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Caught in the Middle: How Sponsors, Sites and CROs Can Work Together Effectively

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Pharmaceutical, biotechnology and medical device companies hire contract research organizations (CROs) to assist them in conducting clinical trials. Since the first CROs were founded in the 1970s, they have grown into a $10 billion industry with over 130,000 employees.[1,2] There are many specialized CROs, but the bread-and-butter functions of most CROs are recruiting and monitoring investigative sites. Only 29% of U.S. sites rate their CROs as excellent, so 71% have at least some complaints.[3] 46% say the involvement of a CRO makes studies less profitable.[4] Despite being considered by many sponsors and sites as a necessary evil, CROs play a role in over 60% of all clinical studies.[5] If all the CROs were to disappear tonight from the face of the earth, any celebration would end before noon tomorrow.

Despite their ubiquity, CROs are often misunderstood. Many sponsors and sites do not know how to work with them effectively. Sites and sponsors often blame CROs for problems that are not the CRO's fault, even problems that the CRO warned them about. When sponsors and sites have an issue, they often first agree to blame the CRO. In fact, "Scapegoating Services" should be part of every CRO request for proposal (RFP).

CROs are not blameless. Like anyone else, they make mistakes, sometimes lots of big ones. That said, they are in a challenging business: Every sponsor, site and study is different, except everyone needs everything yesterday. Study plans are obsolete the day they are written. CROs have to hire, manage and communicate with personnel all over the country, or the world. Profit margins are narrow. Competition is fierce.

True CRO Story

We were managing a study with 30 academic centers. We had contracted with all of the sites multiple times, so we had a very good idea as to what terms each site would accept. We tried to convince the sponsor to change its conservative template or at least give us some negotiating authority. The sponsor did not accept our recommendations because it was concerned that their legal group was overloaded and would complain about the required three to four hours. As a result, their lawyers ended up spending an extra 60 hours on the study and delaying it by about a month for no legal gain. We spent a lot of their money in the middle fighting over the very issues we tried to help them avoid.

Over the next year, many complaints about CROs will be justified. Many others will be based on a misunderstanding of the CRO's role. Many others could have been avoided by a better partnership between CRO, sponsor and site. Regardless, every complaint is an opportunity to improve customer service. Good CROs want to hear complaints so the specific problem can be fixed, SOPs and training can be improved to avoid similar problems in the future, or the customer's expectations can be better informed. The only bad complaints are those allowed to

fester until they destroy the business relationship, so feel free to help your CRO improve its business.

Sponsor Complaints about CROs

Our CRO is arrogant and wants to do the study its own way. CRO personnel are more efficient using their internal methods, so by accepting CRO recommendations, you may save time and money on the study. Although the CRO that wins the contract probably knows a lot about clinical research, many sponsors do not take advantage of their expertise. Ask your CRO to make recommendations, and consider them with an open mind. Focus more on results and less on methods.

True Sponsor Story

We hired a CRO for a study because it claimed to have the investigators we needed for a specialized therapeutic area. What a disaster! Some of the investigators were too busy. Others signed up but didn't enroll. Some had a related but wrong study population. Some were specialists, so weren't appropriate for that study. Some had had a previous bad experience with the CRO.

Our CRO claimed to have the sites we needed for a specialized study, but didn't. Maintaining site databases is notoriously difficult, so it is not surprising if CROs are overly optimistic. Regardless of what they say, most studies need new sites. Ask your CRO to give you profiles of their "stable" of sites for your therapeutic area. Ask for reports of recruiting by (unidentified) site for the last three studies in your therapeutic area, and then pick three of the sites off the profiles and ask if you can contact them for references. If you have time, ask your CRO to conduct a feasibility study and perhaps conduct some preliminary site qualification visits.

Our CRO was totally unable to predict when it would get regulatory approval in its country for our study. Regulatory approval, especially in some developing countries, can be very difficult to predict. In some countries, the culture dictates feedback that is encouraging ("perhaps next week") rather than objective ("we have no idea"). Ask your CRO to provide data on previous regulatory approvals. Make it clear to your CRO that, if it wants your business in the future, false optimism is not helpful.

