Princeton PHARMATECH

One Bad CRO Stat Can Sink Your FDA Approval

When it comes to choosing a biostatistical contract research organization (CRO) for your medical development needs, all too often price is the biggest final determiner.

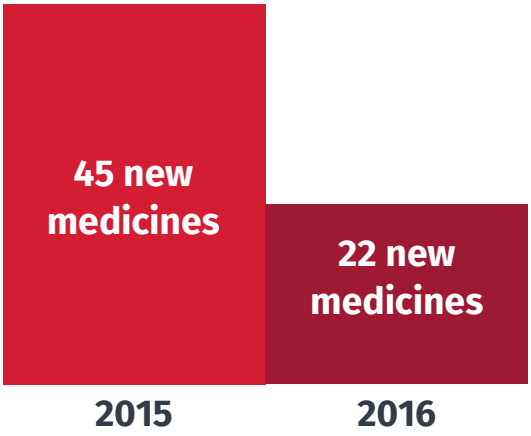
However, a proven record of accuracy, not the lowest price, should be a bigger factor in choosing the right CRO. Small inaccuracies from your CRO can mean big headaches for your organization throughout the FDA approvals process. This is particularly true with regard to data analysis, where even the slightest mistakes can mean the difference between drug approval and rejection or penalties in the form of FDA fines.

Forget outright rejection for the moment, however. Even a minor delay can be severely costly for your organization. It's estimated that the cost of delayed release is $1 million for *each day* your research and development is delayed. There's no CRO inexpensive enough that is worth that kind of cost. In a worst-case scenario, small inaccuracies can mean costs to the tune of tens of millions, jeopardizing the very existence of your business.

Accuracy is especially important in today's environment. In 2016, a scant 22 new medicines were approved by the FDA. That's the lowest number since 2010, and a steep decrease from the previous year, where 45 drugs were approved.

"New drug approvals fall to six-year low in 2016"

- Ben Hirschler, Reuters.com January 2, 2017.



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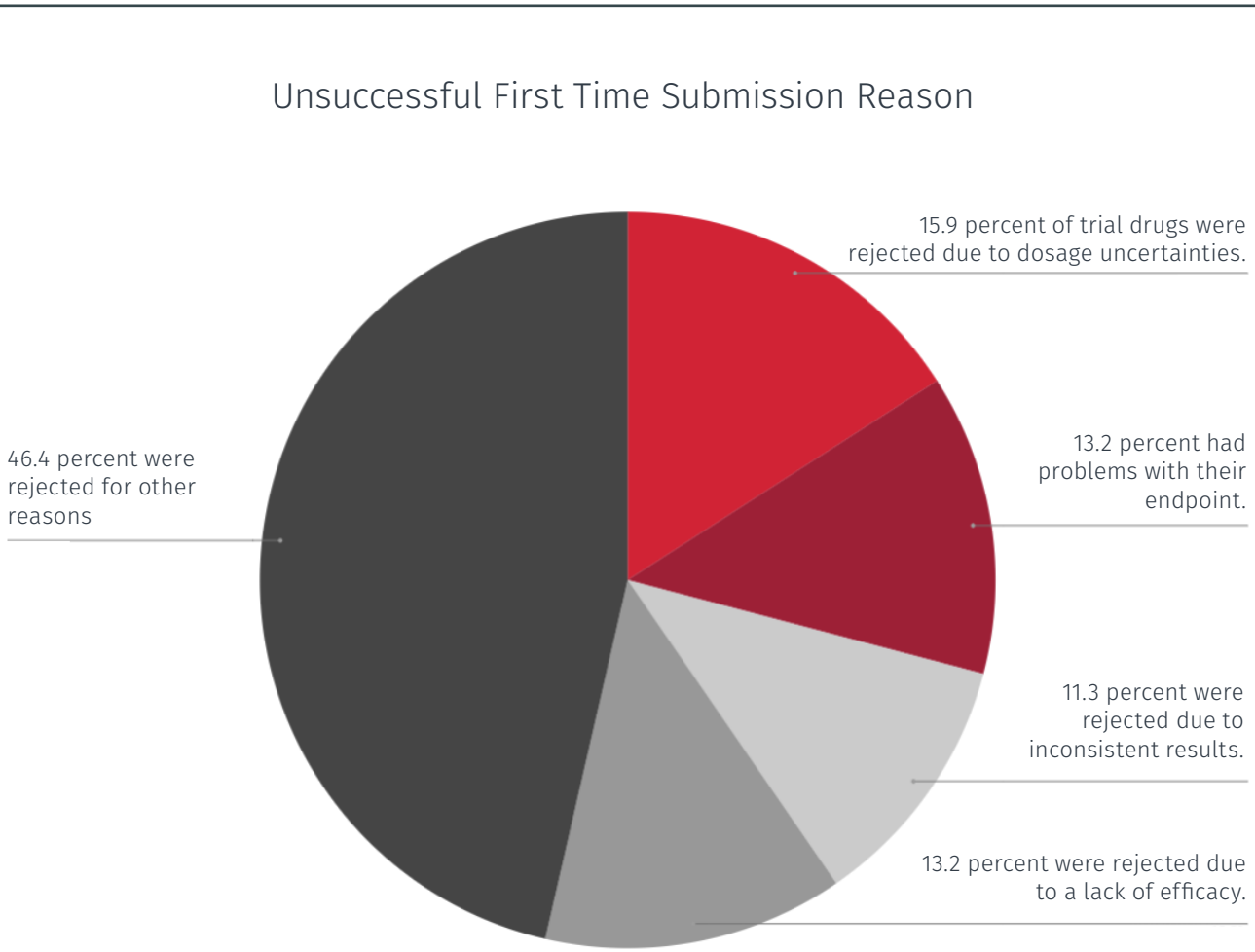
Common Reasons For Rejection

