Getting Your Bad News Early Will Ensure You Don't Fail Tomorrow

It is extremely rare for CROs to move seamlessly through an entire clinical trial without encountering some problems or hurdles. But what you don't want is a situation where the challenges are becoming systemic risks and the trial becomes in need of rescue. Even the best and most capable CROs can experience challenges should they fail to undertake additional planning, particularly for trials that are concerned with rare and complex diseases. Common problems include poor patient recruitment and retention, an unmotivated staff and site team, lack/loss of resources and concerns over the integrity of clinical data can all lead to trials falling behind schedule or even failure. In fact, it is estimated that around 70% of clinical studies are at least a month behind schedule, with sponsors losing between $660,000 – $8 million for each day the trial delays product launch[1].

But don't be too perturbed – with a good relationship, contingency planning and proper resource allocation, the CRO and sponsor can work together to overcome the vast majority of problems in a timely fashion. In this article, we will look at those unfortunate times when despite your best efforts, a rescue study and new CRO are needed. We will walk through some practical examples of how to go about planning and undertaking a rescue so that you can continue to advance your product towards clinic. In these situations, you may be looking at full or partial transition to a new CRO, and we will explore how to do this whilst minimizing disruption to the trial.

For example, in one recent case we were required to come-in during a large phase III clinical study on a women's health target, taking over from a global CRO. The initial study goals were to compare a new drug to a placebo in order to determine its effect in preventing pre-term labor and neonatal mortality and morbidity. The sponsor decided that the study needed rescuing because they became frustrated with the change orders from the originally selected CRO. In addition to this, they felt that the CRO Project Manager was not proactively communicating with the sponsor when it came to handling and solving issues that arose throughout the study.

The main challenge for the sponsor was how to get the trial properly back on schedule, and the project was beset by a number of complex challenges including the closure of non-enrolling sites and the cancellation of all site and vendor contracts – forcing a time consuming and debilitating process of renegotiation. To overcome this, a rapid response team of experienced professionals were deployed to manage an increasingly intricate and detailed process to facilitate an on-schedule transition – starting with tying vendors, irrespective of the volume discounting they provided to the previous CRO (preferred pricing), to previous pricing. Several Outside of United States sites were also closed at transition, with more to follow after – leaving the challenge of filling the enrollment and placebo-controlled groups.

One of the first courses of action saw the data management team transferring all paper records to Electronic Data Capture (EDC) systems. However, this then required the trial to be in a hybrid data collection state for a portion of the trial, further increasing the logistical challenges. The next stage was to complete five batch locks, while ensuring older clinical data had undergone all data cleaning processes, and had been reviewed by the entire project team in anticipation for the final database lock. In addition to this, the drug received US approval during the course of the study, resulting in an understandable but huge loss in enrollment from US sites (which were the highest enrollers at this point). In response, it was necessary to quickly find new sites globally to make up for this loss; with similar demographics and a good supply of willing participants Eastern Europe was seen as the best chance of progressing the study quickly. After informing the sponsor of the new challenges, the cost of expansion in Eastern Europe was mitigated by the closure of non-enrolling sites in the US. It was a complex trail, which by completion, had seen over 1,700 patients enrolled at over 70 sites in eight different countries – the US, Canada, Czech Republic, Hungary, Italy, Russia, Spain and Ukraine.

In another project, a Phase III Pediatric Cardiothoracic Surgery study, we were contracted to undertake a rescue after the project's start-up stalled over the course of a year. The sponsor was driven to drastic action by multiple staff changes at the CRO (which naturally presented continuity issues), but more crucially reoccurring errors within key study documents, despite their continued best efforts.

The study's aim was to evaluate the safety and effectiveness of a drug that may help reduce complications of acute lung injury for pediatric subjects undergoing surgery for congenital heart defects. After so many changes enrollment rates were lagging far behind the sponsor's timeline, a situation exacerbated by an extremely small patient population and the acute nature of the condition.

The immediate challenges for the rescue was to understand where the study currently stood and what roles and responsibilities were needed. Identifying the most critical aspects of the study to address first, and then devise the necessary short and intermediate term plans. Rather than trying to 'dive straight in' so to speak, it was crucial to the study's long-term success that we started with a two-day intensive planning meeting alongside the sponsor, followed by weekly update meetings before revising and refining the new plan. It's at this stage that an experienced team must hold firm, ensure the Sponsor it's not 'more wasted time' and build the rapport that will sustain the next stage. It is always better to get the planning right first time, rather than have to redo work as the project progresses. Time 'sacrificed' here will deliver vast savings later in the project and could literally be the difference between success and failure.

After the initial planning stage was complete, we actioned the data management team to transition the database and complete all data-related validation and documentation. Another area they had to look at was assisting the sponsor and clinical team with modifications to the clinical database, which had a very

dense casebook and multiple local labs. They also needed to audit sites to identify barriers to recruiting subjects in the ICF (informed consent form) and modify the document accordingly – again a process that will deliver an expedited recruitment once the initial work is complete. Meanwhile, the clinical monitoring team launched a multi-pronged enhancement plan that involved site visits by the medical monitor as well as recruiting tools and dear doctor letters – collectively this lead to an almost immediate impact on enrollment. The time used in the extra planning ultimately delivered a trial that finished ahead of even the sponsor's corporate stretch goal – by over a week.

So, what are the biggest takeaways you ask from these differing studies? It may sound *cliched* and an often-repeated mantra for at WuXi Clinical, but the strength of the relationship between CRO and sponsor is critical. It's the single biggest advice we can pass on to anyone – get the team core right and by that we mean sponsor, site and CRO. Trust is therefore the first priority, followed by the experience of the day-to-day team (make sure the people that wow you in the pitch are the same people you get the week after), and be prepared for a CRO that pushes back early (not one that finds excuses later). You might not always like what you hear, but it is often what you need. It's much better to have someone that will under promise and over-deliver. In a rescue, you want all your bad news as earlier as possible, and then from here, you can trust things will improve – and often rapidly.

REFERENCES

1. https://www.atlantclinical.com/rescue-studies

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