True CRO Story

We were working on a fairly rare disease with very strict eligibility criteria. Up front, we said enrollment would be very slow. The sponsor picked the sites, predicting 1-2 enrollments per month per site. The reality was about 1/3 enrollment per month per site. The sponsor was unhappy with *US*. We added some of our own sites and doubled the enrollment rate.

The CRO we want to hire will not waive Article 29 of the year 2000 version of the Declaration of Helsinki, which prohibits placebo controls. ICH GCP refers to the Declaration of Helsinki, but does not specify a version. If you are a U.S. company conducting a study for FDA approval, you can argue that, since the FDA has not formally recognized the 2000 version of the Helsinki Declaration, you are not obliged to comply with it, even in countries that have recognized it. However, the CRO can argue that the current version obviously applies, may be required anyway by local IRB/IECs, and would avoid potential legal liability if a placebo subject is injured.

Our CRO did not make a good-faith effort to represent our position in negotiating the contract with the big sites. Many big sites, especially state and federal entities, must comply with their institution's policies and interpretations of the laws and regulations. Experienced contract negotiators are familiar with the sites' idiosyncrasies. Ask your CRO to ask problematic sites to explain their positions. It may save time for your attorneys to talk to the site's attorneys. CROs may involve lawyers in the contract negotiation, but not to provide legal advice to you in the sense of retained counsel.

Our CRO listed superstars in the RFP but assigned so-so personnel to our study. Months may pass between submission of the RFP and assignment of personnel. CROs cannot hold personnel for a study without compensation. Study schedules are unpredictable. A new study can require a significant percentage of a CRO's qualified CRAs. In smaller, developing countries, a few new studies can overwhelm the country's entire CRA capacity. Include a clause in your contract requiring credentials as good as or better than the credentials of the personnel listed in the RFP. If your study schedule and credential requirements are flexible, you may be able to get better personnel.

Our CRO's CRAs are inexperienced and poorly trained. Every workforce has a mix of experience. However, many CROs hire only experienced CRAs and invest in training. The CRAs at one large CRO, for example, spend an average of 60 hours per year plus about 10 hours per study in training. Expect training programs to be organized and ongoing. Expect your CRO to provide well-trained CRAs with a mix of experience no less than its staff average. Ask for documentation of experience and training. Ask your CRO for the right to approve CRAs assigned to your study. Ask for the right to interview them. If one doesn't work out, do a "post mortem."

True CRO Story

One of our sponsors wants only CRAs with 2 years monitoring experience. Another wants only CRAs that have been working with us for over six months. These rules should be flexible. Five years of study coordinator experience should count for something. For example, we once persuaded a sponsor to accept CRAs with less CRA experience but with relevant nursing experience. They worked out very well.

Our CRO made us pay to fly all their regional CRAs in for training. Some of them monitor only a site or two. We would have saved money with a few dedicated CRAs located centrally. For most trials, the expense of training regional CRAs is more than offset by reduced travel during the study. Plus, less travel reduces CRA burn-out and turnover. Discuss with your CRO the budget implications of regional vs. centralized CROs for your study. Consider webinar rather than face-to-face training.

Our CRO's personnel, especially monitors, keep changing. The average tenure of a CRA at an average CRO is something over two years, significantly lower on average than at sponsors. Turnover is expensive for CROs, so they aren't happy about it either. It appears to be lower among regional CRAs and may be declining in general. CROs may reassign a CRA because of specific therapeutic experience, to reduce travel costs, or poor chemistry with site or sponsor personnel. Don't burn them out with extensive after-hours and weekend travel. Ask your CRO for statistics on staff turnover and work history of the CRAs proposed for your study. Ask to be consulted before any reassignments. Maintain good communications about workload

with your CRO. Ask your CRO to organize training sessions for CRAs that join in the middle of your study. If you negotiate a very low price with your CRO, expect it to be more attentive to other clients.

Our CRO did not meet its enrollment schedule commitments. Only about 16% of studies enroll on schedule.[6] CROs sometimes accept unrealistic schedules from sponsors to get the work, and then hope for the best. Study schedules, especially for enrollment, are affected by many unpredictable factors. Decisions you make on eligibility criteria can slow enrollment. Ask your CRO to provide optimistic, realistic and pessimistic schedules. Expect your CRO to provide clear disclaimers with the schedule. Consider a penalty/bonus clause. Ask your CRO for a contingency plan. Screen back-up sites. Compare the performance of the sites your CRO recommends vs. the sites you select. Expect a CRO with experience in your study's therapeutic area to be relatively accurate in its schedule estimates.

