EBOOK

FIRMA
CLINICAL RESEARCH

SIGNS A CLINICAL TRIAL CRISIS IS LOOMING

Reduce delays and the need for rescues before these issues endanger a study.

Clinical trials have grown in size and complexity in the last couple of decades. Complicated study designs, more data points, outsourced responsibilities, layers of accountabilities and interdependencies all working in concert create management challenges that can often lead to delays. When the average clinical trial takes six to seven years,[1] delays seem almost inevitable.

The process of drug development early on is one of exploration, experimentation and optimization, and study teams expect to respond to new information as it is uncovered. It is nearly impossible to account for new findings in advance, so some delays are unavoidable. But when 86% of clinical trials experience significant delays, and 72% of studies run a month or more behind schedule,[2] what seems like an inevitability at first can quickly turn into a crisis.

From a financial perspective, delays can cost between $600,000 and $8 million per day and potentially result in losing lucrative first-to-market advantage. More alarming is the impact a delayed drug approval process can have on an at-risk patient population. From an ethical perspective, delaying the availability of a treatment can cause irreversible damage—even death. How many patients will bear the burden of seemingly insignificant delays?

Avoiding, if not eliminating, delays that are within our control should be paramount. Countless organizations target improving recruitment and retention, for example. But where else can we improve the clinical trial process to reduce delays and the need for rescues? What are some signs a clinical trial crisis might be looming, and how can we head off delays before they endanger a study?

In addition to patient recruitment and retention challenges, there are four signs a clinical trial might be heading toward a crisis:

1. Protracted database build and lock
2. Unexpected Health Authority requests
3. Contradictory regulatory requirements
4. Study design doesn't support necessary data collection

1. "Biopharmaceutical Research & Development: The Process Behind New Medicines." PhRMA, 2015.
2. CenterWatch. "Report: Sponsors Must Consider Patient Motivation, Partner with CROs for Successful Trial Recruiting." CenterWatch RSS, CenterWatch, 29 Oct. 2019, www.centerwatch.com/articles/23421.

SIGN #1:

PROTRACTED DATABASE BUILD & LOCK

Database build and database lock are two of the most critical steps in the setup and closing stages of clinical trials. They bookend the clinical trial process and can derail a timeline if they're not completed as efficiently as possible. Time to database build at the beginning and database lock at the end, however, have both been getting longer and longer, averaging 73 days and 39 days respectively in 2019–nearly a week longer than just 15 years ago.[3]

Databases that are not built and released in an EDC system before first patient first visit (FPFV) result in downstream delays in patient data entry and database cleaning.

After the last patient has completed the last visit (LPLV), the database lock is expected to occur soon thereafter so the key study results can be revealed shortly. If your biometrics team is waiting until LPLV to start working on the data or has the analysis programs ready but not validated, the process to validate all the programs and clean the data will likely take much longer than was estimated for database lock.

Quarterly database cleaning has been proposed as a possible solution to these challenges but often puts undue pressure on the clinical team, site staff, home trial nurses, and even principal investigators. If the data management team suspects an error and issues a query, the clinical team needs time to review the data, find the root cause and either confirm the data point is correct the way it has been collected or change it appropriately.

Instead, biometrics teams should take full advantage of the time between the moment when the last patient is recruited and when the treatment for the last patient is completed. The length of that fixed period is obviously dependent on the particulars of each clinical trial and could be anything from several weeks to two years, but the horizon is always a known value.

While patient visits and data collection are taking place, the biometrics team can ensure:

- The analysis programs are ready and validated
- A dry run, more if needed, has been performed
- Contents of the analysis outputs have been discussed with the clinical team and agreed upon
- Data is reviewed and continually cleaned as it comes in

Then, at LPLV, the data management team just has just one final step. to complete before database lock: clean the data points from the last several patients for their last visits. Once database lock takes place, the biometrics team should be able to generate and verify final results and deliver everything to the clinical team in less than two weeks. Generating analysis outputs should take little more than a push of a button because all the preparation work has already been completed.

3. "Data Management in the Face of Growing Trial Complexity." Contract Pharma, www.contractpharma.com/contents/view_experts-opinion/2019-04-22/data-management-in-the-face-of-growing-trial-complexity/

SIGN #2:

UNEXPECTED HEALTH AUTHORITY REQUESTS

A well-designed clinical trial aims to answer very specific clinical research questions. Sometimes a health authority, such as the FDA, will issue certain requests to sponsors to alter the design or conduct of clinical trials to better answer those questions.

