Charting a Course Through Complexity in Clinical Trials

Knowledge Sharing Series

Charting a Course Through Complexity in Clinical Trials

Clinical trials have evolved significantly over time with growing complexity that poses challenges for trial designers, implementers, and participants alike. This white paper delves into the historical progression of clinical trials, the various factors contributing to their increasing complexity, and the importance of effectively navigating this complexity. By understanding the evolution of trial designs, the critical role of technology, the significance of the protocol, the gap analysis process, and the power of experience, stakeholders in the clinical trial ecosystem can develop strategies to manage and succeed in the face of complexity.

Introduction

Clinical trials serve as the cornerstone of medical advancements, enabling the development of new treatments and interventions to improve human health. However, the landscape of clinical trials has shifted significantly over the years, introducing complexities that challenge industry professionals in ways never seen before. This white paper aims to explore the journey through clinical trial complexity, from historical perspectives to the current challenges faced by trial designers, implementers, and participants. By tracing the evolution of trial designs, understanding the pivotal role of technology, protocol comprehension, and the significance of experience, this paper offers insights into effective strategies for navigating complexity and ensuring successful trial outcomes.

Evolution of Clinical Trials

The evolution of clinical trials over centuries highlights the steady progression from early cures to incredible modern medical accomplishments. Two hundred and seventy-six years ago, Dr James Lind embarked on a quest to combat scurvy, marking the beginning of the modern clinical trial. Over time, innovations such as double-blind trials, randomization, and adaptive designs transformed the landscape. Recent advancements, including personalized medicine trials like CAR-T and Stem Cell trials, have further amplified complexity. This historical perspective underscores the exponential growth in complexity and sets the stage for understanding the challenges that lie ahead.

Complexity - A look back at Historically Significant Milestones

First Clinical Trial (1747)

The first clinical trial, conducted in 1747 by James Lind, was aimed at finding a treatment for scurvy among sailors in the British Royal Navy. Lind divided 12 sailors into 6 different groups and tested various treatments, ultimately discovering that those who consumed citrus fruits like lemons and oranges experienced significant improvements in their scurvy symptoms. The runner up was cider. Lind didn't publish his findings until four years later because he thought the Navy would be unimpressed with the findings.[1]

First Use of Placebo (1800-1811)

There is a lot of discussion amongst professionals about when placebos were first considered for inclusion in clinical trials. Most place the first use of placebos between 1799-1800, as a part of a debunkment of quackery by John Haygarth, a British physician, and 1811, when it was first included in Hopper's Medical Dictionary.

