

Regulatory requirements for contract research organization

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INTRODUCTION

- A Contract Research Organization (CRO) is a service organization which provides support to the pharmaceutical industry.
- It offers various pharmaceutical research that is essential for conducting clinical trials in the present boom, when various complications are involved in the drug discovery process.
- Various companies are involved in his type of development many examples are the like Lupin , Quintil, Cipla, Zydus, Cadila.
- They are also conduct these type of trails with the collaboration of many multinational companies and these Indian companies are making space in foreign.

BACKGROUND

- There is a growing reliance by sponsors on contracting out part or all of the work of the clinical trial to a sub-contractor.
- Manufacturers often find that they cannot organize every clinical trial that they require. The reasons are many, but commonly reflect;
 - limited staff resources
 - pressures of time.
- Subsequently, the field has expanded to include firms in the areas of;
 - formulation development
 - stability programs
 - pharmacokinetic studies
 - biostatistics
 - data management

An Overview of CROs

- Traditionally, a CRO was viewed by pharmaceutical industry something as;
 - an un-acceptable risk,
 - because of lack of confidence in it terms of their qualification, experience and capabilities.
- However, the modern view is that the in- house staff can be kept for “core needs” e.g.,
 - designing of study
 - selection of CRO.
- A list of qualified CROs is developed based on;
 - The sponsors needs
 - The range of services provided by CRO
 - The therapeutic area of expertise of CRO, and
 - The compatibility with the sponsor

WHEN TO USE A CRO?

- Strategies for using CROs typically fall into three categories:
 - Tactical outsourcing
 - Maximal outsourcing
 - Strategic outsourcing
- **Tactical Outsourcing:** Individual studies or selected activities within a study are contracted to a CRO only when in-house resources become inadequate because of an unforeseen study or a reduction in staff.
- **Maximum Outsourcing:** With this strategy the sponsor outsources nearly all of its clinical development activities to CROs.
- **Strategic Outsourcing:** The sponsor conducts Phase I and early Phase II studies, and hires CROs to conduct larger and routine studies.

FREQUENT CAUSES OF SPONSOR/CRO PROBLEM

- Problems with contract studies can often be traced by;
 - The wrong CRO is selected.
 - Sponsors often make the mistake of assuming that a CRO that has performed well on one study will be equally capable of conducting a study in a different therapeutic area. Some sponsors mistakenly assume that all CROs are the same.
 - The sponsor fails to articulate its needs clearly.
 - Sponsors sometimes issue a request for proposal (RFP) with little more than a protocol outline, and expect CROs to guess what services and resources are required.
- In order to ensure successful outsourcing, the sponsor should focus on three critical steps:
 - Determine accurate study specifications
 - Select the right CRO
 - Manage the study

DETERMINE STUDY SPECIFICATIONS

- Study specifications are a list of activities required to initiate, conduct, analyze, and report the results of a clinical study.
- They include tasks that will be performed in-house and those to be contracted out to one or more CROs.
Importance of Accurate Study Specifications.
- Study specifications are an essential element of the sponsor's request for proposal (RFP) and the CRO's proposal.
- Accurate study specifications also enable the CRO to perform a 'reality check' on the sponsor's expectations.
- This analysis also provides useful criteria for selecting the right CRO.

SELECTING THE RIGHT CRO

- The three most important criteria for selecting a CRO are:
 - Capability
 - Compatibility
 - Cost

MANAGING THE SPONSOR-CRO RELATIONSHIP

- The sponsor should follow three principles for managing an outsourced project:
 - Clarify the role and responsibilities of the sponsor and CRO.
 - Define and use 'performance metrics' to measure study progress. Ensure efficient communication between the sponsor and CRO.

Sponsor Roles and Responsibilities

- Define the study specifications
- Provide information to the CRO
- Monitor results
- Recognize 'red flags'
- Resolve problems
- Approve changes in 'scope'

CRO Roles and Responsibility

- If the sponsor has provided detailed study specifications and the CRO is experienced in the target therapeutic area, it will be possible for the CRO to compare its past experiences with the sponsor's projections.
- CRO roles and responsibilities are;
 - Evaluate feasibility
 - Provide adequate, well managed staff
 - Conduct study activities
 - Manage processes
 - Bring problems and proposed solutions to the sponsor's attention
 - Ensure that the solutions are cost-effective

Performance Metrics

- Their validity is established by demonstrating that they are related to achieving quality, ensuring timelines, and managing cost.
- Performance metrics should be negotiated between the sponsor and CRO prior to the study.
- When performance metrics demonstrate that the CRO is failing to meet the objectives, the sponsor and CRO have a shared responsibility to examine the process and agree on an appropriate solution.
- Most interactions between the sponsor and the CRO will take place between the individual team members and their technical counterparts.
- Discussions between sponsor and CRO technical staff should focus on information exchange and issue identification.

