Zelta

Adaptive Clinical Trial Success via a Unified Data Management and Acquisition Platform

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Adaptive trials — clinical trials whose design allows for planned modifications to one or more trial aspects based on accumulated data — can seem dauntingly complex. However, a more complete understanding of adaptive trials' advantages, combined with a strong partnership between a sponsor, a CRO and its technology partner(s), can simplify such trials and enable more organizations to reap their benefits.

First, one must explore the challenges inherent in delivering a complex adaptive trial design in the real world, followed by study of successful methods associated with adaptive trials. The TOGETHER trial — a project executed by MMS Holdings utilizing the Zelta™ clinical trials platform by Merative — discussed below provides a relevant example. MMS is a data-focused CRO, while Merative is a spinoff of IBM Watson Health that offers the Zelta clinical data management and acquisition platform (formerly known as Merative Clinical Development). This single instance, single-code-based system does not require any integration, so MMS and other CROs can design their trials by picking and choosing only aspects of the product they need for a given trial.

When can adaptive trials be applied?

Adaptive design trials can range from to early-phase studies and exploratory trials to studies conducted to satisfy post-marketing commitments. Using adaptive design in an exploratory setting can allow, for example, evaluation of a broad range of doses, regimens, and populations, giving investigators the opportunity to continue evaluating only the most promising possibilities. The added flexibility that adaptive design offers may also increase acceptability to stakeholders. In short, adaptive designs maximize the trial's potential and utility based on data gleaned through the study.

Traditional clinical trials proceed in three steps: designing the trial, conducting the trial, and analyzing the data collected (typically following a prespecified analysis plan). This practice is straightforward, but it is inflexible. The introduction of prespecified modifications to an ongoing trial's design or statistical procedures in an adaptive approach adds the flexibility to modify elements of study design while maintaining the trial's validity and integrity.

In addition to reducing the number of patients that must be involved in a trial, adaptive designs can reduce the overall number of clinical trials. Executed properly, this approach can lead to more informative and efficient study outcomes for clinical safety and efficacy trials.

Adaptive trial designs have been used extensively in medical device development and lessons learned from those studies are being applied to drug development. They add a review-adapt loop to traditionally linear trial design analysis, a measure often described as "planning to be flexible" or "taking insurance against assumptions." Per the FDA's 2019 guidance document, Adaptive Design Clinical Trials for Drugs and Biologics, four key principles should be considered:

- controlling the chance of erroneous conclusions
- estimating treatment effects
- trial planning
- maintaining trial conduct and integrity

Moreover, it is important to consider which trial aspects to make adaptive, as inappropriate choices or too much flexibility may lead to bias. Adaptive design trials may include:

- modifications to randomization procedures
- abandoned or additional treatment arms or doses
- adaptions to the sample size, based on interim results
- adaptive enrichment to the patient population
- prespecified stopping rules for efficacy or futility

TOGETHER trial Case Example

Beginning in April 2020 (a few weeks after the World Health Organization declared the COVID-19 pandemic), the TOGETHER Trial was formed as an ongoing partnership to find affordable and effective treatments for COVID-19 from existing medications to reduce the pandemic's serious implications on low- and medium-income countries. MMS Holdings used Merative's Zelta platform to design the TOGETHER Trial's EDC system.

MMS anticipated the potential for multiple mid-study changes (also called post-go-live updates) as the study evolved, so they embraced an approach that allowed the database design to be adapted to specific study needs, which have not been insignificant. Since the trial's start, its design complexity has increased by 353%. Consider that, at the time, many adverse events associated with COVID-19, such as loss of taste, were still being discovered and recorded, illustrating the need for adaptive trial design. MMS designed, built, and implemented the study database in less than two weeks due to the urgent need to enroll patients.

The TOGETHER I trial went live in the system, across seven sites, on May 29, 2020, and the first patient record was live in the EDC on May 31. At one site in Brazil, the study database design included four treatment arms aiming to randomize 492 subjects each participating 90 days — the first 10 days for treatment, and the remaining 80 days for follow-up on treatment.

When the trial's second protocol was added (with three treatment arms spanning sites in South Africa, enrolling both low- and high-risk participants based on different sets of inclusion criteria), MMS adapted its design to accommodate more than one protocol, with multiple treatments, simultaneously. So, just two months after study launch, the Zelta database was managing two protocols across seven sites, comprising 42+ subjects and 8k+ data points. Additionally, in that two-month timeframe, three design adaptations were applied and mid-study changes already were being entered into the database.

