'Rescue' Is Not A Dirty Word

Embracing Early Intervention in Faltering Clinical Trials

Lindsey Rios, PMP
Wayne Bowden, MBA
Michelle Bousquet, PhD

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Introduction

Every year, tens of thousands of clinical trials are initiated. Every year, thousands of those trials falter, and, if corrective action isn't taken, some may fail to produce usable data. In an analysis conducted by the Biorasi research team, we discovered that a full third of trials slated to complete within the next year have already passed their predicted completion date[1]. Given the magnitude of the problem, there is not nearly enough light being shed on this pervasive issue by the industry.
In this first white paper in our series, we want to attempt to characterize the scope of the problem facing the drug development industry, and make a case for early, proactive intervention in faltering clinical trials.

The goal of this white paper series as a whole, then, is to take a deep dive into why clinical trials falter and what can be done to prevent those trials from becoming outright failures. We will discuss what "operational failure" in clinical trials means, how to recognize and react to underperforming trials, specific signs that indicate a trial may be underperforming, and the intervention options available to recover a faltering trial together with the associated operational impacts. In our final installment, we will share some case studies provided by sponsors who have been involved in faltering trials and will speak to what has worked from their own experience.

Over the next several installments, we hope to kick off open dialog about study rescue and remove most of the stigma surrounding the topic. We believe that this effort will help sponsors to recognize that trial underperformance is more common than anyone wants to admit, and that recognizing and reacting appropriately to a trial that might be in jeopardy is not an admission of personal failure. No clinical trial goes exactly as planned, and most will continue to run into obstacles during execution. But, if such a significant portion of trials are still clearly losing sight of their goals, there is a tangible need for effective and timely corrective action. If, together, we are able to foster transparency and collaboration around trial underperformance, we can go a long way towards developing effective solutions and reducing the number of trials that go off the rails, or worse, that fail outright.

Defining Operational Failure

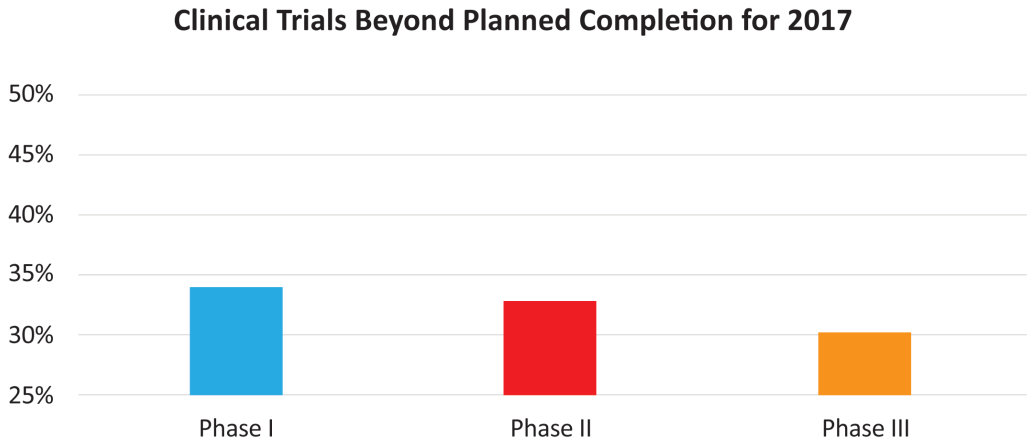
To begin, it is important to properly define what we mean by "operational failure" or "faltering" trials. Over 90% of Phase I drugs do not advance through clinical phases to gain regulatory approval[2]; however these more serious program failures are largely due to issues with the therapy or the program itself. These may include safety concerns, a failure to prove efficacy, or financial and managerial issues that result in abandonment of the program. When we talk about operational failure, however, we are pointedly setting program failures aside.

So then when we say "operational failure" or "faltering" trial, we are referring to a trial that is exceeding its acceptable threshold of time, cost, or quality. Either the trial is behind schedule, it's over budget, or the data being produced is of such low quality that it is unlikely to be used to support an approval. It's impossible to get a global picture of trial budgets or data quality, since most sponsors are rightly very private with such information. The three criteria (time, cost, quality), however, are largely interdependent, so it's not unreasonable to use one as a surrogate marker for the others. Using public domain data from ClinicalTrials.gov, we were able to construct an analysis of how many trials are behind schedule, and use that information to make an informed estimate of how many trials are actually at risk of failing.

