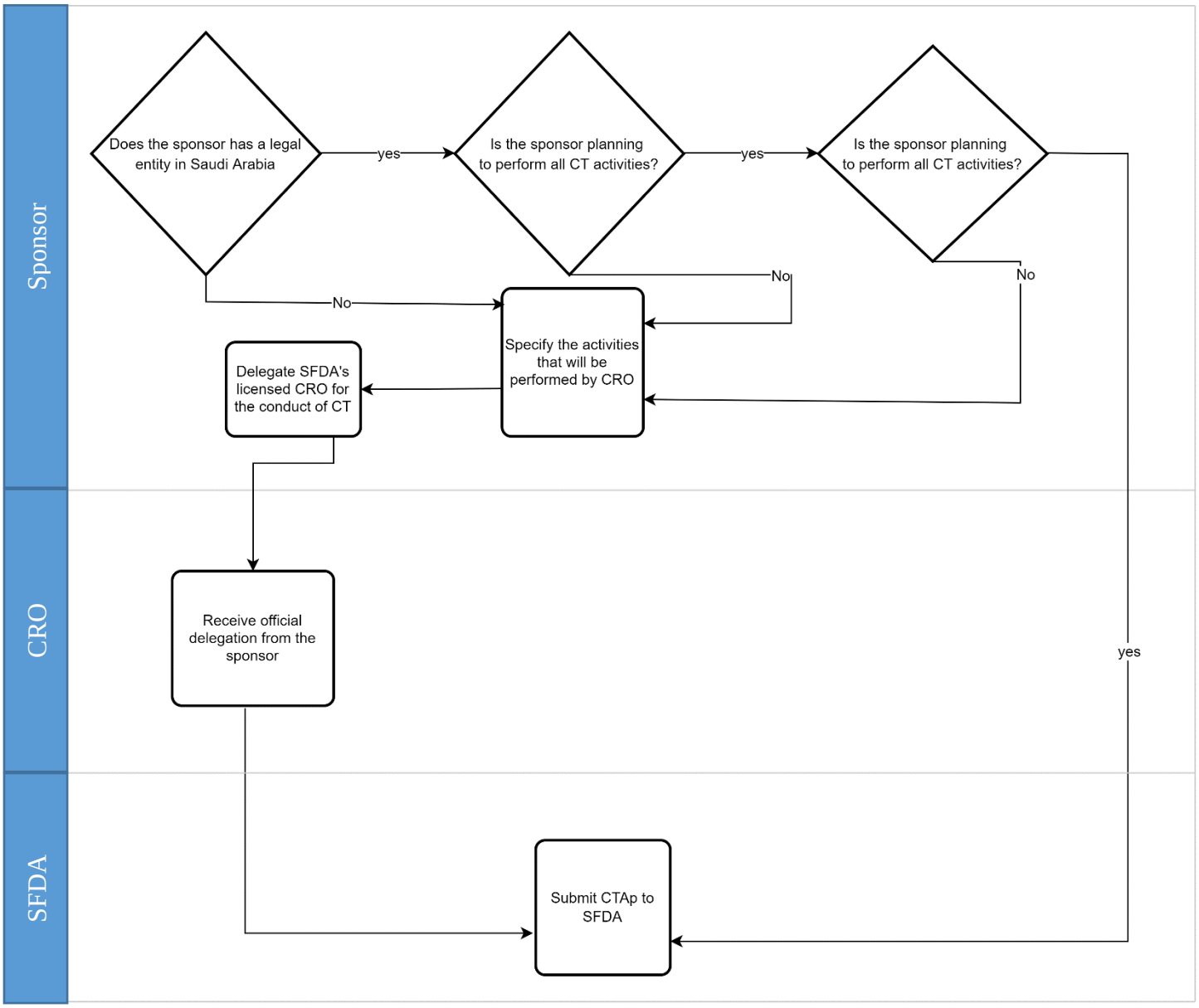

Figure 1: Submission Process Flow chart

3. CONTRACT RESEARCH ORGANIZATION (CRO)

3.1.ORGANIZATIONAL STRUCTURE & SERVICE

This section aims to focus on the licensed CRO organizational structure and the essential services provided to conduct the clinical trials in Saudi Arabia. The organizational structure for the licensed CRO should include departments or individuals that assure the clinical trials are conducted with high quality, in accordance with applicable regulations and trial data are credible and accurate. The organizational structure should reflect on services provided to perform one or more of the clinical trial-related activities, accordingly, the organizational structure should be updated every five years or per institutional policy. (See figure 2)