Sponsor-CRO Study Initiation Meeting

- The sponsor and CRO teams should hold a 'kick-off' meeting prior to initiation of the study.
- The goals of the meeting are:
 - To promote ownership of the study among team members
 - To clarify the roles and responsibilities of the sponsor and CRO
 - To identify the primary sponsor and CRO contacts
 - To present the agreed to performance metrics and audit procedures
 - To define the approach to problem resolution
 - To define those changes that can be agreed upon informally and those that require a formal change order

IDENTIFYING AND RESOLVING PROBLEMS

- They should be identified at an early stage, so that they have minimal impact on study cost, timing, and quality.
- It is important for a team member to inform the project manager of any issue before attempting to resolve it.
- This information will enable the project manager to determine;
 - Whether the problem is an isolated case.
 - It is part of a larger problem that needs to be addressed with the corresponding project manager.

Ten 'Red Flags'

- Red flags are early warning that may not require immediate action, but should be evaluated to determine whether a significant underlying problem exists.
- Each team member may wish to prepare a list of red flags for his/her individual technical area. Typical red flags and the possible significant underlying problems are:
 - Selection of in-experienced investigators by the CRO: The CRO monitoring staff may be inexperienced.
 - Questions from the study site directed to the sponsor: The CRO may not have provided adequate training to site personnel.
 - In-adequate monitoring reports from the CRO: The CRO monitoring staff may not be receiving adequate training and supervision.

CONTRACT RESEARCH

Legal Background

- The arrangements made for the conduct of clinical research will usually give rise to a number of legal contracts.
- For example, there will be a contract between a sponsor and any appointed clinical research organization (CRO); between the sponsor or CRO and the investigator or the institution in which the investigator works.
- It would be unusual to have a contract between a patient participant and the sponsor or investigator, although this may arise where the participant is a private patient of the investigator.

- In contracts relating to clinical research between a sponsor, CRO or investigator/institution much of the detailed provisions concerning precisely how the research will be conducted will be contained in the trial protocol.
- There is no prescribed format for clinical research contracts.
- A standard form must always be adapted to fit the particular study.
- However, the following are a non-exhaustive checklist of points that might be considered for inclusion in a contract.

Study details

- The protocol should be incorporated by reference into the contract.
- The protocol must not be deviated from, except;
 1. As agreed in writing between the parties and approved by the ethics committee.
 2. In the opinion of the investigator, it is necessary to do so immediately in order to protect the health and safety of a research subject.
- A 'key person' clause should be considered. This might specify that identified individuals, or a certain number of staff specified minimum qualifications, will work on the study.
- The contract should address whether the CRO or investigator is allowed to subcontract any of their obligations and, if so, which of them.

Compliance

- A specified party must hold or obtain (and maintain) all necessary authorizations.
- All legal and regulatory requirements (including labeling) must be complied with.
- Compliance with the ICH, Good Clinical Practice Guidelines or equivalent should be required.
- The investigator must obtain ethical approval from relevant ethics committees before beginning the study and refer all amendments.
- The study must be carried out to the highest professional standards.

Timing

- Start date, duration/end date should be identified.
- The number of subjects to be recruited by specified dates should be addressed.
- The options if the recruitment rate is not on target.
- Provision for making status reports, providing interim analysis reports and submitting the final report by specified date should be made.

Data

- Except for the purposes of the study and as required by law, the data must be kept confidential.
- Retention of title by specified parties (in particular the sponsor) in identified documents and materials should be spelled out.
- Protection of intellectual property rights of the sponsor must be covered.
- Arrangements for maintaining safety and security of data, documents and trial supplies should be identified.
- The investigator will maintain all records relating to the study, including case report forms, for as long as is practicable.
- Responsibility and procedure for notification of Adverse Drug Reactions (ADRs) or other unexpected or unusual occurrences in compliance with the legislation needs to be described.

- Payment The contract should specify:
 - The amounts and timing (advance, stage or interim and final) of payments and the payment of reasonable expenses.
 - Whether separate accounts are to be established.
 - Provision for alteration of budget in the event of amendment of the protocol, or extent of services to be provided, and early termination.
 - Materials.
 - Supply of the investigator brochure, updates, product and documentation by sponsor.

- Product Liability
- In relation to liability issues, the contract should cover:
 - Indemnity to be provided by the sponsor for any liability costs and expenses of the investigator arising out of personal injury claims, subject to conditions.
 - Indemnity by the CRO or investigator in favor of the sponsor in respect of negligence, breach of contract by the CRO or investigator.
 - Observance of applicable local guidelines
 - Financial provision for handling of claims (e.g., insurance arrangements).

- Termination
- Appropriate provision for termination, especially early termination, is essential:
 - On specified grounds; sensible to provide for termination by the sponsor on notice without reason, but subject to the obligation to pay for work done at that point.
 - The rights of termination, if any, consequent upon a breach of contract by either party should be described.
 - Termination upon the insolvency, administration or liquidation of either party, or long-term suspension of the agreement (i.e. circumstances beyond the control of either party) should be addressed.

CONCLUSION

- More effective contracting of clinical drug-development activities to CROs can be achieved by applying the following methods:
 - Use a strategic approach to outsourcing
 - Follow the three principles for achieving success with CROs: define accurate study specifications; select the right CRO; and manage the study.
 - Select CROs according to the three Cs: capability, compatibility and cost.
 - Evaluate the CRO's resource allocations
 - Define the performance metrics
 - Ensure efficient communication with CRO