[1] To measure the current timeline success rate for clinical trials scheduled to complete within the next year, we analyzed individual drug programs predicted to complete by December 2017 posted in ClinicalTrials.gov. Trials were filtered for those which are: A.) interventional; B.) funded by industry; C.) in Phases I, II, and III; and D.) in the 'recruiting' and 'active not recruiting' stages. Clinical trials which were past their completion date but have not received verification within the last 2 years were excluded to improve accuracy of the analysis. Using this dataset, we took the ratio of those which had passed their completion date at the time of export (January 2017) against all to complete by the year's end.

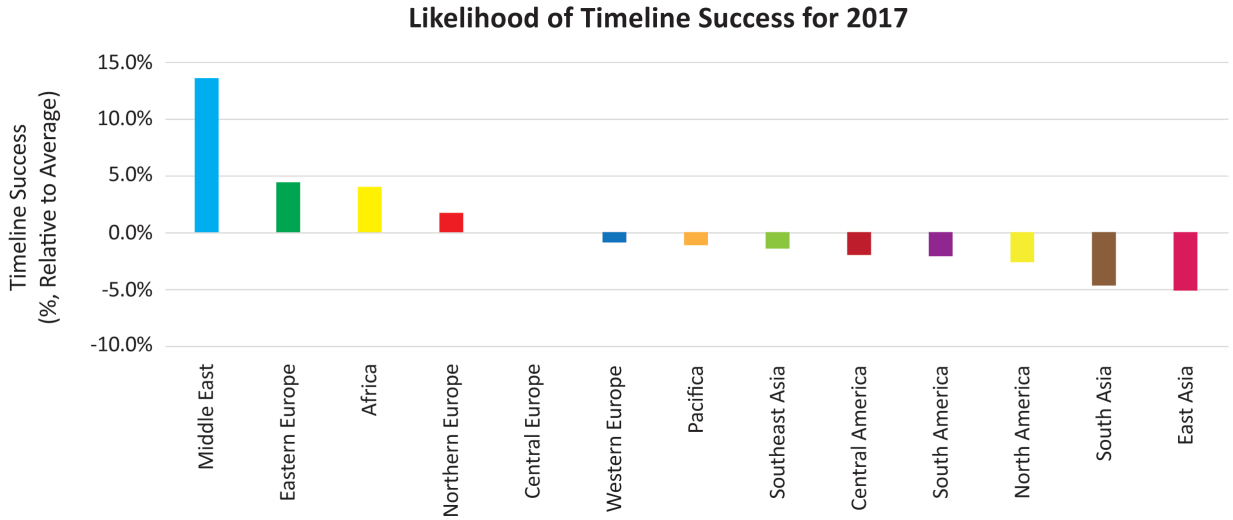
[2] Thomas, David W; Burns, Justin; Audette, John; Carrol, Adam; Dow-Hygelund, Corey; Hay, Michael. (2016). "Clinical Development Success Rates 2006-2015". Biomedtracker, Sagient Research Systems, Informa, San Diego, California, USA; Biotechnology Innovation Organization (BIO), Washington, District of Columbia, USA; Amplion, Bend, Oregon, USA.

Figure 1



When we look at faltering trials by clinical phase, we see that a lot of our suppositions about the difference between program and trial failure are validated. There is a small but gradual drop-off in the number of trials underway, consistent with what might be seen from failing programs being discontinued, from Phase I through Phase III (Fig. 1). The overall rate at which trials miss deadlines, however, is relatively steady across all three phases. This would tend to indicate that program failures, which should theoretically be caught in earlier trials, are not the primary reason for this third of trials that are behind schedule and at risk of failure. Instead, we can only conclude that operational issues are the cause of these trials' underperformance.

Figure 2



Our hypothesis that operational failures are the primary cause for faltering trials is further reinforced when comparing timeline adherence across venues. Since most clinical trials are international and run across some combination of regions, we would not expect to see drastic variations in timeline success between regions due to the therapies themselves. However, when we analyzed the projected timelines of studies in 38 countries spanning 13 regions[3], we found vast differences in the adherence of those studies to their planned completion dates (Fig. 2). Recognizing that program failures would minimize variances between regions, it seems fair to surmise that the trials are faltering for operational reasons in some venues over others.

[3] For a regional evaluation of timeline success, the same export procedure and filters were applied as previously described (1). This time, however, the analysis was focused on 38 countries spanning 13 regions which were selected for having the highest number of ongoing trials. For a relative likelihood of timeline success, we normalized the current timeline success rates per region to the averages of the included individual drug programs.