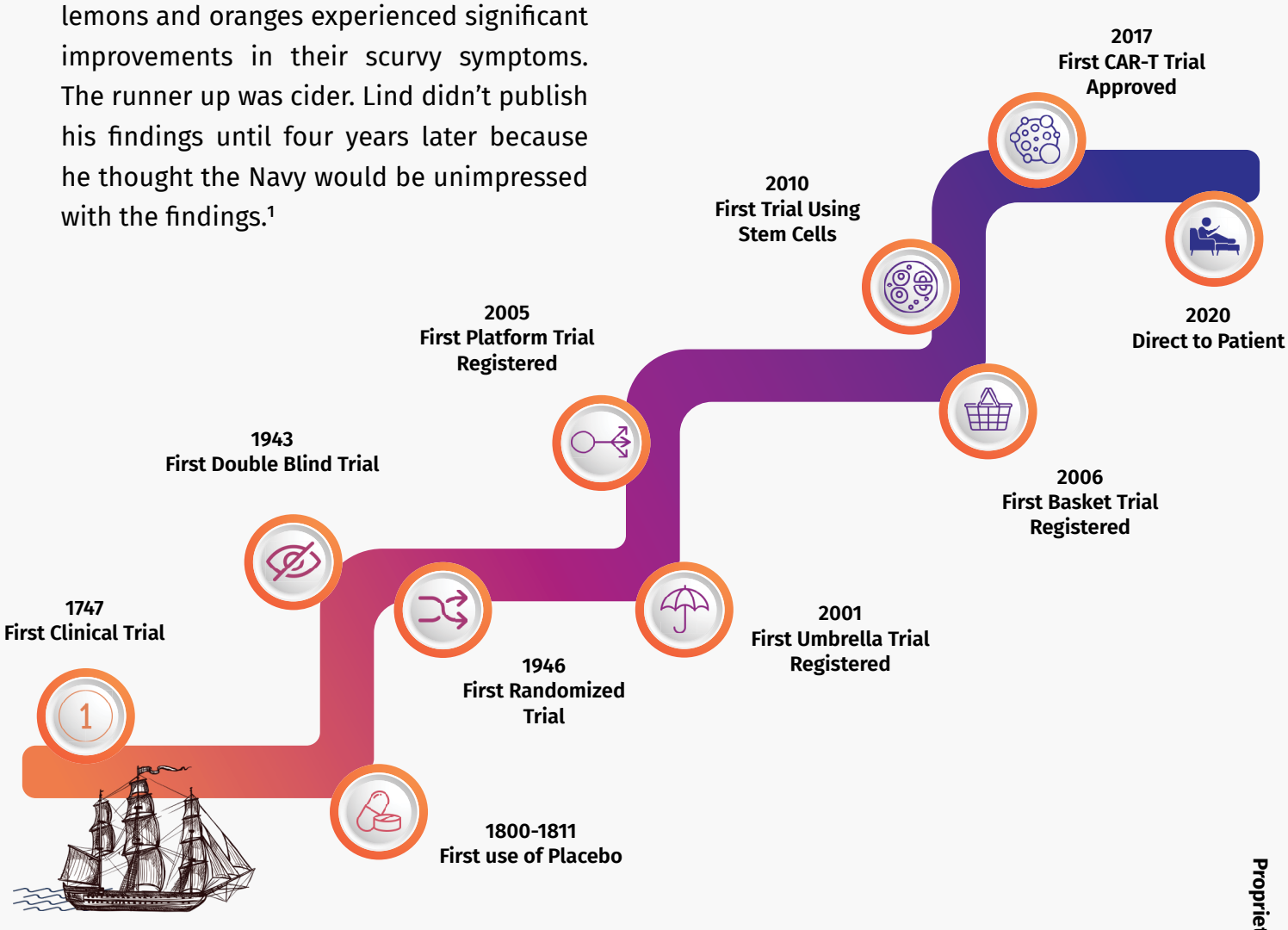


Figure Legend

With each event, the clinical trial landscape transforms, adapting to new methodologies and embracing complexity.

Complexity - A look back at Historically Significant Milestones

First Double-Blind Trial (1943)

In 1943, the UK's Medical Research Council conducted a trial to investigate the effectiveness of patulin, an extract of *penicillium patulum*, as a treatment for the common cold. This trial was noteworthy for being the first double-blind comparative study with concurrent controls in the general population at the time. However, despite rigorous control measures, including a nurse-administered alternation procedure for treatment allocation, the trial ultimately found no protective effect of patulin in treating the common cold.[1]

First Randomized Trial (1946)

The first randomized, controlled trial of streptomycin in pulmonary tuberculosis was conducted in 1946 by the UK's Medical Research Council (MRC). Sir Austin Bradford Hill introduced randomization as a statistical process and implemented it in this trial, concealing treatment allocation until patients were enrolled. The meticulous design, use of objective measures, and the influence of this trial significantly advanced the methodology of clinical research and played a pivotal role in the widespread adoption of randomization in clinical trials across various medical fields.[1]

First Basket Trial Registered (2001)

The first basket trial design was the Imatinib Target Exploration Consortium Study B2225 which was registered in 2001. It was a Phase II, open-label study to evaluate Imatinib in the treatment of malignancies. 186 participants were screened with 40 different types of malignancies. The trial suggested successful results across a subset of tumor types and malignancies and gave physicians data to help diagnose if the treatment would be suitable across multiple tumor profiles.

First Platform Trial Registered (2005)

The STAMPEDE trial was the first platform trial registered and was a multi-arm, multistage platform randomized controlled protocol, recruiting patients with high-risk locally advanced or metastatic prostate cancer starting long-term androgen deprivation therapy (ADT). The STAMPEDE team successfully recruited its last patient in March 2023.

Complexity - A look back at Historically Significant Milestones

First Umbrella Trial Registered (2006)

The BATTLE-1 protocol was designed to be one umbrella trial and four parallel Phase II studies focusing on erlotinib, sorafenib, vandetanib and a erlotinib/bexarotene combination for the treatment of advanced non-small cell lung cancer. A biopsy was taken before treatment so that the most appropriate treatment could be selected, moving us into the nascent area of personalized medicine.