By February 2021, the trial's third protocol had been initiated. The database was now handling three protocols across 10 sites, with 1,750+ subjects and 625k+ data points, as well as 12 design adaptations now applied. By October 2021, Zelta EDC was managing four protocols (TOGETHER's fourth protocol having been added that month) across 22 sites spanning more than 11,000 subjects. The study collected 2.5M data points and undergone 15 design adaptations. The design now included study drug administrations for one, three, 10, and 14 days.

MMS completed 22 post-production changes as the TOGETHER trial evolved. They were instituted through a combination of dedication and teamwork, as well as the Zelta platform's capability to manage the data and exports to suit the study size and its unique requirements. Specifically, MMS was able to generate data sets and exports for specific revisions — an invaluable capability when you consider the time it would have taken to export the data sets of every subject, each time, as well as the need to maintain different protocols within one study database while permitting study users from each protocol to access their respective data.

Enrollment in the TOGETHER trial has continued to increase and now comprises about 30,000 subjects in the trial across 22 sites, producing 6M+ data points. Nine interventions/evaluations have been completed and two are ongoing. Under the current plan, the trial will max out at 55,000 planned subject enrollments.

The 22 mid-study changes applied thus far warrant further discussion, since sites are entering more than 100 data updates per day and continue to enroll patients, so minimizing site disruption to implement changes is essential. The average database lock time for those updates is just 18 minutes. Additionally, 19 of those 22 changes required no lock time at all, despite challenging circumstances. (e.g., some changes took place on consecutive days, or a protocol going live was followed by a mid-study update for another protocol). It remains critical to minimize disruptions and downtime when implementing any changes or updates in the live EDC.

Ultimately, MMS Holdings set out to design and implement the study database as quickly as possible to start making a difference in a worldwide pandemic. The company's efforts were rewarded with the Society for Clinical Trials' annual Trial of the Year award for 2021. It was designed and adapted so that multiple treatment arms can be added throughout the study lifecycle, data can be extracted separately or combined, based on the user's analysis requirements.

Encouraged by our shared success, MMS Holdings is leveraging Merative's Zelta clinical trials solution on additional adaptive trials, as well. In one such trial, the Zelta platform's user-friendly modules (e.g., randomization and IRT) have greatly streamlined the trial's execution. For example, adaptive randomization applied to the study protocol has allowed for adjustments to the randomization schedule, based on the variable or unequal probability of treatment assignment (a tweak intended to increase the probability of success). That trial currently is undergoing its seventh major post-production change in just a nine-month span.

Another example of adaptive trial design applied to our current collaborations is the use of sentinel dosing, which involves dosing one or two people in the first cohort of participants in advance of the full study. Each dosed cohort is examined sequentially to ensure adequate evaluation of safety and tolerability data prior to dosing at the next level. Finally, we are working with pharmacokinetics and pharmacodynamics (PK-PD) samples, which may be adjusted with emerging data. Thus, as new data emerges, adaptive PK-PD sampling will be used to further understand the study drug's pharmacology.

Date	Protocols	Sites	Subjects	Data Points	Design Adaptions
May 2020 (Trial live)	1	7	1		
August 2020	2	7	42+	8k+	
February 2021	3	10	1,750+	625k+	12
October 2021	4	22	11,000	2.5M	15

Table 1 — TOGETHER Trial: By the Numbers

Final thoughts

Adaptive design clinical trials often are more efficient, informative, and ethical than trials with a traditional fixed design, making better use of resources such as time and money, in addition to sometimes requiring fewer test participants. To learn more, contact the authors and visit us at www.mmsholdings.com and www.merative.com/clinical-development.

Additional Resources

Webinar: Achieving Adaptive Trial Success With A Unified Data Management And Acquisition Platform

About the Authors

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About MMS Holdings

Our mission is to deliver high-quality service and technology solutions — rooted in strong science and decades of regulatory experience — that will assist our clients in developing and marketing life-changing therapies to positively improve lives worldwide. MMS emphasizes and values strong internal processes through defining, following, and improving upon the steps that lead to high-quality deliverables.

About Merative

Merative is a data, analytics and technology partner for the health industry, including providers, health plans, employers, life sciences companies and governments. With trusted technology and human expertise, Merative works with clients to drive real progress. Merative helps clients orient information and insights around the people they serve to improve decision-making and performance. Merative, formerly IBM Watson Health, became a new standalone company as part of Francisco Partners in 2022.
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