The SFDA recommends that organizational structure should include the following departments or individuals responsible for:

- Compliance with the local regulations.
- Implementation and termination of the clinical trial.
- Monitoring clinical trials.
- Documentation archiving, data handling and clinical trial reports (e.g., Progress reports).
- Safety and adverse events reporting.
- Select qualified investigators to conduct studies.
- Disseminate appropriate information to investigators.
- Handling of Investigational Product records (e.g., distribution, shipment, destruction, etc.).
- Sample management.
- Quality Management System.
- Delegation of duties.
- Handling contracts and clinical trials agreements.

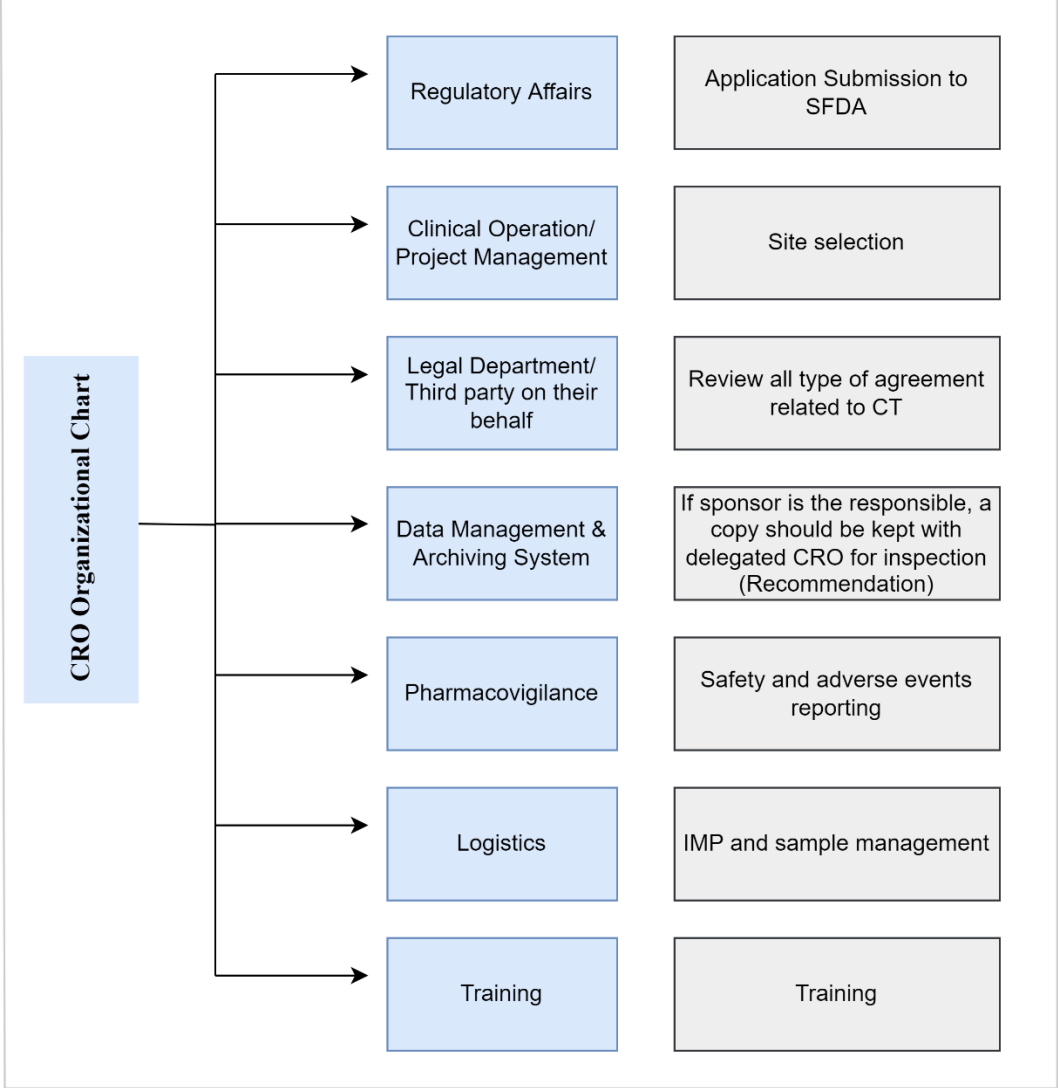

Figure 2: Example of CRO organizational chart

Some of the services provided by licensed CRO need additional regulations to fulfill their responsibilities, such as:

- Monitoring of the clinical trials.
- Trial Master File (TMF).

