Cracking the Code: Strategies for Success in Complex Trials

Drug research and development is facing numerous opportunities and challenges. One major challenge is optimizing the performance of clinical trials, which are progressively becoming more complex in both design and operation. Although complex trials offer significant potential to increase efficiencies, accelerate clinical development, and reduce overall costs, sponsors and their partners must be prepared to capitalize on the opportunity.

Regulators, recognizing both the opportunities and challenges of complex trials, have been adapting to the changing drug development landscape. For instance, to support its goal of facilitating and advancing complex clinical trials, the FDA initiated the *Complex Innovative Trial Designs Meeting Program*[1], offering sponsors the opportunity to interact more with the agency to discuss their proposed approaches to complex trials. Also, in 2022, the EMA addressed complex trials by issuing guidance in the form of questions and answers, covering a range of topics, including the development and execution of master protocols, methods for analysis, and reporting of trial information to regulatory authorities[2].

Here we will enumerate the reasons behind the increasing complexity of clinical trials and show a case study highlighting Medidata's role in a rare disease clinical trial with multiple layers of complexity.

What Is a Complex Clinical Trial?

Not so long ago, clinical trials tended to adopt relatively simpler designs. They often used parallel groups, implemented double blinding for fixed periods, and used standardized dosages to compare investigational products against placebos.

In contrast, the modern clinical trial landscape has seen significant changes and innovations, with a marked increase in complexity in both design and operation. For instance, Phase III trials now collect an average of 3.6 million data points, a more than sevenfold increase compared to 20 years ago[3]. Unplanned protocol amendments[4] and interest in adopting adaptive trial designs that allow for compliant preplanned mid-study changes[5] have increased. Trials must also address many scenarios that can disrupt supply chains, such as temporary product unavailability due to manufacturing problems or natural disasters, and the impact of trial site location on product handling and storage. Moreover, interest has surged in developing drugs for rare diseases—studies that are known for their complex trial designs and operations—with nearly half of all novel drugs and biologics approved by the FDA in 2022 targeting rare diseases[6].

Key factors that are driving clinical trial complexity include:

- ✓ Multipart individualized dosages
- ✓ Increasing numbers of endpoints and procedures
- ✓ Larger diversity of data and data sources
- ✓ Greater focus on patient-centric approaches
- ✓ Remote monitoring methodologies
- ✓ Multiple geographical locations, regulations, procedures, cultures, and languages
- ✓ Bayesian and other methods for statistical analysis
- ✓ Planned and unplanned mid-study changes
- ✓ Adoption of decentralization and other innovative designs
- ✓ Hybrid approaches related to shipments direct-to-patient [DtP], depot-to-site, just-in-time, can differ across a study and even within a site, patient, or visit

For example, in a registration study for a rare disease with a decentralized design and multinational participation that includes the Asia/Pacific (APAC) region, complexities can include ensuring the shipment and delivery of the investigational product (IP), navigating patient privacy, regulatory requirements, regional shipping processes, cultural considerations, local procedures, and providing ongoing help-desk support.

Although increased complexity offers substantial opportunities, it also confronts sponsors and their partners with a growing list of demands that must be considered during planning so that the complexities and risks will not stall the study.

A critical determinant of success in navigating these complexities is strategically implementing appropriate technology. Leveraging the expertise of a technology vendor with extensive experience in complex clinical trials becomes critical to mitigate the risks effectively. Up-front planning and technologies that provide efficiency and flexibility—such as unified platforms integrating electronic data capture (EDC) and randomization and trial supply management (RTSM) systems—allow trials to effectively navigate these complexities to maintain trial integrity and enhance study efficiency and quality.

THE FOLLOWING CASE STUDY ILLUSTRATES THE BENEFITS OF USING AN INTEGRATED EDC/RTSM SYSTEM IN A COMPLEX TRIAL.

CASE STUDY: PROMETRIKA/Biotech Sponsor Rare Disease Study

Background

A biopharmaceutical company (Sponsor) specializing in novel treatments for rare diseases is developing phenylketonuria (PKU) treatment. The Sponsor has partnered with PROMETRIKA, a global, full-service contract research organization (CRO) supporting the biopharmaceutical and medical device industries, to execute a global phase 3 pivotal study assessing the efficacy and safety of the Sponsor's drug candidate in patients with PKU.