Our CRO authorized a site to modify the Protocol without our approval. As the party responsible for the study, you are legally-required to authorize protocol amendments unless you delegate that responsibility to the CRO in writing. Repair the damage as best you can.

Our CRO accepted a local IRB's change to the informed consent form (ICF) without our prior approval. IRB approval of the ICF is legally-required. Sponsor approval is optional, so you can add it to your standard CRO and Site contract. However, by approving the ICF, you may incur legal responsibility for it. You may prefer the right to review changes and propose comments, so the CRO doesn't inadvertently accept a change that causes problems for the study. For example, you may be able to provide the bigger picture for a single SAE that alarms a local IRB.

When our CRO's project manager is out of town, no-one else seems to know what's going on. Project managers know more about their studies than anyone else. However, a good project manager keeps his/her team informed and does not micromanage. Expect your CRO to provide reliable ways to contact the project manager when he/she is traveling, to appoint a well-informed deputy, and to identify alternate contacts for functional areas.

Our CRO has blindsided us more than once with bad news. Your CRO probably wants to confirm the problems, internally discuss solutions, and perhaps fix them before reporting bad news to you. If they report a problem without a solution, they are "inept"; if they take the time to develop a solution, they are "secretive". Agree on issue notification and resolution policies and procedures at the beginning of the study. Agree with your CRO on the frequency of status reports, teleconferences and other reporting methods. Work constructively with your CRO to address problems.

Our CRO bulked-up its fees by including unnecessary project management, when all we wanted was the CRAs. An effective monitoring team requires effective leadership and project management. CROs have a big

True Site Story

The CRO for a current study sends us a monthly report listing each subject's medications. It wants us to indicate "ongoing" or the stop date for each med. This information is completely redundant to the CRFs. To make matters worse, the report is continuous so several subjects may be included on the same page. To file the report with each subject's source docs, we have to make copies over and over.

investment in their CRAs to protect. Their CRAs know how to work within the CRO's organization. Renting them out without project management may not save any money, and increases risk for the sponsor. If all you want is CRAs, hire them through a contract CRA staffing firm. If you are paying for project management, ask them to provide a tentative project plan with their proposal. Ask to see de-identified project plans for previous studies, including typical progress reports. Verify that they are actually doing proper project management on your study.

Our CRO charged us a fortune for CRA travel time and costs. CROs pay their CRAs for travel time. Ask your CRO to recruit investigators and assign regional CRAs to minimize travel costs. However, regional CRAs are less likely to have experience in a specific therapeutic area. If you really want your CRO to charge only for actual time on site, expect a much higher hourly rate, including a surcharge for the additional risk. Review CRA travel costs, especially for expensive, last-minute reservations and inefficient itineraries. Alternatively, ask for an all-in fixed-price site visit fee, and let your CRO worry about the travel costs.

Our CRO charges us $100 per CRA hour, but it pays our CRA only about $25 per hour. CRA rates cover substantial overhead such as supervision, hiring, training and business development. CROs generally blend their CRA rates, charging the same rate regardless of how much they pay the CRA, so the mark-up may vary. Site monitoring is the largest part of most study budgets, so it is usually very price-competitive. Obtain competitive quotes. Ask your accounting department for your internal overhead (burdened cost) rates; they may be higher that your CRO's rates.

Our CRO collected its fees even though the study went very poorly. In fact, because the study ran so long, the CRO made a lot more money off us. The problems may not have been your CRO's fault. If fact, your staff may not have accepted the CRO's recommendations on how to avoid them. CROs that don't make a sincere effort to please their clients won't be in business for long. Some CROs may be willing to risk-share, but there has to be an upside too, and the "expected" price may be higher to offset the additional risk. Expect your CRO to make every reasonable effort to meet its commitments. Create a relationship in which you and your CRO can honestly discuss problems, so they get addressed and you don't get blindsided.

Site Complaints about CROs

A CRO was recruiting sites for a study. It called us, but then didn't return our phone calls; we never heard from it again. The person who called you apparently did not understand the importance of relationships. Expect CROs (and sponsors) to return phone calls that they initiate, if only to say that the site list is full. If the person who made the original call does not respond, contact his/her supervisor to express interest in the study.