Broadly, it is a good sign since such changes are meant to improve the integrity of the clinical trials and enhance the probability of product approval. However, such a request may lead to significant changes to the study design. If a study has been running for a while, the required changes might not even be feasible.

> *The FDA isn't just a regulatory body. The agency can and should be an advisor for the development of your clinical trial protocols.*

Getting unexpected FDA requests during study conduct is a red flag your clinical trial may be heading for trouble. A protocol may appear to meet the needs of the study, but without sufficient input from the FDA before the trial is up and running, there could be problems later on. Should the FDA identify that a key component is missing or inappropriate from a protocol, you might need to plan another trial.

While rescues are sometimes possible by adding more components to an ongoing clinical trial, this approach brings its own set of difficulties and can lead to consistency issues in the data. For example, changing inclusion/exclusion criteria in the middle of a study will give you a different patient population before and after the change. Sometimes this is acceptable and sometimes it is not.

The FDA isn't just a regulatory body. The agency can and should be an advisor for the development of your clinical trial protocols. Utilizing the agency properly and fully from the beginning can save time and effort later on. Take advantage of the special protocol assessments, technical input, and other initiatives available to improve and speed clinical trials. Make sure the agency has had a chance to express views and the clinical team has had a chance to understand and address any questions before a protocol is underway.

SIGN #3:

CONTRADICTORY REGULATORY REQUIREMENTS

The FDA isn't the only regulatory body that should be considered during the design stage. Clinical trials run in the US but targeting global submissions to the EU or Japan could end up with contradictory requirements from the various health authorities that regulate the target countries.

Different health authorities can have different requirements for everything from primary endpoint selection and inclusion/exclusion criteria to primary statistical analysis method and acceptable approaches for handling missing data. If a study is already underway or the protocol has run and some of the data has been collected, it may be too late to make the changes necessary to meet the requirements of the global regulatory bodies despite agreement from the FDA.

CASE STUDY

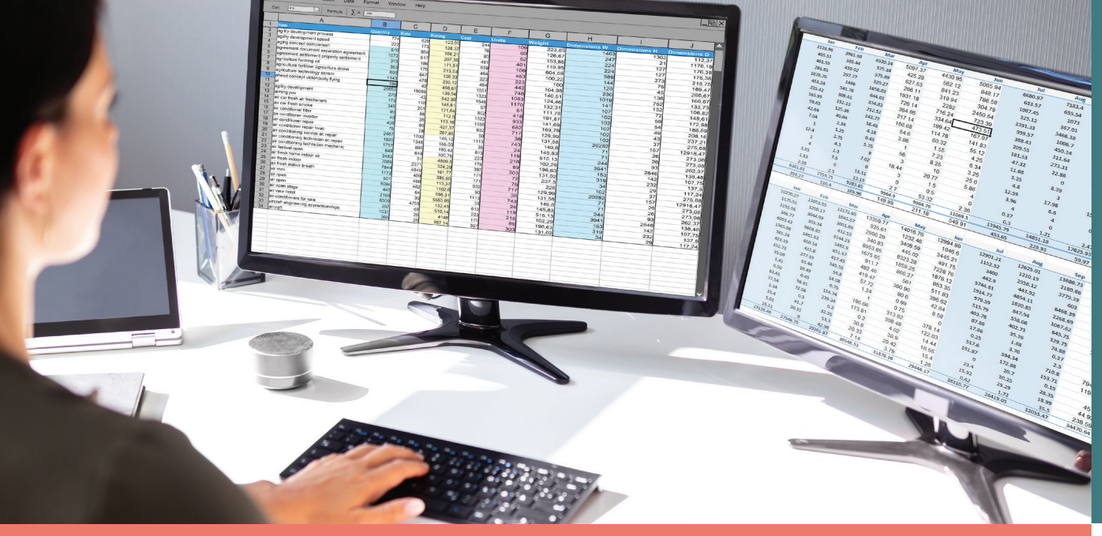
A pharmaceutical company conducted a Phase III clinical trial in an indication in neuroscience to investigate a new treatment for patients. In addition to seeking market authorization in the US, Canada and European Union countries, they also targeted Japan.

