

# Five Essentials for Minimizing Clinical Development Risk

WHITE PAPER

# Table of Contents

Introduction ..... 3

Risk is at an All-Time High ..... 3

**How to Employ Systematic Risk Mitigation** ..... 4

    1. Use Adaptive Designs When Appropriate ..... 4

    2. Track and Analyze Data Management Metrics to Ensure Accuracy ..... 5

    3. Provide Managers with Continuous Information to Make Decisions ..... 5

    4. Standardize Training and Processes at All Sites ..... 6

    5. Team Up with Trusted, Certified Partners ..... 6

Don't Learn Risk Mitigation the Hard Way ..... 7

## Introduction

“The pivotal trial failed,” said a senior pharma executive in private conversation. “I got the call on Friday. I was dumbstruck—given its success in earlier work I could hardly believe it.”

This type of shock is all too typical. Late-stage disappointments in clinical development programs are common, and many times come as a complete surprise to everyone involved.

That’s exactly what happened in 2007 when a biotech CEO received an unexpected FDA rejection letter in response to his company’s application to

market a new biologic treatment of brain metastases. The failed Phase III study had an estimated enrollment of 550 patients<sup>1</sup> with a 25-patient lead-in phase that established methods for evaluating efficacy based on novel radiologic (MRI), neurocognitive, and neurologic progression endpoints.<sup>2</sup>

The CEO attributed the rejection to improper management at a single site among the 92 that participated across eight countries.<sup>3</sup> In the CEO’s view, this led to flawed findings that “really skewed the results.”<sup>4</sup>

## Risk is at an All-Time High

Whether or not the biotech CEO was correct to focus solely on the results from a single site as the reason for his new cancer treatment being rejected, his story speaks to some undeniable realities about complex studies:

- A single site can negatively impact the results of an entire study.

- Variation in site performance increases with the number of cultures, languages and time zones involved in a study.
- Differences in administration of treatment and recorded response data increase with the number, complexity and novelty of procedures performed at each site.

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1 Randomized phase III trial of Xcytrin® (motexafin gadolinium) injection for the treatment of brain metastases in patients with non-small cell lung cancer undergoing whole brain radiation therapy. 2003. Available from: [ClinicalTrials.gov/show/NCT00054795](https://clinicaltrials.gov/show/NCT00054795)

2 Mehta MP et al. Lead-in phase to randomized trial of motexafin gadolinium and whole-brain radiation for patients with brain metastases: centralized assessment of magnetic resonance imaging, neurocognitive, and neurologic end points. *J Clin Oncol* 2002;20:3445-53.

3 Harris G. Where cancer progress is rare, one man says no. *The New York Times*. September 16, 2009.

4 Harris 2009.

## Five Essentials for Minimizing Clinical Development Risk

Add these risks to a growing list of what can go wrong: a competitor may get to market first or a new generic product in the category may slash revenue forecasts. With more multinational studies, larger

patient populations and an increasing number of procedures, the need for systematic risk mitigation is greater than ever.<sup>5,6</sup>

# How to Employ Systematic Risk Mitigation

The main goal of a risk reduction strategy is to eliminate the possibility of a program failing for any reason other than proven lack of efficacy or safety. If a drug works, there should be no reason for the clinical trial to fail. To accomplish this goal, drug and medical device developers must develop protocols and plan programs that cover these five essential functions:

**1.** Use adaptive designs when appropriate.

- 2.** Provide managers with continuous information to make decisions.
- 3.** Standardize training and processes at all sites.
- 4.** Use trusted, certified partners.
- 5.** Track and analyze data management metrics to ensure accuracy.

## 1. Use Adaptive Designs When Appropriate

Adaptive techniques that use selected parameters from patient data to inform planned changes in study design will also greatly improve efficiency and reduce risk. For example, the enormous study of the Zostavax vaccine for herpes zoster started out with a planning estimate that it would take 440 evaluable cases of herpes zoster to show a 60% reduction in a patient self-assessment of pain with 97% statistical power.

After observing the first 200 evaluable cases, the study determined that the variability of the treatment effect was greater than the estimate used for determining sample size. Getting statistically significant results would require 750 evaluable cases. The sample size was adjusted to 37,200 patients to ensure observing the required number of evaluable cases. Costs increased, but the drug developer collected the data needed to bring Zostavax to market.<sup>7,8</sup>

5 DiMasi J, Hansen R, Grabowski H. The price of innovation: new estimates of drug development costs. *J Health Econ.* 2003;22:151-85.

6 Tufts Center for the Study of Drug Development. Boston (MA): Citing Boston Consulting Group, 1993; Peck, *Food and Drug Law J*, 1997; PAREXEL, 2002

7 Oxman MN, Levin MJ, Johnson GR, A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *NEJM.* 2005;352:2271-84; also, supplementary appendix.