3.2.Monitoring of the Clinical Trials

Delegation of Monitoring Responsibilities to a licensed CRO

A licensed CRO who was delegated to perform monitoring responsibilities needs to follow SFDA regulations and provide a written agreement to delegate clinical trial responsibilities from the sponsor to the CRO. The sponsor of a clinical trial will retain the responsibility for oversight of the activities done by the licensed CRO. The sponsor needs to assess the licensed CRO compliance in accordance with SFDA regulation and requirements, the monitoring procedures and monitoring plans developed by a licensed CRO to ensure consistency to the aspects of the trials. The sponsor needs to assure that licensed CROs have a clear understanding of their responsibilities. The licensed CRO should be informed by the sponsor of any information that may affect the monitoring practices for a trial.

Monitoring Methods

This section is intended to help sponsor and/or licensed CRO to identify and design monitoring activities suitable to a given clinical trial application (CTAp). It describes some of the capabilities of on-site, centralized monitoring activities and factors to consider in determining which monitoring practices may be appropriate for a given CTAp.

On-Site Monitoring

On-site monitoring is an in-person assessment carried out by the sponsor and/or licensed CRO personnel at the site at which the clinical trial is being conducted. On-site monitoring can identify data entry errors and missing data in source records or Case Report Forms (CRFs); provide assurance that study documentation exists; assess the familiarity of the site's study staff with the protocol and required procedures; and assess compliance with the protocol and SFDA Guideline for Good Clinical Practice (GCP). On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at a site. On-site monitoring can therefore be particularly helpful

early in a study, especially if the protocol is complex and includes novel procedures unfamiliar to investigators. Findings at the site may lead to training efforts at both the site visited and elsewhere.

Monitoring Plan

A monitoring plan is an essential part of each clinical trial, which contains a description of the monitoring methods, responsibilities, and requirements for the trial. The monitoring plan should include a brief description of the study, its objectives, and the critical data and study procedures, with particular attention to data and procedures that are unusual in relation to clinical routine and require training of study site staff. The monitoring plan is developed by the sponsor/ licensed CRO and should provide the personnel involved in monitoring activity with a sufficient amount of information to perform their responsibilities.

Factors to Consider when Developing a Monitoring Plan

Averting and mitigating risk is generally the focus of a monitoring plan. The types, frequency, and extent of monitoring activities depend to some degree on factors measured during the risk assessment, and including the following (not limited to):

• Study Design:

More intensive monitoring (e.g., increased frequency and extent of review) may be necessary as study design complexity increases. Examples may include studies with adaptive designs, stratified designs, or complex dose titrations.

• Study Endpoints:

Endpoints that are more interpretative or subjective may require on-site visits to assess the totality of subject records and to review the application of protocol definitions with the principal investigator (PI). More objective endpoints may be more suitable for remote verification. Endpoints for which inappropriate subject withdrawal or lack of follow-up may impede study evaluation are likely to need more intensive monitoring to identify the reason(s) subjects are withdrawing and to determine whether follow-up can be improved.

• Study Population:

A study that involves a population that is seriously ill or vulnerable may require more intensive monitoring and consideration of on-site monitoring visits to ensure appropriate protection is being provided.

• Geography:

Sites in geographic areas where there are differences in standards of medical practice or subject demographics, or where there is a less established clinical trial infrastructure may require more intensive monitoring and consideration of on-site monitoring visits.

• Relative experience of the P.I. and of the sponsor with the P.I.:

P.I. who lacks significant experience in conducting and overseeing investigations, using a novel or innovative medicinal product may benefit from more intensive monitoring and frequent communication to ensure P.I. understanding of responsibilities. In addition, the relative experience of a sponsor with the P.I. may be a factor in determining an appropriate monitoring plan.

