



Complexity Is Inevitable — Design Is Essential





Complexity in clinical trial protocols is often cited as a source of site and participant burden and a contributor to study delays. While this is true, complexity can also represent scientific progress and enable meaningful medical advancements. The goal of trials is to drive innovation, so complexity should not be eliminated — but it must be purposeful. Reducing unnecessary complexity is critical to avoid operational inefficiencies. By taking a “yes, and” approach — leveraging data to design protocols that are both scientifically robust and operationally feasible — we can balance innovation with execution and deliver trials that advance medicine without creating avoidable burdens.

Built for Complexity, Designed for Success

The protocol serves as the foundation of every study, acting as both the scientific blueprint and the operational guide. Sponsors have significant influence over what goes into this blueprint, and with thoughtful planning, it is entirely possible to pursue complexity and innovation while enabling practical execution. Balancing scientific ambition with operational feasibility will require compromises, but innovation and practicality are not mutually exclusive. Every protocol element – whether an extra test, procedure, or data point – translates into something the study team must deliver or a participant must experience. More complexity is not inherently negative; what matters is that it is intentional, meaningful, and aligned with the study’s objectives.

“The clinical trial operations process is dependent on the protocol design; at each site and for each participant there are certain steps that happen in a certain order to get to the conclusion,” says Seth Halvorson, general manager of site solutions for WCG. “Decisions made upstream of recruitment have a cascading impact on the outcome. Protocols that do not balance the science with the operationalization tend to be harder to enroll and retain.”

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Problems tend to surface when design choices are made in isolation or without thorough consideration of probable operational impact, particularly related to enrollment and site readiness. Complexity earns a negative reputation when it impedes progress or creates barriers, but this perception can shift through more intentional planning and cross-functional collaboration. “Protocol complexity is going to continue to increase,” says Mette Andersen, general manager of data, analytics, and insights at WCG. “Protocols should be as complex as necessary to enable drug development and still be designed for operationalization.”

Access to data on how protocol requirements impact study outcomes is a powerful asset, especially when protocol design insights and operational metrics are used to guide development. By analyzing results from prior designs, sponsors can better understand potential operational challenges, anticipate barriers, and proactively implement solutions. This data-driven approach

ensures that complexity serves scientific goals without compromising feasibility.

“If we better align protocol design with operational support, we can start with a better foundation using the right data and be prepared to offset likely impacts for smoother execution,” says Halvorson. Andersen adds, “Using past and present data to guide design decisions means challenges can be addressed proactively rather than reactively, making complexity manageable rather than problematic.”

When study design and operationalization are disconnected, costs rise, timelines lengthen, and participant experience suffers. In addition, failing to incorporate operational feasibility during design often leads to avoidable amendments. Depending on when they occur, amendments can significantly delay progress and inflate costs.



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The Cost of the Disconnect: Burden & Amendments

A disconnected operational landscape plagues clinical trials. A Phase III trial averages 5.9 million data points, an increase of 11% per year since 2020, and more than one-third of the data doesn't support key secondary endpoints.^{1,2} 70% of trials experience startup delays and 70% exceeded their budget by more than 50%.^{3,4}

Unnecessary data collection adds complexity that slows trial execution and worsens the participant experience. Ethical considerations also cannot be overlooked; overburdening participants in what Andersen calls the “frenzy for more data” undermines both trust and trial integrity. Protocol design must strike a balance — collecting what is truly needed while safeguarding feasibility and participant well-being.

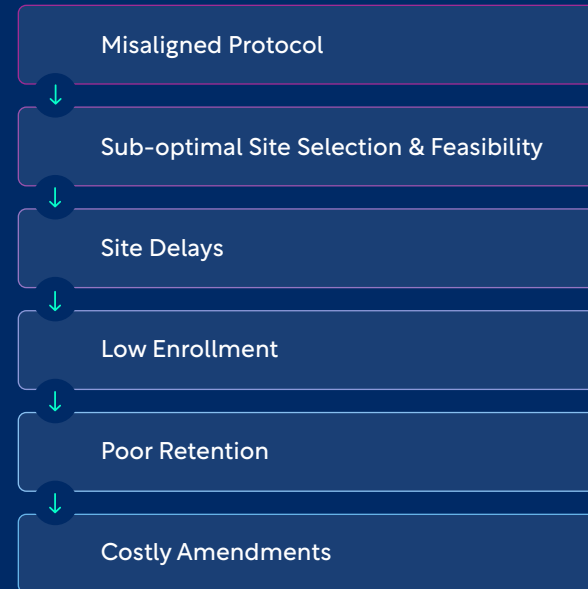
Protocols designed without fully considering the inherent relationships and dependencies among the various processes in the study has a compounded impact that often leads to delays, low enrollment, and poor retention, according to Halvorson. Studies designed without the patient or site at the forefront can become unnecessarily burdensome to recruit, eventually triggering amendments.

“When siloed decisions are made on interconnected processes, you have operational inefficiencies,” Halvorson says. “Addressing this after the fact often leads to an amendment.”

