

Clinical Researcher

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Let's Get Personal: Scaling Clinical Research Down to You and Me

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Clinical Researcher

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Clinical Researcher—June 2024 (Volume 38, Issue 3)

Contributors to this issue weigh in on the theme of “Let’s Get Personal: Scaling Clinical Research Down to You and Me” by focusing on the design and delivery of research participation opportunities for special populations, the research team’s relationship with trial management technologies and quality management tactics, and various aspects of patient centrality and personalized or precision medicine in today’s clinical research enterprise.

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CHAIR’S MESSAGE

Keep GOing for it Together!

Elisa Cascade, MBA, 2024 Chair of the Association Board of Trustees for ACRP



The ACRP 2024 annual conference opened with a green suit and jumping jacks

Surrounded by 1,400 members ready for learning and discussing the facts

With a Clinical Trials Day selfie wall

And a vibrant Exhibit Hall

We kicked off with inspiration, education, and connection as our three tracks

Inspiration

We are inspired by our Academy Board and our Board of Trustees

By our Fellows, Diversity Advisory Council, and other committees

Including our 40,000 certified

And the excellence they provide

We are all “Advancing People Advancing Help,” the mission of ACRP

Education

Nearly 100 sessions to hear from the community and learn

Inspiring meaningful discussions everywhere you would turn

An FDA talk with zest

A Busy Brain test

Compliance, Leadership, AI, and other topics compelling us to return

Connection

Connecting with friends and so many inspiring new people to meet

The ACRP Chapters, Partners in Workforce, and others to greet

Researchers and sponsors did unite

And together we can fight

To make the clinical research profession a career path that is concrete

...And More

Whilst this commentary was written as a poetic review

Clinical research professionals know this to be true

We work hard and take pride

In the care we provide

Thank you truly for all that you do!

—ACRP—

P.S.: You can now [explore photos and blogs from ACRP 2024](#), as well as access all recorded ACRP 2024 sessions that correspond to your conference registration type (Full, Weekend, or One-Day Registration) in ACRP Learning (go to learning.acrpnet.org/my to access your My Courses Dashboard and please use your ACRP username and password to login). If you did not attend the full conference in Anaheim and would like to access additional sessions, you can purchase Replay Packages of the six content tracks. Please visit the [ACRP Course Catalog](#) and filter by “Recorded Conference.”

PEER REVIEWED

Improving Cardiovascular Research for Transgender and Gender Diverse Populations

Kirti Salunkhe, MD; Tara Coffin, PhD, MEd, CIP; Sharad Adekar, MD, PhD, CIP



Transgender and gender diverse (TGGD) individuals face an increased risk of cardiovascular disease (CVD). There is an unmet need to identify the root causes of CVD health disparities in this population. More research and evidence-based strategies are needed. Additional factors to be addressed include possible bias and discrimination in healthcare settings, paucity of representation of TGGD competent care providers, and insufficient resources to encourage and accommodate TGGD individuals wanting to participate in clinical research.

Regulatory authorities, notably the U.S. Food and Drug Administration (FDA), have critical roles to play, as do institutional review boards (IRBs), sponsors, investigators, and patient advocates. Recommendations include adopting community-based research methods; employing scientifically and ethically sound study design; revising participant-facing recruitment and research materials to utilize gender-inclusive language; providing TGGD continuing medical education for staff; and engaging patient advocates familiar with issues faced by TGGD individuals. These measures should help to increase TGGD representation in CVD clinical studies, leading to improved treatment options and health outcomes.

Background

Good cardiovascular health is central to overall wellbeing. Over the years, research has supported the development of evidence-based treatments for conditions ranging from hypertension to genetic and congenital malformations; from use of medical devices to formulation of life-saving drugs, and advancement of strategies aimed at improving prevention of CVD. CVD is an equal opportunity condition, affecting both cis-men and cis-women, and is the leading cause of human mortality and morbidity.^{ 1–5 }

Decades of data from CVD trials have identified important risk factors fueling CVD rates, including tobacco use, hormone therapies, weight gain, poor dietary choices, and lack of physical exercise.{6} These risk factors are applicable across the sex and gender spectrum. However, clinical research also highlights the presence of sex-specific risk factors and treatment outcomes associated with CVD. For example, there are lower implantation rates of electronic cardiac devices in cis-gender women when compared to cis-gender men despite comparable indications, and less use of drug-eluting stents in women, despite demonstrated efficacy.{7–9} Similarly, sex-specific research indicates that there is an increase in cardiac risks from tobacco use in premenopausal people assigned female at birth (AFAB). Unfortunately, these findings are often limited to the cis-gendered populations represented in the clinical research setting and lack generalizability to TGGD individuals.