• Electronic data capture (EDC):

The use of EDC system with the capability to assess quality metrics (e.g., missing data, data error rates, protocol violations) in real-time could help identify potentially higher risk sites for the purpose of targeting sites in need of more intensive monitoring.

• Relative safety of the investigational product:

A study of a product that has significant safety concerns or for which there is no prior experience in human clinical trials may require more intensive monitoring and consideration of on-site monitoring visits to ensure appropriate Clinical Investigator (CI) oversight of subject safety.

• Stage of the study:

A restricted approach to monitoring may be used where appropriate, with more intensive monitoring at initiation and during the early stages of a trial, once procedures are established, less intensive monitoring might suffice. Similarly, a restricted approach could be used for relatively inexperienced P.I.s.

• Quantity of data:

Some centralized monitoring tools may be more useful as the quantity of data (e.g., size or duration of the trial, number of sites) collected increases.

3.3. Trial Master File (TMF)

This section will discuss the quality control and the agreements related to the Trial Master File (TMF), which contains essential documents associated with the conduct of the clinical trial, and

allows the sponsor/ licensed CRO to manage trial activities and provide access to monitors, auditors and inspectors.

Agreements and accessibility:

The sponsor has the ultimate responsibility for the trial activities and oversight. Therefore, the sponsor should allow access to the TMF for licensed CRO and specify the parts to be accessed by the licensed CRO to fulfil their responsibilities.

The clinical trial agreement and other documents and procedures agreed between all parties should outline the arrangements for the TMF in some detail such as, but not limited to:

- The structure of the TMF.
- The TMF access arrangements.
- Preparations regarding the archiving of and access to data/documents held in centralized systems.
- Which party holds the TMF or which parts of the TMF if divided, and type of documents that each party should hold.
- If an electronic TMF is used, the details and the control of the system should be specified.
- Arrangements for managing correspondence.
- Arrangements for when the trial is completed, retention times and how the TMF would be made available and accessible for inspections (including inspections related to the licensed CRO's responsibilities).
- Arrangements for auditing and/or monitoring and how this would be achieved.
- Procedures in case of an involved party closing down its business for any reason.
- Arrangements of the role of the CRO after trials closeout.

Quality of TMF:

The sponsor and /or licensed CRO should implement risk-based quality checks (QC) or review processes to ensure the TMF is up-to-date and that all essential documents are appropriately filed in the TMF. Areas to consider during QC and review include, but are not limited to the following:

- All essential documents generated available in the TMF;
- Documents correctly indexed, filed in the appropriate locations and added to the TMF in a timely manner.
- Documents only accessible according to the assigned roles and permissions.

- Review of the audit trail (for eTMF).

There should be a suitable overall table of contents to enable the location of essential documents in the TMF to be traced. The documentation should be filed in each appropriate section of the TMF in chronological order.

In the case that a sponsor has subcontracted a licensed CRO for certain tasks, the sponsor is responsible for ensuring the archiving of the documentation generated by the licensed CRO from following its internal procedures. The sponsor's TMF may be transferred to a licensed CRO for archiving (e.g. an external archive), but the quality, integrity, confidentiality and retrieval of the documents is the responsibility of the sponsor.

If the sponsor arranges the external archiving of the investigator TMF on behalf of the investigator/institution, (who should hold control of their part of the TMF), consideration should be given to personal data protection and confidentiality from an unauthorized access, so:

- The archiving arrangements including location of the (electronic) archive should be formally agreed and documented between the sponsor and investigator/institution;
- A formal procedure should be in place such that the documents are only released from the external archive or (remotely) accessed with the approval of the investigator/institution;
- The documents should be physically or electronically transferred directly between the investigator site/institution and the archive facility independent of the sponsor, thereby ensuring that the sponsor/ licensed CRO does not have access to the investigator TMF.

Retention requirements for the documentation and medical files held by the investigator/institution should be formalized, for example, in an agreement between the sponsor, the investigator and the institution. It is the responsibility of the sponsor to inform the investigator/institution in writing, as to when trial documents no longer need to be retained.