Study Stats:

- 20 countries in North America and Europe
- 800 patients
- 20 Japanese patients living in the US

The trial was successful and demonstrated the treatment was efficacious and safe, and the application was approved by the US FDA and CHMP in Europe. However, when it was reviewed by the PMDA in Japan, there was a concern about too few Japanese patients. To address this issue, the company had to complete an additional clinical trial in Japan. The product was finally approved after the additional trial also showed positive results, but at what cost?

Consulting with the PMDA earlier would have allowed the team to enroll more Japanese patients in the first trial, saving time, effort and money, as well as making the treatment available sooner to struggling patients.



Companies conducting multinational clinical trials to save costs or meet protocol enrollment goals quickly should also watch out for contradictory endpoint requirements. Gaining regulatory approval to initiate a clinical trial does not mean the study design will meet requirements should you choose, after the fact, to submit the final products for approval globally.

Additionally, changing target market strategies mid-trial can have disastrous effects on data integrity and timelines. Once a study has started running, there is very little room for making major changes, and running another trial to meet the requirements of the EMA or PMDA, for example, would most certainly delay the approval. It is not unusual for an application to be approved in one country and not another.

Shifting analysis strategies might be possible, but if the data has not been collected with the desired endpoint in mind, even the very best analysis cannot cover missing information. In short, a deficient study design cannot be rescued by a revised analysis method.

SIGN #4:

STUDY DESIGN DOESN'T SUPPORT NECESSARY DATA

Finally, there are few things more disappointing than when the data collected from a clinical trial won't support the study objectives, especially at such a late stage in the development process, and it usually comes down to one of three reasons:

1. Drug or device didn't work as expected
2. Didn't choose the right endpoint
3. Didn't choose the right analysis method to effectively detect the product's effect

Number one is clearly something that cannot be avoided. Two and three, however, can. If a study design is insufficient to support the data necessary to make conclusions about the study, the entire trial has essentially been wasted.

Ideally, a clinical team would see this clear sign of a looming crisis early on, but this is rarely the case. In a study on the impact of global protocol amendments, researchers found more than half of all protocols–57% to be exact–had at least one significant amendment,[4] many of which were deemed "avoidable."

THE IMPACT OF ENDPOINTS

In general, multiple endpoints exist to measure the treatment effect—for example, clinical endpoints, measurements from medical images, or biomarkers.

Among those endpoints, some directly reflect the patient's disease status, and others may be closely linked to possible causes of the disease. However, it is rare that all endpoints would be weighted equally. Some are more sensitive to the treatment effect of the drug or treatment under investigation.

Determining an appropriate endpoint during the planning stage can make a clinical trial run much more effectively by creating a clear focus and the strongest method of measurement possible.

Designing a clinical trial requires making and relying on assumptions to structure the protocol, and assumptions must be put to the test. The goal is to ensure those assumptions are both reasonable and scientifically sound. The most efficient way to prevent assumptions that could derail the data is to involve statistical experts from the biometrics team long before you need sample size calculations.

4. Getz, Kenneth A., et al. "The Impact of Protocol Amendments on Clinical Trial Performance and Cost." SAGE Journals, Tufts Center for the Study of Drug Development, 22 Feb. 2016, journals.sagepub.com/doi/abs/10.1177/2168479016632271.

DATA & DIVERSE PERSPECTIVES

Once the clinical trial strategy and design phase begins, if your team doesn't include statistical experts, this is already a sign of a potential crisis. Structuring data collection to acquire a meaningful measurement of effectiveness, choosing the best methodology for analysis, understanding and planning for regulatory requirements, and ensuring appropriate interpretation of the data all benefit from a diversity of perspectives.

The most successful, well-run studies are often those that have been built on a foundation of collaboration between the various stakeholders across the many stages of the clinical trial. An experienced biometrics team can be an invaluable resource to a sponsor's existing biostatistics staff, not just when the clinical trial is underway but at the very beginning of the design process, too.

ABOUT FIRMA CLINICAL RESEARCH

Firma is a boutique contract research organization (CRO) that believes a patient-centric approach is the key to unlocking positive outcomes in the drug and medical device development process. Using an integrated suite of specialized solutions, Firma makes the clinical trials process easier and more valuable for patients and produces higher-quality data for sites and sponsors.

info@firmaclinical.com | firmaclinical.com |