First Trial Using Stem Cells (2010)

In October 2010, the first participant was enrolled into a groundbreaking new trial, GRNOPC1, focusing on the use of embryonic stem cells. This therapy was focused on therapy for spinal cord injury. Although this trial eventually went on hold due to adverse findings, it opened the door to an exciting new branch of medicine.

First CAR-T Trial Approved (2017)

The first CAR-T (Chimeric Antigen Receptor T-cell) therapy trial to receive FDA approval in 2017 was the treatment known as Kymriah, developed by Novartis. Kymriah was approved for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). In this therapy, a patient's own T cells are modified to target the cancer cells, offering a highly personalized and potentially curative treatment option for patients.[2],[3]

Direct to Patient (2020)

Direct to Patient was a concept that was on the edge of the clinical trial world for a while, but the events of 2020, the global shutdown for the Covid-19 pandemic, drove the requirements to have a mechanism for clinical trial medication to be delivered to trial participants without them going to hospitals or clinics who were inundated with infected individuals. This moved Direct to Patient technology from something people were just thinking about to something that was absolutely vital to keep clinical trials operating and those vulnerable participants safe.

The unassuming beginnings of Dr James Lind's pursuit have blossomed into a realm characterized by intricate protocols, adaptive strategies, and personalized interventions. It is clear to see that there have been more innovations, changes to how clinical trials are designed and run in the last 20 years than in the previous 250. And on the surface, we are correct. Clinical trials have gotten more complex, and with that complexity comes challenge. The consideration then is, how do we adapt to those changes?

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149409/
[2] https://aacrjournals.org/cancerdiscovery/article/7/10/OF1/6073/First-Ever-CAR-T-cell-Therapy-Approved-in-U-S
[3] https://www.nature.com/articles/nrd.2017.196

Navigating Complexity

Enabling Complex Clinical Trials Through Technology

The first answer which comes to mind is always technology: new and more adaptable technology. Technology has emerged as a critical enabler in managing the complexity of modern clinical trials. Adaptable systems, such as RTSM (Randomization and Trial Supply Management) platforms, play a pivotal role in handling intricate trial designs. These platforms empower trial designers and end-users to efficiently manage adaptive trials, platform trials, and umbrella trials by providing flexibility to adjust trial parameters in realtime and support seamless participant pathway modifications. Technology significantly contributes to the successful implementation of complex trials.

There are many complex elements which are needed to support complex clinical trials and having a framework which allows both the builder and the end user to rapidly change the system setup is incredibly powerful. If we consider basket trials, platform trials or umbrella trials; opening and closing participant groups, adding and removing compounds, changing which dose levels can be set, updating the maximum tolerated dose level for a participant population, changing the system in real-time is instrumental during the implementation of the described trial designs.

However, when the implementation of these complex trials is considered, the technology is only one aspect of the equation. The complexity equation includes multiple variables which when considered together, truly create the full picture of what is required to approach and support complexity.

The Protocol - A Blueprint for Complexity

Another variable of the equation is the clinical trial protocol. The pivotal precursor to contemplating and orchestrating the implementation of RTSM is an exhaustive review of the clinical trial protocol. Serving as the nucleus of the trial, the protocol encapsulates the essence of “Why?” the trial exists, articulating its objectives and guiding its execution. A nuanced comprehension of the protocol, inclusive of cross-references, footnotes, and contextual subtleties, is paramount for precise system design and effective trial administration.

Conducting a comprehensive, end-to-end reading of the protocol establishes the bedrock for navigating the complexities inherent in the subsequent phases of trial management. Whether the trial’s objective is to extend life expectancy, enhance quality of life, or impede disease progression, these goals are articulated within the protocol. Moreover, the protocol initiates the delineation of the path toward these goals. Amidst the intricacies lie crucial cross-references and footnotes that provide contextual depth, introduce exceptions, and highlight nuanced details essential for shaping the overall trial design. These intricacies are often overlooked when focusing solely on the schedule of visits or trial design diagrams. Therefore, the inaugural reading should encompass the entire protocol without exceptions, and for enhanced clarity, the presence of a highlighter proves beneficial.

