

The Challenges of Building an Effective Structure for Sponsor-CRO Partnership

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Introduction

The growth of contract research organizations (CROs) as an industry is inevitable. When the global economy is thriving, life science companies are inclined to develop more products and hire CROs to complement in-house work. When the economy is in a slump as it is today, those companies still hire CROs, but for a different reason: to help cut overhead costs.

Studies confirm the CRO industry's growth. Among pharmaceutical companies, more than 65 percent of sponsors participating in a 2008 survey said they use CROs in clinical trials¹. Over the past decade, the annual growth for drug sponsor spending for CRO services has outpaced annual increases in global spending in new drug development, 13.4 percent versus 9.1 percent, according to a 2010 research by the Tufts Center for the Study of Drug Development². Not only are pharmaceutical companies increasingly outsourcing clinical trials, there is also a growing trend toward hiring foreign CROs and conducting clinical trials offshore. Sponsors are attracted to "offshoring" outside of North America and Western Europe for a number of reasons, including: availability of human resources and technical skills, cost advantages, and the availability of "naïve populations," which refer to people who have not been diagnosed or treated for particular conditions. The latter is important in reducing the number of variables affecting a clinical trial. Among the most popular places for offshore clinical trials are the so-called BRIC countries, known for their large populations and equally large market potential: Brazil, Russia, India, and China³.

Whether a clinical trial is being outsourced locally or offshore, it is likely that the use of CROs in clinical research will continue to grow. Given this trend, the relationship between a sponsor and a CRO has never been more critical to the overall success of the pharmaceutical industry and yet the sponsor-CRO collaboration is fraught with challenges. How can both parties turn a business relationship into an effective and successful partnership? How can this partnership help reduce the time and cost of getting their product to market? We will explore these questions and consider some strategies.

Common Issues Facing Sponsor-CRO Relationship

The sponsor-CRO relationship is meant to increase efficiency, in terms of cost and time, for both parties. Sponsors save time and money by utilizing the CROs' staffing resources and expertise, which are readily available at relatively lower costs. CROs increase efficiency and generate more revenues by maximizing their overhead costs. For example, a CRO may use the same staff to support multiple clinical trials for different sponsors in the same region.

For a sponsor, efficiency is perhaps the biggest advantage of hiring a CRO to conduct a clinical trial. In the process, it must entrust to the CRO a large part of the responsibility for the overall quality and success of a clinical trial. Once the CRO accepts such responsibility, it faces a lot of pressure to meet the sponsor's expectation of a successful clinical trial executed under specific timelines and budget. Given this context, the sponsor-CRO relationship faces numerous challenges, such as the following:

• Poor Communication Stemming from Vaguely Defined Expectations

When communication between a sponsor and a CRO breaks down in the thick of a clinical trial, it is likely that the problem stems from vaguely defined expectations. The parties cannot operate efficiently based on assumptions. From the outset, the sponsor must clearly define what it expects from the CRO, including a complete list of study specifications and requirements, corresponding timeframes, as well as

GCP regulations that apply to the CRO. A sponsor should also thoroughly review the CRO's standard operating procedures (SOPs) for conducting clinical trials to ensure that the CRO's standards are up to par with the sponsor's standard of quality.

Under U.S. Food and Drug Administration (FDA) rules, sponsors can transfer clinical research duties and functions to the CRO, but the sponsor is ultimately responsible for the integrity of the data generated by the clinical research. The International Conference on Harmonization (ICH) E6 GCP Consolidated Guidance—which has been adopted by the FDA and regulatory bodies in the European Union, Japan, Australia, Canada, and other countries—has a similar provision allowing the transfer of trial-related duties to a CRO, but it also states that the ultimate responsibility for the quality of the trial data always resides with the sponsor.

The importance of sponsor responsibility over clinical trial results is highlighted in a recent case, in which the FDA found a CRO to have widely falsified and manipulated clinical research data. The agency warned sponsors that hired the CRO during a certain period to re-evaluate clinical tests or even repeat studies⁴. So even though it was the CRO that was found guilty of violations, sponsors ultimately carry the burden of any regulatory action.

In addition to defining its expectations early on, the sponsor should get the CRO's input in developing a project plan. This is particularly critical when hiring a foreign CRO because often cultural differences and language challenges can add to communication issues between the parties.

On the part of the CRO, it must not promise things that it cannot deliver. The CRO should make a commitment based only on what it can realistically accomplish. After making a commitment, it should allocate all the necessary resources to deliver what it has promised within the timeframe agreed upon. For communication to go smoothly, both parties must be accessible and responsive, especially when unexpected problems arise.