Our CRO won't let us talk directly to the sponsor. Your CRO probably is not trying to be an obstacle or protect its turf. The sponsor probably hired it to field your questions and issues. Your CRO may appear unresponsive to your communications because it is waiting for direction from the sponsor. When you lose patience and contact the sponsor directly, it may be very responsive and blame the CRO. Ask your CRO to make the communication process transparent, keeping you informed about the status of your question or issue. Expect it to anticipate questions with

prepared answers and build an FAQ file over the course of the study that you can reference.

Our CRA is supposed to be an expert on the study, but he/she always tells us to call someone else. Sponsors contract with CROs to provide, or not provide, specific services. Expect your CRA to know his/her protocols. The sponsor may not permit your CRA to answer certain questions, e.g., about subject eligibility. Expect your CRA to get a lot of the answers for you. Ask your CRO to clearly delineate who should be called about which topics.

When we have a question, we never know whether to ask the CRO or the sponsor. Your CRO and the Sponsor may not have worked out who you should contact. Ask the CRO or sponsor to provide a directory of who to contact about which questions.

Our CRO and sponsor provide inconsistent information. CROs and sponsors do not always share information with all their study personnel. Ask your CRO or sponsor to clearly delineate who should provide which information, and to copy all parties on communications.

Our CRO keeps complaining about same issues but the sponsor doesn't seem to have a problem. Your CRO and the sponsor have different roles and somewhat different objectives. For example, the sponsor may care, and your CRO not care, that your investigator is a thought leader. Your CRO probably does not have the authority to enforce compliance, so all it can do is pester you. If you want to resolve the issues, possibly to your disadvantage, explain your position to the CRO and sponsor and ask for a decision that both will accept.

Our CRO makes unreasonable demands on us. CROs often work to the sponsor's requirements. The person at the sponsor may be inexperienced or unfamiliar with your site. Discuss the problem with your CRO and sponsor; ask them to confirm the requirement in writing. If the requirement is not in the protocol, the study handbook, the contract, or GCP, and extra work is created, invoice for it.

CRO CRAs often nail us for trivial things that sponsor CRAs are flexible about. Site, sponsor and CRO perspectives on what is trivial may vary. Some CROs are stricter than others, even though it costs them time to be strict. A sponsor may have hired a CRO to monitor especially strictly, e.g., if it's a pivotal study. Ask to see the relevant sections of the CRO's standard operating procedures. Sponsors may hold your CRO's CRAs to a higher or less flexible standard than their own. Request clarification from your CRO and sponsor as to the appropriate degree of strictness required. Provide specifics. If you disagree, tell your CRO and sponsor in writing and offer to terminate the study at your site if it will be a problem for them.

Our CRA takes forever to monitor our site, consuming a lot of our coordinator's time. Some CRAs are slower than others, and not necessarily because they do higher-quality work. Ensure that the study files are ready for inspection – up-to-date, correct and organized – prior to the visit. Ask your CRA how to improve the efficiency of his/her visits. Minimize the disruption by scheduling specific times for your CRA to interact with your study personnel. If that fails, request a different CRA.

Our CRO wants us to bring in every subject for a special meeting so we can explain a new risk in the study and obtain their signature on an informed consent form (ICF) amendment. We just want to mail them a letter. If, in the judgment of your IRB, an ICF amendment is required ASAP, you need to bring them in.

Our new CRA wants us to do things differently than the old CRA. CRAs sometimes have different understandings of what the sponsor and protocol require. Document "unwritten" requirements and have your CRA sign and date them. If they change, ask your CRO to confirm the change in writing. If extra work is created, invoice for it.

We are having real problems with our CRA, both on substance and personal interaction. You need a healthy relationship with a competent CRA. If it is not too uncomfortable, discuss your issues with your CRA. If necessary, document your concerns in a polite but assertive letter to your CRA's supervisor. Include specifics. Expect your CRO to respond to your concerns in a timely manner. If it does not, contact the sponsor. The CRO or sponsor may audit your site to determine the facts.