Navigating Complexity

Key considerations when reviewing a clinical trial protocol

Assessment of the specific details during protocol review. Once the trial's overarching structure and objectives are clear, the subsequent steps focus on adding depth and substance:

Trial Design: Understand the structure, regularity of visits, and potential changes throughout the trial.

Blinding: Determine whether the trial is blinded or open-label and identify who is blinded.

Randomization: Scrutinize the randomization schedule, ratio, and whether the trial is stratified.

Treatment Arms: Examine the configuration of treatment arms and identify any unique aspects, such as crossover phases, re-randomization, or adaptive phases.

Participant Population: Define the characteristics of the participant population. Consider whether there are plans to expand this population and determine the targeted recruitment number.

Medicinal Products: Evaluate the involvement of medicinal products. Assess the potential addition or removal of products during the trial. Determine if the treatment is personalized or general and understand the administration protocols.

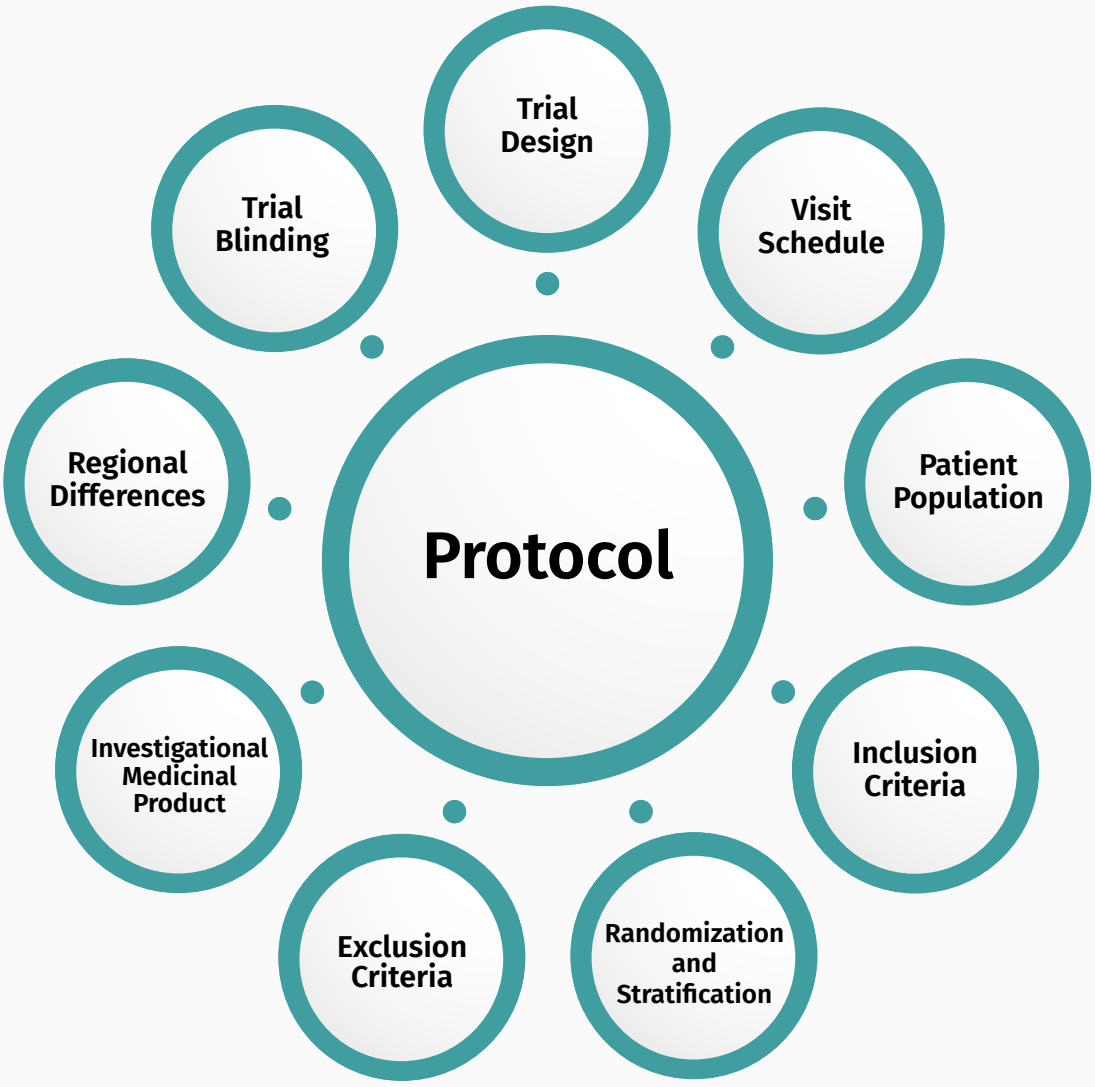
Inclusion and Exclusion Criteria: Carefully review the criteria for including and excluding participants. Consider whether these criteria should be incorporated into the system.