• Poor Management by Sponsor

At one end of the spectrum, there are sponsors that manage their CROs on the basis of a crisis. They entrust almost everything to the CRO until a crisis emerges. At the other end of the spectrum are sponsors that micromanage, expecting the CRO to replicate the sponsor's processes instead of taking advantage of the CRO's own methods.

Striking a balance between the two extremes is key to effective CRO management. Contracts between a sponsor and a CRO help define their relationship and the management approach for such a relationship. A quality agreement should outline roles and responsibilities, expectations, timelines, deliverables, and quality standards and GCP requirements that apply, while a service agreement should spell out any transfer of responsibilities and delineate other business terms of the sponsor-CRO relationship. Sponsors also typically use audits to monitor CRO performance and a provision about audits can be included in the quality agreement.

The contracts between a sponsor and a CRO can serve as the basis of a CRO oversight program. A good program should include a methodology for documenting issues or deviations during the trial and a corrective and preventative action (CAPA) plan which includes a process for escalation of issues that are deemed critical. Clinical trial staff turnover at the CRO and/or sponsor is inevitable and can lead to inefficiencies and bottlenecks. Therefore, an oversight program should also include a provision for delegation of responsibilities in case clinical trial staffers leave.

• Lack of CRO Transparency

Sponsors generally want to be aware of the activities of their CROs and trial sites. Some sponsors have complained about a lack of transparency on the part of CROs on such things as billing and status of trial activities and issues, while CROs want sponsors to define the extent of the CROs' work more clearly⁵.

An example of a lack of transparency is when a CRO hires subcontractors without discussing the decision with the sponsor. When a CRO subcontracts some of its tasks, then there is a blurring between the CRO's and the subcontractor's responsibility, and it is more difficult for regulatory authorities to draw the line. A study on CROs by the Centre for Research on Multinational Corporations cited this example: A CRO subcontracted the monitoring of a clinical trial site in Peru without informing the Peruvian regulatory agency. While the study did not find any proof that subcontracting in clinical trials have led to harm of trial participants, it said, "The fragmentation of the implementation of clinical trials does increase ethical risks." This fragmentation of tasks also blurs the oversight of the trial.⁶

• **Lack of Common Platform**

A sponsor may be using an electronic platform but its CRO or clinical trial sites may still be using either a paper or a hybrid (combination electronic and paper) system. Even when all parties involved use electronic tools, they may not have the capability to consolidate their different tools into one platform or to connect with each other for collaboration.

A lack of common platform is inherently inefficient even in simple tasks, such as searching for and tracking of SOPs and essential documents, and routing, review and approval of documents. Collaboration in writing reports or amending SOPs can take longer. Without a common platform (or at least common tools that the sponsor and the CRO can share), sponsor monitoring and assessment of the CRO and the trial sites can be very challenging. Reporting of deviations and other quality issues may not be in real time or close to real time, increasing the sponsor's risk of noncompliance. The quality processes of the CRO and clinical trial sites will not be visible to the sponsor, making monitoring more difficult.

Five Strategies for Building an Effective Partnership

Clinical research is the third most frequently outsourced service by pharmaceutical and biotech companies (next to hiring consultants and analytical testing), according to a Q4 2011 survey conducted by Nice Insight, a firm that provides quarterly marketing intelligence reports in the materials science and life science markets.⁷ The more sponsors use CROs to conduct clinical trials, the more regulatory agencies will scrutinize sponsor oversight of the CROs. In the United States, for example, the FDA has increased the focus on sponsor, CRO, and monitor inspections. In 2011, the agency updated (after 10 years) the Bioresearch Monitoring Compliance Program Guidance Manual in response to concerns about clinical trials. It also issued a draft guidance titled "Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring" in the same year.

Now more than ever, it is important for sponsors and CROs to build effective partnerships that will ensure successful clinical research. In some cases, the sponsor and the CRO may enter into a formal partnership, in which the CRO will trade part or all of its service fees in exchange for an equity stake in the sponsor company. In this type of relationship, the CRO would share in both the risks and the commercial success of the clinical research.

We will discuss the more common type of sponsor-CRO relationship: transactional relationship. The term "partnership" refers to a close and

strategic transactional relationship based on mutual trust and respect. Both parties must build the partnership. Gone are the days of a top-down approach, in which the sponsor is presumed to know everything. To be truly effective, both parties must take advantage of what each one can bring to the table.

Here are five strategies for building an effective sponsor-CRO partnership. These strategies can serve as the "structure" of the partnership—each strategy serving as a pillar that will keep the relationship strong.

• **Establish a Collaborative Environment**

Most problems related to poor communication (discussed above) can be avoided, or at least minimized, by establishing a collaborative environment from the onset of a sponsor-CRO relationship. Contracts (quality agreement, service contract) can help shape a collaborative environment by defining expectations, study requirements, corresponding deliverables, applicable GCP regulations, and audit requirements. A sponsor should also demand in the contract to be informed immediately if the CRO plans to use a subcontractor.