Moreover, the fact that geographically proximal regions (e.g. Central and South America) have similar timeline success rates strengthens the point that our metric is primarily measuring operational failures.

The bottom line is that while drug development programs fail for a myriad of issues, individual clinical trials falter largely due to operational errors and oversights. We believe that an operational failure rate of 33% is far too high for any industry, but for an industry driven by patient safety and well-being, it is intolerable.

What Is Operational Failure in Clinical Trials

Now that we've established that operational mistakes cause clinical trials to falter, and falter at an alarmingly high rate, we need to look into the kinds of operational mistakes that can result in missed deadlines. Largely, these can be broken down into three groups: planning, oversight, and response. Often, it is a combination of errors across all three categories that causes trials to stall, but each one is important in and of itself.

Planning

The success or failure of a clinical trial can often be predicted by the level and quality of planning undertaken before a trial begins. A modern, multi-venue clinical trial is an incredibly complex undertaking requiring intricate logistics, quality human resources, precise budget and timeline projections, and an overabundance of caution. A breakdown in any of these steps is enough to seriously delay and endanger a clinical trial, but our extensive experience with trial rescue informs us that it is often the last two that tend to go awry.

Projecting timelines and budgets is as much an art as it is a science. Poor planning and budgeting is one of the top reasons that trials fail to meet time or cost goals. This is largely self-evident and obvious: if your projected timeline is poorly thought out or doesn't take into account the unpredictability of running a trial, it will always fail to match up to actual timelines. Similarly, if your budget is contingent upon achieving best case scenarios, it will not be long before your trial is over budget.

Unfortunately, the reliance on CROs by most drug developers tends to put proper projections at odds with financial goals. For a CRO, the incentive is to present as rosy a picture as possible when bidding on a project. The financial motivation incentivizes timelines that seem unbelievably short, and budgets that seem unrealistically low. It is critical for sponsors to have internal teams that are skilled in modeling the course of a trial and creating realistic baselines against which to compare bids.

This is where an overabundance of caution becomes the critical factor. We know from experience that no trial ever goes completely according to plan. A good project plan will account for this, both in the initial timelines and budgets, but also with contingency planning and prebuilt response mechanisms. No plan is complete without an understanding of potential failure points and ways to prevent them or to mitigate their impact, along with more general risk mitigation plans in case the unexpected occurs. Risk management and mitigation should be addressed and planned for by the CRO, in collaboration with the sponsor, before the project begins.

Oversight

As obvious as it might seem to point out that trial progress needs to be carefully measured, it still needs to be touched on, because so many still fail to do it. The simple reason measurement is so important is that most operational failures can be recognized and prevented long before they occur. Slow enrollment can be spotted and corrected well before an enrollment deadline is missed. Budgets can be regularly analyzed against actual costs incurred and estimates to complete, and revised before a catastrophic overrun occurs. Data should be monitored continuously for quality, trends spotted and issues resolved early, and data formatted and cleaned long before database lock. The tools to enable continuous active measurement exist and are widely available, and it's only the inertia of habit that keeps these tools from being deployed and utilized more regularly.

The biggest takeaway for oversight is that it is not enough to check in at infrequent, pre-scheduled intervals. With advances in communication and data processing technology, trial administrators can get detailed information on the health of their trial on a minute by minute basis. This data can then be used to assess projected time, cost, and quality against the initial model. Moving from a scheduled, intermittent monitoring and reporting methodology to one with continuous monitoring can drastically reduce the risk of a trial failing, and allows for early intervention in the event of previously unforeseen problems.

Response

We have already touched on contingency planning and progress assessment earlier. How a trial manager responds to unfavorable events is perhaps the biggest indicator as to whether a trial will falter and then ultimately fail. Creating specific response plans for likely scenarios allows trial managers to successfully navigate around setbacks and pitfalls. Creating and training on response mechanisms for unplanned events allows your project to weather the unpredictability inherent in modern clinical trials. Not having contingency plans in place is the quickest way to turn minor issues into major trial killers.

Most importantly, creating a formal response plan gives trial managers the freedom and confidence to report problems in a clinical trial early. Early reporting is the key to being able to stage a successful intervention and a successful trial. Without an approved response plan, though, many trial managers are hesitant to report setbacks and problems until it's too late. In our conversations with sponsors and CROs alike, we have seen a steady thread of fear in project managers to report issues. Many see it as a threat to career advancement, or report an unwillingness to disappoint their supervisors. Still more feel like initiating a rescue or any type of intervention falls above their pay grade.