Navigating Complexity

Regional Differences

Investigate any regional variations, including age ranges or medication types. Note that, globally, adult trials typically start at age 18, but certain countries, such as Japan, may have different starting age requirements, like 20. Navigate the delicate balance between global labeling requirements, recognizing that medications may need distinct handling or identification as country-specific types to comply with regional labeling guidelines.

The protocol is the guiding document for the trial, but unfortunately, it is not exhaustive. There are some things that will never go into a protocol but are vital when setting up an RTSM system. This is why the second phase of determining complexity will always involve a gap analysis. In reality, the gap analysis process already began with the first review of the protocol, and with each reading uncover new areas to explore and understand.



Navigating Complexity

Gap Analysis: Illuminating Hidden Details

While the clinical trial protocol serves as a guiding roadmap, it often falls short in capturing all the intricacies of the trial. This is where the gap analysis is significant, aiming to uncover the hidden details essential for comprehensive system design. Questions related to medication logistics, blinding procedures, treatment arms, participant populations, and regional variations surface during this critical phase. Collaborative engagements between clinical and trial teams become imperative to ensure a thorough understanding of the trial's operational prerequisites.

This marks the transition from "your system or my system" to "our system," where both parties are deeply invested not only in the outcome of the RTSM build but in the success of the trial itself.

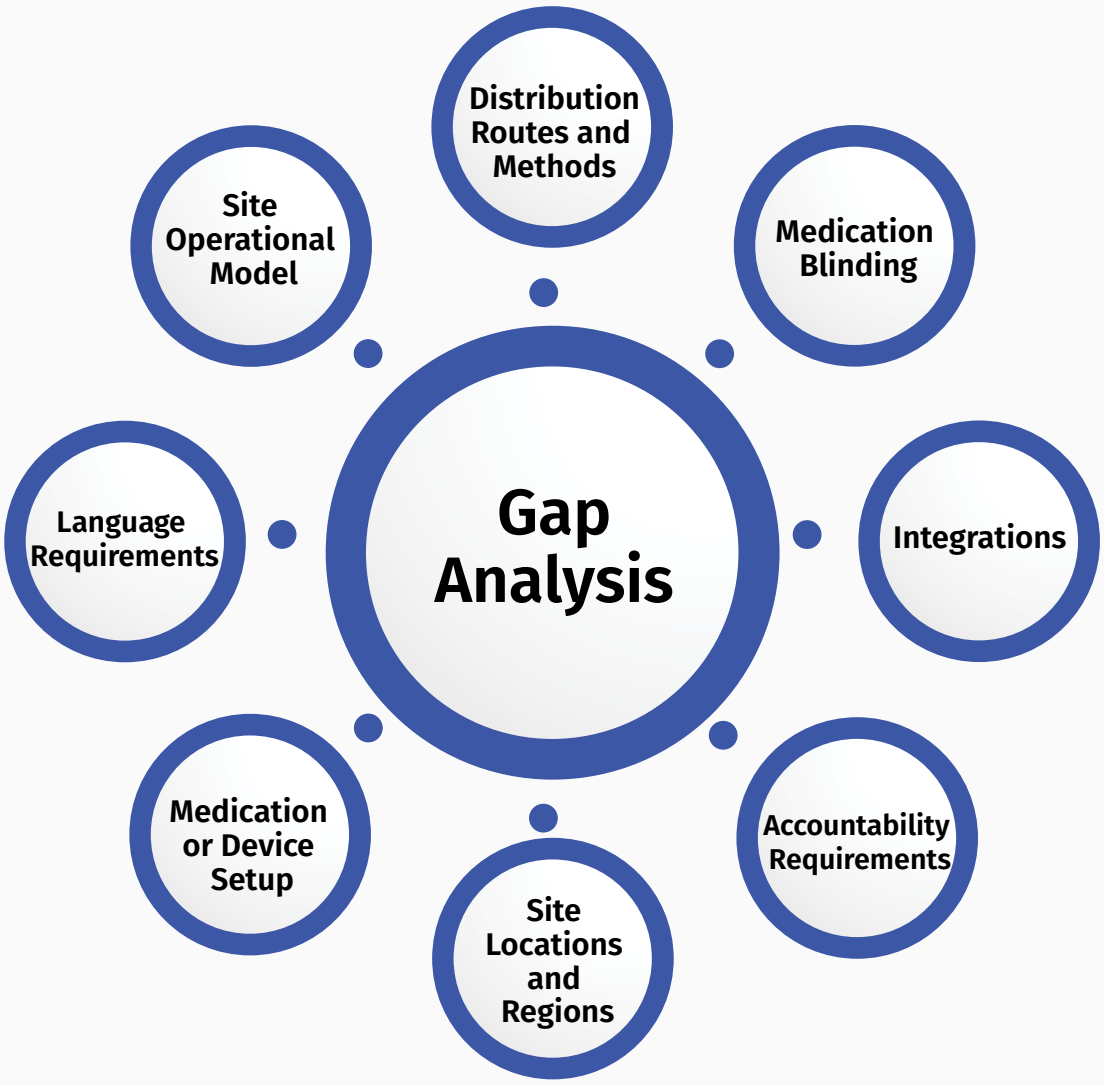
During this collaborative phase, numerous questions are exchanged, ensuring that all ambiguities are addressed. At this juncture, the final piece of the complexity equation comes into play. Our process involves scrutinizing the protocol, probing for details to fill gaps, and considering the technological capabilities. Yet, to truly balance the complexity equation, experience becomes the indispensable factor.