The sponsor has to find the middle ground in managing the CRO by giving it ample "space" to execute the clinical trial and at the same time monitor the CRO's activities closely. On the part of the CRO, it should maintain transparency and provide necessary information to the sponsor on a regular basis, prioritizing any issues that need input from the sponsor.

• **Share Compliance Responsibilities**

FDA regulations (21 CFR 312.25) and ICH E6 GCP Consolidated Guidance (Section 5.2) both allow transfer of clinical trial duties from the sponsor to the CRO, but the sponsor retains the ultimate responsibility for the clinical research. The FDA specifies that responsibilities that are not made in writing are not considered transferred. Under the FDA's 2011 draft guidance on "Oversight of Clinical Investigations," the sponsor may transfer the task of monitoring investigators and the clinical trial, but the sponsor is responsible for the oversight of the CRO's monitoring duties. Regulatory compliance is typically covered in a service agreement between the sponsor and the CRO. In addition, the sponsor and the CRO should have policies and procedures addressing regulatory requirements that are specific to the clinical trial (drug accountability, site initiation, clinical investigator's qualifications, etc.). A project management plan should identify all tasks related to the clinical trial, the person(s) responsible for each task, deliverables, critical events, and study milestones. The plan should be developed through a collaboration of all stakeholders from both the sponsoring company and the CRO. A sponsor should thoroughly discuss and review a CRO's SOPs as it relates to the monitoring of clinical sites to ensure that monitoring activities meet the sponsor's standards for monitoring quality.

• **Maintain a High Level of Transparency and Accessibility**

As sponsors feel increased pressure from the FDA and other regulatory bodies to provide oversight to CROs, they also increase their demand for transparency on the part of the CROs. Conducting audits, both at trial sites and at the CRO, is one way for the sponsor to ensure transparency. The study on CROs by the Centre for Research on Multinational Corporations showed that auditing of trial sites is a widespread practice, with the typical trial site getting 5.5 monitor visits a month mostly by the CRO, but also sometimes by the sponsor.⁸ In addition to audits and monitor visits, all stakeholders should be aware of the status of the clinical trial. It is essential that all stakeholders have access to critical information in order to be on the

same page. Sharing of information is key to transparency and a smooth sponsor-CRO relationship.

In terms of accessibility, the sponsor must be committed to being responsive and flexible when unexpected issues arise. Sponsors expect CROs to be transparent. In the same vein, CROs expect sponsors to be responsive to them.

• **Establish Appropriate Performance Assessment Criteria**

The sponsor and the CRO should agree on performance criteria for assessing the CRO's success in conducting the clinical trial. The criteria should cover quality of work, productivity, timeliness, efficiency, coordination with the sponsor and other CROs (if there are other CROs involved). The criteria should be measurable. There should be a process for tracking and addressing CRO performance issues.

An electronic quality and compliance system can provide both the sponsor and the CRO with the tools for assessing and monitoring performance throughout the clinical trial. An effective system should have the capability to generate key performance indicators (KPI) and other assessment reports that will show the CRO's performance over time (monthly, quarterly, etc.).

• **Use an Effective Platform for Clinical Research**

While it is true that some sponsors and CROs still use paper or hybrid systems to manage clinical research, the first four strategies mentioned above can be implemented more effectively with the help of an electronic system. Establishing a collaborative environment (first strategy) is easier with the help of an electronic system that the sponsor and CRO can share. Compliance efforts can be shared more equitably between the sponsor and the CRO (second strategy) with a system that automatically notifies the sponsor of any serious CAPA or other issues in real time or as close to real time as possible. Likewise, the automatic notification system boosts transparency (third strategy) of the CRO's activities because the sponsor will be immediately alerted when there are serious issues.

Choose a robust electronic platform that can manage and streamline all the critical aspects of clinical research: processes, documents and records, SOPs and procedures, monitor reports, tasks, training, CAPA, risk management, and audits. The same platform can be used to manage the activities and performance of the CRO and clinical trial sites, as well as in conducting audits and assessing CRO performance (fourth strategy).

Conclusion

Sponsors are relying on CROs more and more to conduct clinical research, and the trend is expected to continue. With the growth of CRO use, the sponsor-CRO relationship is evolving and expanding offshore. In turn, regulatory authorities are putting more emphasis on sponsor oversight of CROs. To a great extent, the future success of the life science industry in bringing new products to market rests on the ability of sponsors and CROs to work together successfully, so it behooves both parties to strengthen their partnership with the help of the right structure, tools, and strategies.

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8. *Supra* note 3, page 81.

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