Our CRO doesn't understand our problems with the clinical trial agreement (CTA). The sponsor may be have contracted with your CRO for a low-cost message-carrier who does not understand CTAs. Unless the CRO is using its own CTA template, it has to work with the sponsor's template, with minimal flexibility. Normally, when CROs see a problem term in the template, they ask the sponsor to remove or change it. If the sponsor refuses, the CRO has to represent the sponsor's position as best it can. Expect your CRO to represent the sponsor's interests in negotiations, even if it disagrees with some of the sponsor's positions.

Our CRO low-balled us on the study budget so it could keep the savings. Study budgets are divided in two parts: the pass-through budget, which consists of third-party costs such as investigator fees that the sponsor pays without a CRO markup, and the labor budget, which covers the CRO's own fees. CROs do not get to keep the savings on the pass-through budget. In fact, if they save money on the pass-through budget, most sponsors will not let them move the savings to the labor budget. Expect your CRO to represent the sponsor's interests in negotiations, even if it disagrees with some of the sponsor's positions.

Our CRO delays paying us what we are owed so it can keep the cash in its own bank account. If the CRO is writing the checks, it disburses payments based on strict rules such as collection of complete and accurate CRF pages. If it breaks the rules, the money comes out of its own pockets. CRO and sponsor internal systems generally are not optimized to speed payment to sites. Your CRO's arrangement with the sponsor may or may not allow its cash flow to benefit from delaying payment. Expect your CRO to monitor your site and disburse payments on a timely basis per the contract. Sponsor payments to the CRO should have no connection to CRO payments to you, but CROs are increasingly seeing delays in their sponsor payments as well. If the sponsor is not sending the funds to the CRO, the CRO will probably not pay you, and will probably take the blame. If payments are delayed, notify the CRO in writing and then the sponsor. Include details and an invoice. If a monitoring visit is excessively delayed, request waiver of the requirement to pull CRF pages until monitoring is back on schedule. If payment is late per the contract's payment criteria and schedule, the sponsor is in breach of contract, and you can stop work after

exhausting any remedies specified in the contract. If results are not forthcoming, some sites hold the data hostage as a last resort, but that may end the relationship.

Our CRO imposed additional reporting and other costs on us that are not specified in the protocol. The sponsor may not have told your CRO about those requirements until after the study started. If it is a frequent problem, increase your regular fee schedule a bit to cover these costs. If they are not GCP and you were not informed about them in writing prior to signing the contract, you are not contractually required to do them. If they are a burden, ask the CRO or sponsor to confirm that they are necessary. If they are, ask for an increase in the budget. If reporting is required by the contract, you may want it specified. If a protocol amendment requires additional work, ask for a budget increase.

Our CRO will not pay us what we were owed at the end of the study. CRO/sponsor contracts have a time limit after the study for pass-through invoices to the sponsor. Ask your CRO what the limit is. Submit invoices for open charges, allowing adequate time for the CRO to review and forward them to the Sponsor before the deadline.

Our CRO doesn't help us get third-party reimbursement for our subjects. CROs are not reimbursement experts, and are not paid to provide that service. Ask your CRO for information resources and the appropriate IDE reimbursement category.

Summary

All of the above complaints can be addressed, or at least understood, with six steps:

- If you are a sponsor, know your partner before committing to the relationship; if you are a site, get as close to this ideal as you can.
- If you are a sponsor, designate at least a project manager-level person to manage the CRO. Focus on deliverables, quality and budget; do not micromanage or monitor the CRO's work as if it were a site.
- Ensure that all parties have a realistic expectation of the other parties' requirements and contributions; agree on a detailed statement of roles and responsibilities; ask your CRO for their statement of service standards, e.g., that the project manager or a deputy can always be contacted within two hours during business hours.[7]
- Analyze the issue with an open mind, including your own responsibility.
- Address the source of the problem rather than the symptoms.
- Communicate.

Many sponsors are developing preferred provider relationships with a short list of CROs, so the lessons learned from each study can improve performance on future studies. Sites can't choose their CROs, but they can learn from each experience and apply it to future studies.

Clinical research is fraught with difficulties, so successful studies require that all parties commit to working together constructively, and sometimes go above and beyond the call of duty. If any member of the team thinks it's just another study, or just another CRO or sponsor or site, you need a different member for your team.

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