A JAMA study of the years 2000-2012 sheds light on just how crucial it is to work with an accurate CRO, not just an inexpensive one:

- 15.9 percent of trial drugs were rejected due to dosage uncertainties.
- 13.2 percent had problems with their endpoint.
- 11.3 percent were rejected due to inconsistent results.
- 13.2 percent were rejected due to a lack of efficacy.

In short, a significant percentage of drugs was rejected not because they didn't work, but because the research wasn't done properly. Data analysis is a crucial area in drug development, something that shouldn't be rushed over or purchased on the cheap.



"Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs 2000-2012,"

- Leonard Sacks, Hala Shamsuddin, Yuliya Yasinskaya, JAMA Network January 22/29, 2014.

Once Made, Mistakes Are Difficult To Reverse

A single line of code can make all the difference between usable results and GIGO -- “garbage in, garbage out.”

Big problems arise when the mistake isn’t in a small line of code, but in the data itself. Minor mistakes in the very DNA of your study can be much more difficult to correct further down the line.

For example, even small p-value calculation errors create GIGO results. If your p-value is less than 0.05, it works. If it’s greater than 0.05, it doesn’t. Not only does your p-value need to be accurate so you know whether or not your drug works, the FDA needs to be able to check your work.

It could get even worse than that. If a CRO picks the wrong endpoint or has other, non-reversible errors, none of the data will be usable. You will have to start again from scratch. In other cases, poor data *might* be usable, but could result in a major or critical finding during an FDA audit at considerable expense. The best quality data, provided by a high-quality CRO specializing in data analysis, isn’t just usable, it’s reusable. This is one of the best areas where your choice of CRO begins providing value over time, not just related to this specific project.

It All Starts With The Estimate

Here's a common tale resulting from choosing a CRO on price alone: There are additional costs the CRO didn't budget for. These additional costs come at a time when you can least afford them. At this point, you have little choice but to pay. You choose not to work with the CRO again, but what good does that do you now?

Certainly, you must work within the budget that you have. But that doesn't mean the lowest price quoted to you will always be the "best" -- or even be the price you end up paying.

When choosing a CRO, you must first ensure the accuracy of the estimate itself. When reviewing proposals, remember these tips:

- **Apples to Apples:** Make sure when comparing proposals that you're comparing apples to apples. Ensure comparability of line items to again, make sure apples to apples are being compared. We'll talk more about this later, but you want to dig as deep as possible into the education, capabilities and knowledge of the CRO team. These are the key differences between a quality vendor and one who is merely cheap. It also begins to provide some sense of the quality of the work.
- **Rethink Your Bid Grid:** While bid grids allow apples-to-apples evaluation of costs, they're not without their drawbacks. Bid grids can be vague and not specific enough. The more detailed the bid grid, the more accurate your estimate will be. You will also get a better sense of value provided versus overall cost.
- **Contract Cost:** Consider the cost of how detailed your instructions and guidelines have to be. Higher quality CROs require less instruction to provide quality results. The more instruction you have to provide, the more man hours you're burning. In a best-case scenario, a more experienced and skilled biostatistical CRO can provide you with suggestions rather than burning hours trying to understand your problem.
- **Look at Value, Not Cost:** CROs often charge much higher rates for additional work found outside the original scope. Avoid this by being very clear about your needs up front. Score the value provided by each CRO, then look at each of those scores in terms of what the CRO estimates their total costs to be. This provides you with a far better cost metric than simply looking at what the final bill will be.

