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As a life science veteran with several decades of experience working in Sponsor organizations and CROs, I have been fascinated by the sequence of events and decisions that lead to a clinical trial rescue. I have personally been involved with four clinical trial rescues. Most were large, phase III pivotal drug trials for market clearance. Three were awarded to mid- to large-sized CROs and one was awarded to a smaller CRO. The total costs of the four trials ranged from approximately $4.8M to $18.5M *in the beginning*. One of the Sponsors could not financially recover and went out of business.

The rate of rescue trials is not published, but the risk and exposure in clinical research is not unusual.

A clinical trial rescue is perhaps one of the worst realities that prior decisions during the due diligence, proposal review, bid defense, and ultimate award to a CRO partner failed. What ultimately goes wrong? Well, many things, but they all boil down to the Sponsor's internal review processes, the influence of special persons or parties, the experience of the Sponsor's clinical operations team, the trial protocol itself, and the specifications for delegated services.

How might the Sponsor be to blame?

- Wants cheap and/or fast solution
- Wants "name-brand" CRO
- Influence of partnership selection by special persons or investors
- Specifications were not accurate or not properly disclosed
- Lacks adherence to FDA feedback prior to commencement
- Clinical protocol wasn't fully vetted for operational compliance by stakeholders in the development stage

- Overly optimistic enrollment rate
- Underestimation of drop-out rate
- Impossible milestones set by executives or board of directors
- Inexperienced with oversight
- Poor communication
- Critical staff turnover

How might the CRO be to blame?

- Disconnect between the business development and clinical operations teams
- Acceptance of proposal assumptions and capitulation to the Sponsor when research standards, best practices, and reasonableness should prevail
- Lack of cost transparency
- Change of assignment from "A team" to "C team" after the bid defense and contract execution
- Inability to set proper expectations with extremely demanding Sponsor who has unrealistic expectations
- Inability to anticipate risks
- Poor communication
- Misunderstood transfer of obligations and contractual negotiation and execution
- Staff turnover

There are ways to mitigate the risk of trial rescue or repeating a clinical trial when identifying the right Sponsor-CRO partnership.

Let's review an actual case study to identify what went wrong, how much the trial costs ballooned to after the rescue, and how to avoid the squandering of resources.

Rescue Trial Case Study

A Sponsor receives a few bids for their phase III pivotal trial in the US. About 750 subjects and 30 US research sites are planned to participate over two years. They select and contract CRO 1 with a history in the targeted indication *and* a promise by the executive team to save money by employing a risk-based monitoring plan and reducing monitoring visits, including those up front in the beginning of the trial. CRO 1 claims that clinical research associates (CRAs) will only perform their first interim monitoring visit after 3,500 data fields are complete at each site. *CRO 1 concludes that this method can save the Sponsor around $1M.* The all-in total spend including pass-through costs is around $8M under this plan.

As the trial starts, none of the research sites are being monitored in a meaningful way to catch errors in dosing subjects, e-diary entries, and other operational problems. Some research sites enroll subjects slowly and are delinquent in entering their data for their subjects. A handful are not visited by the CRAs for approximately a year, until 3,500 data fields have been entered in the electronic data capture (EDC) system. To compound these problems, nine of CRO 1's original trial team have been replaced by new team members within 10 months of trial start-up and initiation.

As a few research sites complain to the Sponsor that they hadn't been visited and ask for more monitoring visits, *the Sponsor's CEO sits on any decision to act*.

After 11 months of mounting problems with continuous enrollment, the Sponsor's CEO engages with CRO 2. The Sponsor's CEO terminates his US clinical lead who became unpopular for sounding the alarm of risks and identifying solutions. The Sponsor's CEO replaces the terminated employee with a non-US staff member with less experience.

The Sponsor CEO constrains CRO 2 with how much more he is willing to pay for the trial rescue, which is not mutually agreed upon contractually for several months. The trial continues to enroll subjects during this time under CRO 1 with the ineffective monitoring plan.

Fourteen months from the time major risks have been identified, the trial is formally transitioned to CRO 2.

CRO 2 is under-resourced for the job at hand because of the restrictions the Sponsor CEO has placed on their service costs. The Sponsor CEO demands to assign and pay for only four full-time CRAs. Pandora's box is opened after interim monitoring visits reveal significant data integrity issues, and CRO 2 produces multiple change orders to address insufficient quality data, and the requirement to add 8 new research sites and enroll 400 more subjects. The high work burden placed on CRO 2 staff is unreasonable and fatigue affects the trial team. The addition of 5 CRAs and a clinical project manager are needed despite the Sponsor CEO's debate over the cost increases and refusal to shoulder any responsibility. The duration of the trial was one year longer than originally anticipated.

It is, therefore, easy to see how this clinical trial was derailed by early positions and decisions made by both the Sponsor and CRO 1. Both can be blamed for lack of transparency and unreasonableness. Further, promises by CRO 1 that a Sponsor may get quick, cheap, and quality must also be suspect. CRO 2 could not have anticipated how poor the clinical data really was until they performed several visits at each of the 30 original research sites.

The trial ended up costing the Sponsor $16.25M. CRO 1 and CRO 2 had key staff resign due to burn-out and other reasons. This is not clinical research at its finest.

Opportunities to Learn and Make Better Decisions

For all three parties in the case study above, several key mistakes with lasting consequences were made.

The Sponsor was:

- Motivated by cheap and fast
- Contractually inexperienced at conveying transferred obligations
- Indecisive in moving to action and could have, but did not, temporarily suspend trial enrollment when red flags appeared in the beginning
- Lacked appreciation for Sponsor trial lead who sounded the alarm early
- Ineffective at trial management and oversight
- Unreasonable with terms of service costs and expectations

CRO 1 was:

- Motivated to win business by presenting faulty proposition for $1M savings
- Unable to set proper trial execution expectations
- Ambivalent to reputation risks on business and disaffected trial team
- Devoid of addressing or admitting problems
- Ineffective at communication, trial management, and operations

CRO 2 was:

- Motivated to capitulate to the Sponsor's assumptions to win the rescue business
- Naive to full risk and cost exposure of unknown data integrity issues
- Ambivalent to reputation risks on business and disaffected trial team
- Unable to set proper trial rescue execution expectations

The Key Take-Away: By placing a greater emphasis on the CRO due diligence process and by identifying a more collaborative, transformational Sponsor-CRO partnership, many life science company executives can improve their chances for positive results in their clinical trials, and avoid the embarrassment of having to explain the costs of a trial rescue or repeat trial to investors, board of directors, and key constituents.

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