When the responsibility for the TMF is transferred, the agreements between the sponsor and the investigator/institution or licensed CRO should cover such eventualities and should require the investigator/institution or licensed CRO to notify the sponsor in such circumstances. The sponsor should take appropriate actions in such circumstances to ensure that the TMF remains available for inspection for the required archiving time and that patient-related source documents have not been in the sole custody of the sponsor at any time.

4. CLINICAL RESEARCH ASSOCIATE (CRA) EMPLOYEES

This section emphasizes the Clinical research associate (CRA) employees' qualifications. The sponsor and\or licensed CRO should select monitors qualified by education, training and experience to monitor the clinical trial and perform their respective task(s). The SFDA recommended that CRA employees should be:

- A citizen or legal resident in Saudi Arabia; the legal resident should be authorized to work in Saudi Arabia in compliance with the applicable local regulations for local companies and institutions.
- The sponsor or licensed CRO should submit documents proof of CRA education, training and experience qualifications (e.g., current curriculum vitae and training certificate) in accordance with the SFDA Regulations and Requirements for Conducting Clinical Trials on Drugs.

5. AGREEMENTS

This section highlights some terms and conditions in the clinical trial agreements and\ or contracts between the sponsors, licensed CRO, principal investigator (PI) and the site institution.

5.1.Regulations

- The clinical trials agreement and additional agreement(s) used for a clinical trial should be submitted to the SFDA in bilingual (Arabic and English).
- The clinical trials agreement and additional agreement(s) used for a clinical trial should be reviewed by the legal department, consultation legal office or licensed attorney.

5.2.Terms and conditions

Essential information should be included in the clinical trial agreement. The terms and conditions of the agreements should follow and state the local regulations in Saudi Arabia besides the international regulations.

5.2.1. General

- Parties (sponsor, licensed CRO, principal investigator and site institution (s) & personnel in each party).

- Responsibilities of each Party (sponsor, licensed CRO, principal investigator and site institution).
- Details of the Clinical Trials (title, protocol number, location of the clinical trials, & territory) and a Copy of the Clinical Trials Protocol attached with the agreement as an appendix.
- Subcontract and delegated task for licensed CRO.
- Pharmacovigilance pathway and safety reports in accordance with SFDA regulations and the international regulations.
- Sponsor's Anti-Bribery Policy and Compliance, and Anti-Bribery Law in accordance with Saudi Arabia regulations and international regulations.
- Sample exportation according to the National Committee of Bioethics (NCBE) regulations.
- Term and time schedule (effective date, terms & termination).
- Fees, payment terms and payment schedule.
- Definitions for important terminology in the agreement
- Study Site
- Manner of Performance
- Labor law and regulations in accordance with Saudi Arabia regulations.
- Items Supplied by the sponsor
- Subjects' recruitment and Consent of the Subjects
- Monitoring the study and Monitoring plan.
- Reporting
- Record retention
- Data Protection
- Confidentiality
- Communication and public affairs
- Audit
- Liabilities
- Insurance
- Termination of the agreement
- Assignment and Delegation.
- Independence

- Contract Amendment
- Waiver
- Notice
- Force Majeure
- Quality assurance audits and inspection
- Severability
- Heading
- Governing Law

5.2.2. Inspection

- SFDA may conduct an inspection visit to the Sponsor, licensed CRO, principal investigator, and clinical trial centres for the purpose of determining compliance with the GCP and applicable local regulations.
- The licensed CRO, principal investigator and site institution (s) should notify the sponsor for any inspection, which related to the institution(s) or/and the clinical trial conducted in Saudi Arabia.

5.2.3. Documents & Data retention

- **Sponsor with a legal entity in Saudi Arabia and licensed CRO**

The essential document(s) and data generated from conducting the clinical trial in Saudi Arabia should be kept for at least 15 years after completion or discontinuation of the trial or at least two years after registering the investigational medicinal product (IMP) at SFDA according to the clinical trial objectives.

- **Sponsor without a legal entity in Saudi Arabia**

The essential document(s) and data generated from conducting the clinical trial in Saudi Arabia, the sponsor should delegate a licensed CRO to keep them for at least 15 years after completion or discontinuation of the trial or at least two years after registering the investigational medicinal product (IMP) at SFDA according to the clinical trial objectives.