Collaborative engagements between clinical and trial teams become imperative... This marks the transition from "your system or my system" to "our system"

Navigating Complexity

This phase becomes a pivotal juncture where the hidden details prompt stakeholders to contemplate the operational dynamics of the clinical trial. It's common to encounter responses like "let me get back to you on that," and that's entirely acceptable. At this stage, the focus has been primarily on drafting and refining the protocol, gaining regulatory approval, and ensuring the acceptability and safety of the medication. Consequently, some attention may have shifted away from the operational requirements of the study.

It is the collective responsibility of both the sponsor team and RTSM experts to redirect this focus, preventing a loss of sight regarding the true end users of the system—namely, the Investigators, sub-investigators, nurses, and pharmacists who will be actively engaging with the patients. Achieving optimal results hinges on a robust collaboration between the RTSM experts and the Sponsor. This collaboration should evolve into a true partnership, with both sides working in concert to develop the most resilient and stable system possible.



Revealing the Complexity Equation

Balancing Complexity - The Experience Factor
Experience fosters the shift from asking "what do you want?" to "what do you need?" Experience also provides a fresh perspective, allowing for a holistic view of trial designs and promoting simplicity in the face of complexity. Experience proves invaluable in navigating the complexity of clinical trials. Beyond technology and protocol comprehension, experience equips trial designers and implementers with the ability to anticipate challenges, identify inconsistencies, and simplify complex scenarios.

The individuals closest to it have spent so long on it that they become micro-focused on the detail. By working through the protocol together and evaluating the protocol with fresh eyes, any potential mismatches can be identified and queried. Then, this review is expanded out to any supporting documentation, and the evaluation continues. The increasing complexity of a trial introduces challenges in identifying inconsistencies. As implementers of these systems, we amass a repository of standardized questions applicable to every study we undertake.

$$\frac{Collaboration * (Protocol + Gap\ Analysis)}{Technology + Experience} = A\ Robust\ RTSM\ System$$

Each protocol is unique, no matter how similarly they are written, and must be considered on its own merit. What the client usually means when they ask for a system to be set up like another trial, is that they want the resulting system to operate in a similar way. That is one of the reasons why asking the team what they need is more successful, more meaningful, than asking what they want.

Experience here is also a fresh set of eyes. By the time that a protocol is ready to be turned into an RTSM system, it has been worked on for months, or years, gone through several drafts, and been sent to the FDA, EMA, or other agency multiple times, and had so much feedback that it only slightly resembles the first draft.

Conceptualizing the participant journey becomes integral, where we meticulously map out the intricacies at each stage.