Planning and training can offset inertia and failure to escalate, and should result in a healthier workplace culture and lower likelihood that your clinical trial will fail to produce results. Viewing study intervention in a healthy new way will also empower your team to call for an intervention as soon as it's necessary rather than waiting and hoping. Earlier intervention has a lower cost and a much higher likelihood of returning the study to its original track, but even later intervention can still result in a successful study instead of a study repeat or even a cratered program.

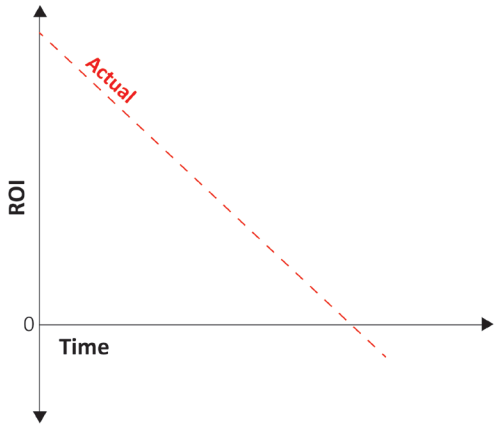
Introducing Return on Intervention

If it seems that there is a strong bias towards early intervention in our analysis, it is because we firmly believe that early intervention is a crucial factor in reducing the number of faltering and failing trials. Our model for this belief is a concept that we call "Return on Intervention", or ROI. All economic activity has a return on investment - the measure of whether an activity produces more value than it costs or not. A single clinical trial is certainly an economic activity for stakeholders, but often represents such a small percentage of an overall drug development program's cost that judging the impact of a single intervention on total return on investment is not meaningful and would not produce any actionable insights. Our version of ROI, the trial rescue "return on intervention", seeks to simplify this by measuring the value of a rescue attempt within the context of a single trial, and absent the larger implications of the program as a whole.

Trial rescue ROI is not a static figure. As shown in Fig. 3a, it begins in the positive and slopes downwards into the negative in a predictable and steady manner. Even at a very rudimentary level, this is intuitive and makes sense. Very early on in a trial, the cost of an intervention is minimal - something as simple and low-impact as an assessment or trial review. This kind of activity is also very valuable, as it can catch and correct potential issues before they manifest as hits to the cost, quality, or time of the trial. As the trial timeline progresses, though, the cost of a rescue or intervention becomes increasingly higher. Instead of a simple review, it might involve bringing in additional sites, modifying trial protocols, reworking supply chains, or replacing an existing sponsor/CRO partnership.

Meanwhile, the alternative cost of doing nothing becomes more attractive as the study approaches its ultimate end, however late that may be.

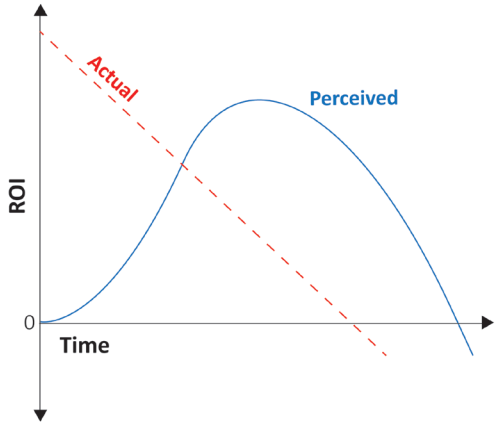
Figure 3a



Complicating the ROI model is the perceived need for an intervention or rescue by trial stakeholders (Fig. 3b). While the return on a rescue is highest at the beginning of a trial, the perception of a need for rescue is at its lowest point. Early on in a clinical trial, managers tend to shrug off the need for independent review and analysis. This is especially true if no problems have presented themselves thus far. Even when issues do come up, many study teams adopt a "wait and see" approach before bringing the issues up to their supervisors or calling in for outside help. As these small "wait and see" problems fail to go away on their own, and as small problems snowball into larger ones, managers finally begin to recognize a need to initiate a rescue, even as the return on intervention continues to diminish. At some point, the perceived need for rescue is checked by the pending completion of the study and/or the realization of one's inability to get any reasonable return on a rescue investment. Here, the perceived need for rescue plummets.