Indeed, accuracy is one of the best places to find value. An internal review can easily cost as much as the contract itself if your research and data analysis isn't accurate. Then there's the specter of an FDA review process, whose costs are almost unqualifiable and certainly highly unpredictable. This review process could easily cost several times as much as the contract. Compare this with a best-case scenario, where a quality vendor can add to your research and provide useful feedback rather than just crunching numbers.

Consider how accurate an organization who cannot provide an accurate estimate will be. An inaccurate estimate won't be the last time you suffer from inaccuracies. But as expensive as additional costs might be, they could pale in comparison to further inaccuracies down the line. A CRO that can't provide you with an accurate estimate might not have a solid handle on the industry as a whole, almost ensuring further inaccuracies later down the line.

How Do Inaccuracies Happen?

It's so easy for inaccuracies to enter your research that it's a minor miracle when you *don't* have them. The common denominator for you is high cost delays in your product development cycle. Common reasons for inaccuracies include:

- The trials aren't designed properly or are designed with incorrect endpoints in mind.
- High turnover creates chaos in the data collection process.
- Regulatory requirements or regulatory feedback are not properly understood.
- Trial data is inconsistent and does not detect data that is either incorrect or fraudulent.

Once inaccuracies creep in, everything that comes afterward is going to be sub-optimal at best. Accuracy isn't an event, it's a process and it's one that runs throughout the whole of your clinical trials. The good news is that choosing a CRO specializing in data analysis can help your organization to find where you got off track. From there, you can have a strong sense of what is salvagable, what isn't and where you can begin again.

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What Happens When You Have Inaccuracies?

The cost of delaying your drug release is one concern and perhaps the biggest. However, it's not the only one. Other snags enter the picture, each with their own cost in terms of time, money and other resources.

- **Verification Issues:** The FDA won't just take your word for it. They will verify your biostatistical data using their own methods. The FDA will find inaccurate information in your reports even if you didn't. That's not just costly, it's embarrassing.

- **FDA Audit:** A major or critical finding from an FDA audit is a pharmaceutical company's nightmare. It means additional resources shelled out and the potential for severe fines and penalties. The only thing that could make an audit worse is knowing that you didn't cause any problems, but rather your CRO failed to do its job.

- **Shareholder Dissatisfaction:** Inaccurate data and the delays flowing from that can create serious dissatisfaction among your shareholders and other investors. A rejection of Celgene's multiple sclerosis drug due to insufficient evidence caused company stock to tumble 8 percent. Acorda Therapeutics shares dropped 26 percent after rejection of a Parkinson's treatment. There are also incalculable costs in terms of reputation.

Need help preparing an RFP? Schedule a one-on-one with a Princeton expert.

- **Rescue Studies:** Poor data can render a study completely unusable. In this case, you will need to run a rescue study which will either leverage what good data exists or effectively start over again from scratch.

At best, there's going to be a lot of backtracking. At worst, the financial costs could be too much for your organization to bear. A CRO specializing in data analysis can act as a shield against further inaccuracies creeping into your research documents. They can also help you to find areas where you can salvage existing research and where you need to start from scratch.

How To Effectively Plan Your Clinical Trials

Accurate studies begin with effective planning. Increase the chances getting the most accurate study from the most qualified CRO:

- **See Quality Data as an Investment:** Clinical data is your organization's most valuable asset. View quality data as an investment, not an expense. Budget accordingly, both at the trial stage and at the stage of data analysis.
- **Involve Biostatisticians Early On:** Hire a biostatistician from the very beginning of clinical trials. This ensures proper study design, including analysis procedures and hypothesis testing. A qualified biostatistician can also regularly report regulatory feedback.
- **Centralize Your Data:** Every new vendor handling data increases the risk of inaccuracies. On the other hand, data centralization means quicker turnaround times, shorter learning curves and greatly increased quality.

Effectively planning guides you toward the right CRO by putting your priorities in the right order, giving you a better sense of what the right CRO is beyond simply the one with the lowest estimate.

The Importance Of Data Analysis

Data inaccuracies aren't just difficult to fix. In many cases, they can be difficult to detect until you're actually submitting your new treatment to the FDA. That's not just going to cost you a lot of money. It's also going to leave egg on your face in terms of shareholders and other members of your community. Fortunately, with good data analysis, you can find problems in your testing early. What's more, a CRO specializing in data analysis can help you figure out what went wrong, what you can still use and what needs to be done over again.