"When the EDC and IRT are in separate systems, you build into the EDC and then have to go back and forth between systems to check that the randomization is occurring and matches with the kits. When EDC and IRT are on the same platform, it's a big plus because you can see the data flowing from one to the other just by switching to another tab. Medidata can also partner with us when it is a highly complex trial to support with the build."

Benny Chan, Senior Biostatistical Standards and Implementation Specialist, PROMETRIKA

The Challenge:

The adaptive study design addresses multiple layers of complexity. Part 1 consists of a dose-escalating period of up to 15 weeks; patients are treated with an individually titrated dose (iTD), the highest dose the individual patient can tolerate. Once an iTD is selected, the patient progresses into the 4-week, double-blind, placebo-controlled, randomized withdrawal period. This is followed by an open-label dose extension period lasting up to 36 months.

Although patient stratification, iTD, and dose escalation are relatively straightforward and not uncommon individual elements of many trials, this particular trial combined all of these elements, requiring multiple levels for dosing and stratification factors. Given the number of kit types and different treatment regimens to be considered, these processes can quickly escalate in complexity. Additionally, patients are offered the option of a fully virtual experience to make the trial more accessible, thus requiring DtP shipment of medication.

In this trial, all the kits are manufactured and packaged in the US and shipped to international depots. A global trial with such an arrangement requires appropriate mechanisms to handle depot-to-depot transfers. The trial team chose a hybrid of DtP and the more traditional depot-to-site-to-patient approach, which creates logistical challenges. Added to an already complicated study design, these operational requirements create another layer of complexity.

The Solution:

Early in the study planning phase, it was evident that the trial would require a flexible and scalable system capable of accommodating dynamic mid-study changes that would be key to its success. After careful consideration, the team opted for Medidata Rave RTSM, which allows for treatment and randomization scenarios to be quickly and seamlessly altered with limited or no downtime for systems, sites, or users. Furthermore, it was determined that Medidata's integrated EDC and Rave RTSM functionalities offered a lower risk profile, especially for data flow, and reduced the risks associated with integrating an Rave EDC with independent systems.

With integrated EDC and RTSM systems, changes can be made that do not affect earlier enrolled patients and allow new patients to enroll under a different set of conditions.

Medidata's long history of navigating complex trials provided a level of assurance that the design and RTSM processes would be optimized through collaboration with Medidata's experts from the onset of the study build. Medidata's team has extensive expertise and industry knowledge of RTSM, including randomization algorithms, complex dosing, titration schemes, and supply strategies. Medidata's helpdesk support, which oversees both EDC and RTSM, is available to provide ongoing comprehensive insights into system operations.

"Medidata's RTSM solution gives PROMETRIKA a competitive advantage to support our sponsors' highly complex clinical trials. The integration of IRT and EDC shortens trial implementation and validation timelines. PROMETRIKA is proud to be an accredited Medidata RTSM CRO partner."

Miganush Stepanians, PhD, President and CEO, PROMETRIKA

"The help desk has access to both Rave EDC and RTSM. So, when there are issues, you have complete support in the background—they can see how data flows from one part to another. That's another part that I like about RTSM."

Benny Chan, Senior Biostatistician, PROMETRIKA

The Impact:

Medidata's integrated solution effectively handled all the challenges. The choice of a combined EDC and RTSM system facilitated seamless access to EDC data and real-time information on investigational product dispensations or kit requests. Additionally, incorporating fully remote virtual experiences and DtP medication shipments within the system improved overall study efficiency, patient accessibility, and patient recruitment and retention.

The sponsor had noted the benefits of an integrated system.

Summary

Challenges and opportunities are inherent in complex clinical trials, emphasizing the need for sponsors and their CRO partners to strategically plan during the early stages of study design to maximize trial outcomes. This case study underscores the significance of adopting the right technology to effectively navigate the design and operational complexities of these trials.

Download a copy of our white paper to learn more about how Rave RTSM supports complex clinical trials.

"This is the first time that I've actually worked with Rave RTSM and I've been very happy and impressed with it. Especially as an end user, when you're ready to do analyses, it's nice to have it all together on one platform."

Senior Director, Biostatistics, Study Sponsor

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