8 Department of Veterans Affairs (US). Trial of varicella zoster vaccine for the prevention of herpes zoster and its complications. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Dec 29. [Cited 2008 Aug 12]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00007501>

### 2. Track and Analyze Data Management Metrics to Ensure Accuracy

Continuous efforts to maintain the highest level of data accuracy from the outset of a study are vital to risk mitigation. Allowing data errors to remain undetected—even at a single lab or site—can compromise the overall study results, and at the very least will delay site closeout and database lock.

Data management metrics play an essential role in ensuring this level of accuracy. For example, a spike in query rates might indicate that test procedures are being administered inaccurately or study Case Report Forms (CRFs) are being improperly handled. An effective data management system will flag this trend and alert managers to investigate the root of the problem: perhaps the issue is personnel turnover

or a staffing problem at the site, leaving an untrained staff member to execute study functions. This could obviously have disastrous ramifications if left undetected over even a short amount of time, and must be addressed as early as possible.

Delays in data submission following patient visits, a build up of unresolved queries and high average time to resolve those queries all indicate performance problems that increase the risk of poor-quality data. Keeping a close eye on these metrics with systems that immediately flag and diffuse issues will keep this risk to a minimum and prevent latent problems from surfacing at the time of database lock or submission.

### 3. Provide Managers with Continuous Information to Make Decisions

Managers need relevant site metrics such as patient data for a quick analysis to make key decisions about the course of a study. When information is unavailable, or comes too late, it increases the risk that something can go wrong or a problem could go unnoticed. Mechanisms must be put in place to deliver the right information to the right eyes at the right time, from the field to the boardroom.

In the field, advanced EDC systems like the digital pen can transmit information between sites and data analysts in hours, conveying both patient data and

detailed metrics on the operational performance of each individual site. These performance metrics can be used to identify problem sites, to highlight areas needing immediate attention and to share best practices from sites that are meeting and exceeding study goals.

In the boardroom and across all levels of study management, the flow of actionable information depends on the availability of immediately accessible, dependable reports.

### 4. Standardize Training and Processes at All Sites

To avoid problem sites like the one identified by the biotech CEO mentioned earlier, implement consistent training and processes across your entire study. Use a web-based clinical management system to ensure that all sites have one, consistent platform

to use during the course of a study. This platform should facilitate the flow of information between sites, monitors and managers, so site performance can be tracked and information can be shared remotely.

### 5. Team Up with Trusted, Certified Partners

When outsourcing programs to sites around the world, it's extra important to choose research partners wisely. Confidence in a CRO's ability to perform must be rock-solid, even more so than for domestic studies.

The selection criteria used must capture the qualities most crucial to the trial's success. For example, instead of asking a potential research partner to estimate the cost of x number of monitoring visits for the sake of an easy price comparison, consider asking whether x visits are necessary for the trial. The CRO may have the capability to more efficiently handle much of that labor continuously, and remotely, for a lower overall cost. To help make sure that procurement activities aren't based on counterproductive qualifiers, it's important to consult with a trusted group of research veterans who will ask the right questions.

Hire a CRO that has access to high quality sites and, if your trial's footprint is global, make sure your study

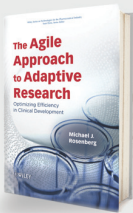
team has more than just feet on the ground in the countries where you need them. Large multinational CROs with an abundance of regional offices might seem like a turnkey solution, but you may also want to consider turning to a global network of certified CROs.

Assuming that all network members have been meticulously trained and vetted to adhere consistently to the highest standards of research accuracy and efficiency, a network can have several advantages over a single CRO. They often have closer, more home-grown cultural relationships with the sites and patient populations who will be participating in your study, making enrollment and retention goals much easier to achieve. A network can also offer the advantage of individually empowered CROs who can proactively manage your study based on fluctuations in data and metric trends—safely within the realm of network, scientific and regulatory compliance. The regional branches of large multinational CROs are often too insulated with extra layers of corporate infrastructure to reliably practice this kind of flexibility.

# Don't Learn Risk Mitigation the Hard Way

As many sponsors have learned, one undetected issue can be the difference between a new drug or medical device getting to market and an FDA rejection letter. Risk comes with the territory in any

type of research, but by carefully planning a trial and incorporating mechanisms to minimize risk, sponsors can be confident that the trial has the highest chance of success.



## Additional Resources

Health Decisions' CEO Dr. Michael Rosenberg's book:

[The Agile Approach to Clinical Development: Optimizing Research Efficiency, by Wiley.](#)

Buy now on Amazon

## About Health Decisions

Health Decisions is the leading contract research organization (CRO) in Adaptive Clinical Trials committed to shortening development timelines and maximizing pipeline value for pharmaceutical, biotech and medical device companies. Through Agile Clinical Development — a strategic three-pronged approach that combines adaptive design, adaptive operations and proprietary technology — Health Decisions delivers real-time performance metrics that enable sponsors to make the most of competitive market opportunities. Health Decisions is headquartered in Durham, NC, with over twenty years of experience helping sponsors exceed development goals in Phase I-IV clinical trials across all major therapeutic areas.

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