How assumptions in protocol design are a root of trial failure: Avoiding “unicorns” in clinical trial protocol design

Picture a clinical trial protocol design that shines on paper: meticulous endpoints, comprehensive data collection and exhaustive patient monitoring. Now imagine trying to execute it in the real world, where screening instruments are impractical—or worse—insensitive, where stipulated procedures and timings make patients’ lives unbearable, and where narrow inclusion/exclusion criteria make the patient search akin to seeking a needle in a haystack. **This is a “unicorn protocol”—magical in theory, but mythical in practice.** The reality is that as drug development complexity has increased, so too has the gap between protocol design and operational reality. Today’s trials collect 88% more data points than a decade ago, incorporate 86% more endpoints, demand 70% more procedures and must satisfy 61% more eligibility criteria.[1] While this increasing sophistication can drive scientific rigor, it also fuels the challenge of unicorn protocols.

The solution lies in creating an empathetic ecosystem for trial design. This approach integrates multiple critical voices—sites, patients, caregivers and operational experts—as early as possible in the protocol development process.

The rising cost of assumptions

The consequences of assumptions in protocol design are stark. Studies risk failing to progress to their next phase due to operational issues, most potent of which are arguably poor patient recruitment, adherence and retention. Eighty-two percent of Phase III trials require at least one substantial amendment, taking an average of 260 days to implement.[2] The effects extend beyond budgets and timelines, affecting patient access to new treatments, site resources and ultimately, the pace of innovation.

Consider the burden on research sites. On average, sites respond to 81 feasibility assessments and participate in 30 qualification visits annually, translating to approximately $350 million in industry costs.[3] Put another way, sites can spend one full week each month simply completing feasibility questionnaires. These administrative demands compete directly with patient care and study execution time.

Assumption-based protocol design creates a troubling paradox: the more sophisticated trials become, the harder they are to execute. Without early input from sites and patients, protocols risk becoming academic exercises rather than practical road maps.

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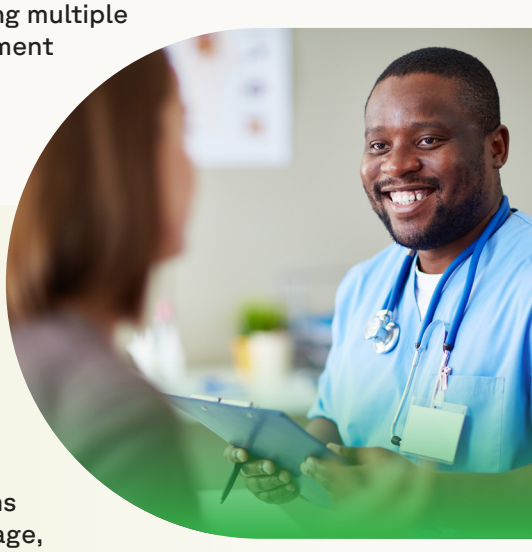
The voice of sites: Understanding operational reality

Operational burden on research sites manifests in multiple ways, with protocol amendments as one example. With an average of 3.5 substantial amendments per study, sites must constantly adapt their processes, retrain staff and update documentation.[2] Given varying ethics committee approval timelines, sites can find themselves caught in an ongoing cycle of amendments before completing the previous changes. Even in an optimal scenario, this complexity increases the risk of protocol deviations.

Visit complexity presents another challenge. Extended visits strain site resources and staff scheduling while potentially deterring patient participation. Even with these increased time commitments, site compensation hasn't necessarily kept pace with the expanded workload.

Structured site engagement programs can help address this issue, tackling multiple aspects of trial execution and providing sites with a voice in the development process. This early collaboration helps identify potential operational hurdles before they become costly amendments.



The voice of patients: Beyond traditional patient centricity

Mean procedures per visit have risen from 11 in 2009-2011 to nearly 14 in 2020, creating a heavier burden on participants.[1] This procedural intensity, combined with longer visits, can make trial participation unsustainable for many patients.

Protocol tolerance (the ability of patients to comply with study requirements) must be evaluated before trial initiation, not after problems arise. This requires engaging patients and caregivers at the preclinical stage, going beyond regulatory requirements to understand the practical implications of protocol demands.

This starts with assessing the appropriateness of screening procedures and continues on into the trial itself. For patients with specific conditions, some common trial procedures may be challenging or inappropriate. For instance, the much-used walk test might well be unsuitable for patients with neurological conditions—an insight that, if captured early, could prevent an amendment and its resulting delays.

Meeting patients where they are, rather than where protocols assume they should be, can yield unexpected insights. The 2023 CISCRP patient participation survey revealed that while trust and participation were down among Black patients, interest increased significantly when trials included digital health elements for reporting.[4] Such findings demonstrate how listening to patient communities can reveal practical solutions for improving trial accessibility and retention.

Compassionate clinical trial design

Creating feasible protocols requires a holistic approach that accounts for diverse stakeholder needs. This mindset extends beyond the basics of patient-centric trial design to encompass several critical dimensions.

Representative populations

Diversity in clinical trials isn't just about demographics. It's also about access and ability to participate. While regulatory bodies have made strides in addressing disparities for some underserved populations, other groups may require further attention—for example, conditions like dyslexia can impact memory, organization and time management—factors that directly affect trial participation but are often overlooked in protocol design.

Ethical sustainability

The environmental impact of poorly designed protocols extends beyond operational inefficiency. When patients drop out due to untenable trial demands, re-recruitment can double the carbon footprint through additional site visits, drug deliveries and data collection activities. Even minor protocol requirements can have tremendous environmental consequences.

Social determinants of health

Social determinants of health (SDOH) drive between 30% and 50% of health outcomes,[5] significantly impacting trial results. However, capturing these factors presents challenges due to lack of consensus on priority measures and inconsistent documentation. Protocol design must account for broader datasets to avoid including only certain population segments, which can further compromise the validity of diversity and inclusion data.

From theory to practice: Implementation steps

Implementing a compassionate protocol ecosystem requires systematic preplanning and validation:

1.

Early engagement: Incorporate site and patient input during protocol development, not just after design completion.

2.

Real-world testing: Validate protocols with actual sites, patients and technology before finalization.

3.

Flexible design: Build in appropriate adaptability for real-world conditions while maintaining scientific rigor.

4.

Comprehensive assessment: Evaluate protocols through multiple lenses—patient burden, site feasibility, sustainability impact and accessibility.

The path forward

Success in clinical trial design isn't achieved through a single voice but through the harmonization of multiple perspectives. This approach requires early planning and stakeholder engagement, but the return on investment is faster recruitment, better retention, fewer amendments and ultimately, accelerated delivery of new treatments.

At Fortrea, we support this evolution through structured programs that facilitate meaningful dialogue between sponsors, sites and patients. Our approach combines deep site engagement through our Site Advisory Boards, early protocol optimization with comprehensive support throughout the trial life cycle, helping sponsors transform scientific ambition into operational success.

To explore our solutions, **contact us**

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