Proper data analysis further means increased value for your research. This is because when you have proper, verified data that is then analyzed by experts specializing in data analysis, the data can't just be used, it can be reused.

View data analysis as a necessary layer of product development. A properly qualified CRO specializing in data analysis is a form of oversight for both your own research and that performed by other CROs. They allow you to more transparently form your expectations as well as hold any partners you work with accountable.

Questions to Ask Before Selecting a CRO

Prior to final selection, ask these questions of your potential CROs.

- **Who will be doing the work?** Ensure you have a team of people with deep experience working on your new product. Ensure the CRO's team has expertise directly related to your product, including data analysis. Inaccuracies easily creep in when people with the wrong experience are put on your new drug or treatment.
- **How long has your team been in place?** More stability means greater accuracy. What's the turnover rate? How long has the longest employee working on your project been there? What about the newest? What's the average tenure for the team?
- **What relationships do you have with past clients?** Many times, intangibles decide whether or not medical development firms continue to work with CROs, such as how well each of the two teams gel. Metrics won't tell you a lot about how agreeable a team is, but the number of repeat clients will.
- **What are your policies and procedures?** Drill down into an organization's structure to understand internal processes. Ask about accreditations to understand strengths and expertise better. Inspect equipment and facilities ensuring they're up to industry standards as well as your own. Does the team have data analysis specialists or is everyone wearing a lot of hats?
- **What are personnel management procedures like?** Look at overall staffing levels. Are there enough people on the team to give your project the attention it deserves? Beyond the resumes of team participants, what are their job descriptions? How many people are working on data analysis? Look at training records, ensuring familiarity with most recent best practices. While you're on site, watch people doing their jobs.

- **What are the facilities like?** Facilities themselves that are important as well. Ensure quality and compliance on a site visit. Access maintenance records for insight into overall commitment to accuracy and quality. For data analysis, it's important to know if the company sees computing equipment and software applications as an investment or an afterthought.
- **How transparent in the process?** While research is being conducted or data being analyzed, you can look at what's happening in real time. How will you know what is happening and when? Do you have the ability to look into the process? If so, how much?
- **What security procedures are in place?** In the 21st Century, security is one of the most important considerations for any medical organization. This must be as important to your CRO as it is to you, especially when they're trafficking in highly sensitive data related to data analysis. Security isn't just about digital records and IT procedures. It's also about the physical facilities.
- **What happens when there's a crisis?** Every CRO must have a crisis management plan in place for the unfortunate event that something -- anything -- goes wrong. What's theirs? And how do they plan to communicate any issues to you if and when they arise?
- **How do you design your studies?** You definitely want to know how the sausage gets made. Look at the design and how they obtain and analyze their data. Focus on the process rather than just the end result. This is particularly crucial when working through the data analysis stage.
- **What is your turnaround time?** Not every CRO will wait until all the data is in to begin providing results. Many begin providing data after several subjects completed the trials, allowing you access to data in earlier stages of the clinical trials process. As long as the information is accurate, that's great for your organization. While you're at it, ask how they conduct interim analysis.

- **How do you arrive at endpoints?** As we have discussed elsewhere, endpoints are hugely important when it comes to biostatistical research. You'll want to ask not just about what the endpoint is, but how CROs arrive at endpoints to ensure accuracy.
- **What kind of clinical trials are you familiar with?** Different CROs have different areas of expertise. This is true both of the field of medicine they work in and the clinical trials they run. What's more, different types of clinical trials require different forms of data analysis. Is the CRO you choose to work with familiar with the clinical trial you're working on?

Ask these questions continually, auditing your relationship with a CRO every two to three years.

Need help analyzing data? Schedule a one-on-one with a Princeton expert.

What Your RFP Should Include

Craft your RFP to find the least expensive organization at great peril. Information you should include in your RFPs includes:

- **Background Information:** CROs write better proposals when they have a better sense of organizational history is. Who are you? What do you do? Where do you plan to go? Likewise, provide valuable context about your new drug.
- **Specifications and Timelines:** Important details provide needed context. This helps potential CRO partners to craft the most accurate estimate possible. This is likewise true of when you expect certain benchmarks to be hit.

Your RFP should likewise request information about the following:

- **Employee Profiles:** Who will be working on your project? What experience do they have? Have they been published in relevant journals? What projects have they worked on similar to yours? How many people are working on data analysis?
- **Company History:** How large is the company? What is their experience working in your field on new treatments such as yours? What size organizations do they typically work with? Do they know how to craft a solid regulatory submission statement? Is data analysis an area of expertise?
- **Client References:** If you are working on a new treatment for liver cancer, the best possible reference is one for a study conducted on liver cancer. The next best is one on cancer in general. Just because a company can conduct a study about glaucoma doesn't mean they can conduct one about cancer. This is especially true of conducting data analysis.
- **Clear Rates:** When working with the best, most accurate CROs, contingencies occur requiring changes in the scope of work. You can plan for contingencies better with a clear statement of rates, even if you can't predict the future.