In adaptive trial designs, the fluidity of participant journeys prompts questions: Can participants transition seamlessly between treatments? How are washout periods handled? Considerations of toxicity and interactions, particularly in oncology trials, become pivotal.

The frequent recourse to "let me get back to you on that" doesn't stem from a lack of protocol knowledge in our sponsor counterparts but rather from our inclination to prompt a fresh perspective, urging them to examine the protocol through a new lens.

Revealing the Complexity Equation

Simplicity emerges as a foundational principle in the design of RTSM systems. This imperative gains heightened significance in the context of intricate trial frameworks such as basket or umbrella trials and the evolving domains of personalized medicine, exemplified by CAR-T or stem cell trials. The analogy of an iceberg aptly characterizes the construction of a robust RTSM system. While end-users interact with the visible top 10%, engaging in logins and transactions within a user-friendly interface, the submerged complexities persist out of sight. Behind this façade, custom functions and computer logic operate to orchestrate seamless participant progression along the prescribed treatment paths.

These complexities underscore the rationale behind the transition from paper records to automated systems in the realm of clinical trials. The progression beyond rudimentary participant lists and treatment group delineations, reminiscent of the conventional cards stored in envelopes, necessitated a more sophisticated data management approach. Automated systems emerged as indispensable tools for not only data storage but also for executing pivotal functions such as randomizations, re-randomizations, and the seamless transfer of data between systems. Paramount among these functionalities is the critical task of maintaining the blind—a safeguard against unauthorized access to confidential information—an imperative in the landscape of clinical trials that continually pushes the boundaries of complexity and confidentiality.

In designing complex clinical trial systems, simplicity emerges as a foundational principle. This principle recognizes that regardless of the protocol's complexity, end-users, particularly site investigators, require intuitive and user-friendly interfaces. The focus shifts from overwhelming end-users with intricate details to providing them with a streamlined experience that aligns with their primary responsibility – patient care. A calm and rational approach, underpinned by the lessons of experience, ensures that the design remains clear and functional.

In the context of RTSM, every data entry by the Investigator should serve a purpose, representing a meaningful decision point. A common scenario involves requests to record phone visits and check-in visits directly in the RTSM rather than the EDC system only. However, in instances where this has been implemented, a recurring issue emerges: investigators are disinclined to input data as there's no apparent benefit. The Investigator then skips the entry into the RTSM system. If the study follows a linear schedule, which most trials do, there's an issue, but the issue is only discovered when it's time for the Investigator to record the next dispensing visit. The situation snowballs, and now it's a critical data request with a patient waiting anxiously at site. All of these challenges could be mitigated by recognizing that investigators have more significant priorities than entering redundant data into the RTSM system without clear benefits.

Navigating Complexity for Success

Conclusion

The design principles that are followed for complex clinical trials are the same as those for their simpler counterparts. The only difference is stopping to take a momentary pause before beginning and and trusting the process:

- Read the protocol
- Work with the study team to understand how the system needs to work
- Understand how a patient gets from enrollment to completion
- Take a step back and look at the system as an investigator would
- Look for those areas that are open for interpretation
- Build it and test it thoroughly
- Continuously monitor the system and support through the operational phase

The capacity to craft an intricate system replete with advanced features and aesthetic appeal holds limited value if the system is not valued and underutilized. Experience teaches us that simplicity is key, and even more so when the protocol is already complex.

In conclusion, the journey through clinical trial complexity requires a multifaceted approach. The evolution of clinical trials reflects the ongoing push for medical progress, and each trial's unique complexities demand tailored strategies for effective implementation. By embracing collaboration, leveraging technology, fully comprehending protocols, conducting thorough gap analyses, and drawing upon experience, stakeholders can chart a successful course through the intricate landscape of modern clinical trials.

Meet the **Author**

Siobhan McKenna-Power has over 20 years of experience delivering with regulated system, with over 8 years designing RTSM systems for clinical trials. She first developed an interest in clinical trials when her father took part in multiple Phase III drug and device trials due to his progressive Chronic Obstructive Pulmonary Disease and was eager to contribute in her own way when the opportunity presented herself. Siobhan is a strong believer in first time quality and works with our sponsors to understand complex protocols. Siobhan has a keen understanding of what the needs of the end user are and works to ensure that even the most complex trials are easy for investigators to work with, and that patient safety is the foremost priority of any RTSM system.

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