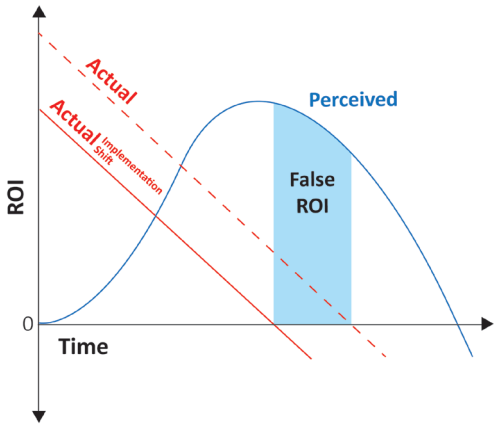
The final complication in a trial rescue return on intervention analysis is what we call the "implementation shift"(Fig. 3c). All but the most basic of interventions require a certain amount of lead time – time to finalize an intervention decision, assemble an intervention team, contract, and start intervention activities. From Biorasi's more than a decade of experience handling trial rescues, we've learned to expect that this lead time will be no less than four months. This implementation shift has the effect of shifting the ROI curve left along the trial timeline by at least four months, moving the actual rescue ROI and the perceived need for rescue lines even further out of sync.

Figure 3b



In Fig. 3c, we've highlighted an area of the graph we think of as the "False ROI" in blue. This area presents a particular danger to sponsors - it's an area where it seems like ROI is still positive, and it coincides with the peak in typical sponsor interest in a rescue intervention. However, when accounting for the implementation shift, the actual ROI in this area may well already be negative. The point at which it may no longer makes sense to attempt an intervention can occur somewhat before most researchers and project managers think it does, but it also means that earlier interventions can bring substantial gains to a trial. The takeaway is that however early into a trial stakeholders think is the best time to initiate a rescue, the the optimal point for an intervention is likely earlier.

Figure 3c



An Early Warning/Response Model

All of our research into the process of a trial failure and our experience in trial rescue has resulted in one conclusion: the optimal way to reduce the number of faltering trials is to introduce an industry standard early warning/intervention methodology. Predicting the success or failure of a trial ahead of time is difficult to say the least, but waiting for issues to build up until they overwhelm the trial team greatly diminishes the impact of any possible intervention. Moreover, not every trial needs a full, third party intervention to succeed, as we will discuss in a future white paper in this series. What every trial does need, however, is a mechanism to ensure early on that everything is proceeding according to plan and that there is no buildup of problems waiting to escalate into a full-on failure.

The best way to achieve this is through an independent review very early in the study. Three to four months into a study is a good point, but can change depending on the phase of the trial, the timeline involved, and the complexity of the indication, study design, and drug being tested. This review should be undertaken by a team that is not directly working on the trial. This could be an external team brought in from a third-party CRO or consulting firm, or could be a team within a sponsor's organization that is removed from the day to day of managing that specific trial. The main point is that the review team is not regularly involved with the trial and can look at all of the facts with fresh eyes.

Each clinical trial is unique, so it's impossible to create a shorthand or rule of thumb guide for whether and when a trial needs a rescue. Introducing an independent trial assessment early on can help answer the fundamental question every trial manager eventually asks: "Is a rescue right for me, and when do I start it?" When an assessment is performed routinely and combined with proactive realtime measurement, the perceived need for trial rescue can be brought back into line with the actual rescue ROI, and result in fewer operational failures, shorter trial completion timelines, a higher likelihood of approval, and significant cost savings. Most importantly, planning for routine early assessment can help us all to reinforce a desperately needed culture shift in the drug development world: "rescue" is not a dirty word. Once we move past the stigma of admitting that our trials need help, we can begin to make a serious dent in dropping the percent of faltering trials from an abysmal 33% to something closer to zero.

About the Authors

Lindsey Rios, PMP
Vice President, Project Operations

Lindsey Rios has been with Biorasi for nearly ten years, and understands complex projects better than anyone. Ms. Rios heads up a large, geographically dispersed team, and contributes heavily towards Biorasi's operational excellence.

Wayne Bowden, MBA
Director, Client Solutions

Wayne Bowden is an accomplished researcher and executive, combining the scientific knowledge to understand the most intricate details of clinical research, and the business experience to shepherd those trials to success.

Michelle S. Bousquet, PhD
Associate, Program Development

Dr. Bousquet joins Biorasi after a career as a pre-clinical investigator focusing on small molecules and gene editing techniques. As a member of the program development team, Dr. Bousquet utilizes her expertise in the design and execution of clinical programs.

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Biorasi Global Headquarters
Address: 19495 Biscayne Blvd. Suite 900
Miami, Florida 33180
Phone: 786.888.2129
Email: info@biorasi.com