Your RFP is the primary tool you use to select your CRO. Spend time on it, but also make sure that it's set up to provide you with the information you need -- all of it.

Ways You Can Improve Your RFP Process

If you want to select for a CRO that can provide the most accurate results and quality data analysis, you need to look for ways to begin improving your RFPs. Some quick and easy wins in terms of how your organization can better craft an RFP to select the right CRO, not simply the cheapest, include:

- **Better Preparation:** Avoid working with a CRO designing a program fitting their wants rather than your needs. Often times, that means a bare-bones proposal with a low price and lots of hidden costs later on. A well-formed clinical plan helps partners to craft an accurate proposal tailored to your needs. You don't have to finalize every last detail, but the more preparation you can do, the happier you will be with the results.
- **Include All Details You Have:** Too much information is better than having not enough. You can't provide what you don't have and that's fine. In other cases, you might defer to the expertise of the CRO. At a minimum, include the number and location of clinical sites, how many patients will be studied, enrollment dates, the duration of all follow-ups, proposed or required case report forms (CRFs), assessment schedules and monitoring frequency. Don't be afraid to ask potential CROs what information they might find useful.
- **Trust, But Verify:** Always verify information the CRO provides you. Ask for at least three references from companies with drugs very similar to yours. Three years of financial statements can help you evaluate whether or not a CRO will even exist long enough to complete your clinical trials. Staff turnover can be disruptive to your project and should be examined closely. Don't ever work with a CRO without a site visit, ensuring compatibility between your organization and theirs. As stated above, a CRO specializing in data analysis is an excellent, cost-effective way to ensure the integrity of your entire study.

Close attention to this process can help you to be more satisfied with your CRO partners.

The Importance Of Patients

To yield optimum results, your research process needs to be well designed and properly executed. That all begins with patients used in the clinical trials, however it doesn't end there. The work needs to be checked. A quality CRO specializing in data analysis can provide you with key indicators to monitor. This, in turn, provides another layer of added value. A good data analysis CRO looks at the whole picture, including what other partners have done. It's not enough that one part of the process is correct -- the entire process must be correct. No matter what stage of research you're at, here are some guidelines for your organization or its partners to determine if patient quality in a study is fudging your results.

- **Know What You're Testing:** You're testing a new drug, but what are you testing for? Are there specific effects you're looking for? Specific side effects? Objectives must be clearly defined for your CRO to get the most accurate and usable data.

- **Ensure Homogeneity:** In addition to clearly defined objectives, you need a clearly defined sense of what types of patients your CRO should be looking for. It is not uncommon for patients with the same diagnosis to have heterogenous symptoms. For best results all patients should have no only the same symptoms, but to roughly the same degree. Anything else ensures heterogeneity, which means less accurate results.

- **Control for Demographics:** Social homogeneity helps ensure more accurate results. Where this is not possible, CROs must control for demographic, physiological and social features in the patient pool. For example, height, weight, age and gender will all impact the study, especially in terms of dosage. Patients with a language barrier might not properly understand instructions. These factors must be considered by your CRO when putting together a patient pool.

- **Comorbidity Matters:** Where possible, all patients should not only have similar symptoms, but a similar lack of other symptoms as comorbidity can impact results.

The patient pool is absolutely crucial when it comes to getting accurate data. Make sure your CRO partners are on the same page as you in terms of getting the right patients for the study. In cases where there are problems with your patient pool, a qualified CRO specializing in data analysis can help you to find where everything went wrong and what you can still salvage.

The Right Way To Choose A CRO

Remember how much accuracy matters from the very beginning. A low bid doesn't necessarily lean a low cost. Indeed, a higher cost CRO can provide greater value, for example in the form of data centralization or reusability of quality data. From overages in billing to the costs of delaying to the specter of an FDA audit, you simply can't afford to make price the main determiner when it comes to choosing your biostatistical CRO.

This is especially true when you have a significant data analysis lift. Schedule a one-on-one briefing today with a Princeton Biostatistics expert about how to prepare an RFP that will enable your organization to produce accurate results within your timeline.

Get your one-on-one briefing with a Princeton Biostatistics expert today.

How One Bad Data Point Can Cost Your Company Millions

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