One of the most expensive outcomes of siloed decision-making is the proliferation of avoidable amendments. Since 2015, the prevalence of protocols with at least one amendment in Phases I-IV increased 19% with a mean of 3.3 amendments implemented per protocol; 45% of amendments were deemed avoidable. The direct cost for a Phase III protocol amendment is estimated at \$535,000.^{5,6}

The Fragmentation Problem

Fragmentation creates a domino effect:



Integrated, interoperable data helps break this cycle by connecting every step of the trial process. When sponsors can see how early decisions affect downstream outcomes, they can intervene sooner, prevent bottlenecks, and keep studies on track.

Driving Decisions and Accountability with Data

When protocols are designed to balance the need for complexity and operationalization, it leads to a better starting point and fewer delays. Protocol data identifies things like complexity, procedures, and participant burden; while operational metrics track, for example, startup times, enrollment rates, and retention.

Harnessing operational and protocol data is transforming how sponsors plan and manage trials.⁷

By correlating protocol data with operational outcomes, sponsors can see how protocol design decisions affect real-world performance. This approach makes it easier to make the right decisions upfront to reduce amendments, reduce timelines, and reduce site and participant burden. The result is a trial that is much more effective and efficient, maximizing opportunities for success.

“A large dataset with comparable trials becomes really important,” Andersen shared. “You can benchmark against similar studies to see what worked and didn’t work. How might we optimize our protocol design to reduce burden? How many procedures are enough? What might be the best countries and sites to select for the trial?”



“It’s not going to predict a clinical trial; that’s too complex. But it’s about giving you that starting point and identifying areas of potential risk that you want to start to look at in terms of mitigating.”

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Andersen added that while no model can fully predict a clinical trial, data provides a powerful starting- and reference point; predictive analytics allow sponsors to start to forecast site performance, enrollment rates, and retention challenges before studies launch.

“It’s not going to predict a clinical trial; that’s too complex,” she explained. “But it’s about giving you that starting point and identifying areas of potential risk that you want to start to look at in terms of mitigating.” The right protocol design takes into account the mix of country and site selection and the appropriate recruitment strategy to hit targeted timelines.

WCG is leading innovation in this area. Leveraging a massive protocol and operational data set, WCG provides unparalleled operational intelligence and real-time feedback to look at predictions for a given trial design, including participant burden, site burden, and trial complexity – and the impact of those factors on trial timelines.

The Shift Toward Data & Alignment

Organizational shifts are needed for sponsors to move from reactive trial management to proactive, data-driven decision-making. It starts with a leadership commitment to changing processes and bringing all of the stakeholders together to use data to inform discussions and support decision-making.

“The more information you have and the more you understand the context around that information and can contextualize that data, the better your decisions are going to be,” says Andersen. “It’s mission critical.”

The right starting alignment can lead to smarter, more connected trials:

01

Combine Operations and Protocol Design Early

Complex science and operational feasibility must be united from the outset of a trial to prevent avoidable amendments, reduce site and participant burden and build in mitigations for necessary complexity.

02

Let Data Drive the Protocol

Prioritize data tied to primary objectives. Add secondary and exploratory elements only when there is real value, as this will keep studies lean, efficient, and participant-friendly.

03

Break Silos to Speed Execution

Connect the processes from protocol design through site selection, study startup, and recruitment and retention. Connectivity cuts delays and reduces costs.

04

Treat Operational Metrics Like Endpoints

Monitor site performance and study execution with the same rigor as clinical outcomes. Strong operational execution is critical for study success.

05

Use Insights to Pivot Proactively

Leverage real-time performance metrics to spot risks fast and make timely, informed decisions to keep the study on track.

Reducing Fragmentation Through Analytics

10-20%



enrollment acceleration from using artificial intelligence/machine learning to identify optimal trial sites.⁸

30-50%



improvement in identification of top-enrolling site selection using AI.⁸

83%



of sites showed improvements in data quality when statistical data monitoring was used.⁹



Connect with WCG today to learn how you can turn integrated data into streamlined studies.

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Resources

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3. Greissbach, A., et al. "Resource use and costs of investigator-sponsored randomized clinical trials in Switzerland, Germany, and the United Kingdom: a metaresearch study." *Journal of Clinical Epidemiology* (2024).
4. Deloitte. 2024 Global Life Sciences Outlook: Rethinking Resilience in Drug Development. 2024.
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6. Getz, K.A., et al. "The Impact of Protocol Amendments on Clinical Trial Performance and Cost." *Therapeutic Innovation & Regulatory Science* (2016).
7. Driver, C. "How Unified Platforms are Reshaping Clinical Trial Economics." [PharmExec.com](https://www.pharmexec.com). 2025.
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9. de Viron, R., et al. "Does Central Statistical Monitoring Improve Data Quality? An Analysis of 1,111 Sites in 159 Clinical Trials." *Therapeutic Innovation & Regulatory Science* (2024).



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