TGGD individuals face additional barriers to obtaining safe and accessible healthcare, and poorer health outcomes when compared to cis-gendered individuals.{10} This trend persists when it comes to cardiac health. For example, recent data indicate that for AFAB individuals and those who identify as transgender, the odds of developing CVD in their lifetime are 2.66 times higher than cis-gender women. Similarly, for gender non-conforming individuals, the odds of developing CVD are 2.21 times higher than cis-gender individuals.{11} TGGD individuals are also at a higher risk of encountering significant barriers to safe and responsive healthcare services, compounding disparities in disease prevalence and contributing to poorer health outcomes overall.{12}

Many of these trends can be attributed to bias and discrimination in the healthcare setting, a lack of TGGD competent care providers, and a general dearth of clinical knowledge.{12,13} These trends are also explained in part by the lack of representation in clinical research. Without representation in cardiac research, important risk factors are overlooked and options for care for a population experiencing higher rates of CVD remain limited.

Additional research is needed to build an understanding of how the social determinants of health contribute to poorer outcomes. There is also an unmet need to identify how hormone therapy and other gender affirming care may influence risk factors or responses to other care. This work is critical to ensure TGGD individuals have access to safe and appropriate healthcare.

Current State of CVD in TGGD

Current guidelines speak to CVD risk factors common to all populations, including active or passive tobacco use, physical activity, diet/nutrition, weight management, lipid profile, glycemic status, and blood pressure. However, these fail to capture the social determinants of health that may uniquely impact TGGD individuals, nor do they capture variables presented with the uptake of gender-affirming care, such as gender-affirming hormone replacement therapy (GAHT).

While limited, current research does indicate that GAHT may impact cardiac health. For example, one study noted that transgender men receiving hormone therapy had a three to five times higher risk of thrombosis and twice as high risk for stroke as compared to cis-gender men. There was also an elevated risk for myocardial infarction in transgender women undergoing GAHT compared to cis-gender women.{ 14,15}

Optimal cardiovascular outcomes are dependent upon markers of physical health, but they are also strongly linked with parameters for emotional and mental well-being. Many TGGD individuals speak to the impact of family rejection, bullying, and lack of social acceptance, leading to an increase in stress responses and maladaptive coping mechanisms. This in turn can lead to increased lipid levels, a predisposition to diabetes, depression, anxiety, and loneliness.{ 16,17} Yet data about these factors and how they affect members of the TGGD community are lacking.

Unmet Need: The Lack of Data

Despite the implications of increased CVD risk among TGGD individuals, there remains a dearth of research specifically identifying the underlying causes or developing equitable interventions. This may be due to a limited understanding of the nuances of CVD in TGGD individuals by the medical device and biopharmaceutical companies that facilitate clinical trials. However, this deficit is also observed in the wider healthcare setting, manifesting as limited continuing medical education on CVD in TGGD individuals, as well as a lack of representative providers, researchers, site-level staff, patient advocates, and research participants. This underrepresentation may cause harms associated with a lack of safe and appropriate treatment options.

Bridging the Research Gap: Roles of Continuing Medical Education, Sponsors, Investigators, and Regulatory Authorities

The reality is that increased cardiovascular morbidity and mortality among TGGD individuals is driven by both physical and psychosocial etiologies. Research gaps and the relative lack of safe, appropriate clinical care compound these issues.

Providing Investigators with Continuing Medical Education to Address Issues Related to TGGD Individuals

There is a need to provide healthcare professionals and investigators with relevant continuing education and training about possible cardiovascular health disparities associated with TGGD individuals. This can be done by updating the current medical school curriculum and adding appropriate, required continuing medical education. These updates should be facilitated by advocates, community leaders, and other key stakeholders from the TGGD population.

Developing and Assessing Eligibility Criteria

It is also important for sponsors to design clinical trials for TGGD populations, either by focusing research objectives and recruitment on TGGD patients or by ensuring that existing clinical studies recruit a representative sample that includes these individuals. This requires careful consideration of eligibility criteria, accurately reflecting the intent to enroll individuals across the sex/gender spectrum. Throughout protocol development, sponsors and investigators are also urged to critically assess research methods and approaches, to avoid perpetuating discrimination and microaggressions that may otherwise go overlooked.{ 18} This includes careful consideration of research outreach and recruitment methods.

TGGD populations are often defined as “difficult to reach” in terms of research recruitment. While this may, in part, be due to ineffective outreach and recruitment methods, recent data indicate that there may be other barriers prohibiting participation. One study found that researchers viewed interactions with potential minority participants as challenging. Importantly, this perception ultimately led to providers withholding clinical trial opportunities.{ 19} With such findings in mind, bias (common in the clinical research setting), must be accounted for.

Community-based participatory research methods can be utilized to identify and resolve any potential bias. There is specific emphasis placed on the importance of integrating community members from the beginning, to ensure research objectives and methods align with the needs and concerns of the intended community. By partnering with TGGD individuals, sponsors and investigators can ensure that research objectives address concerns and needs expressed within the specific community, optimizing the contextualization of lessons learned over the course of the research.{20,21}

Regulatory authorities and IRBs can play important roles in assessing accessibility of clinical trials for TGGD populations. A key component of assessing the criteria for research approval is considering the equitable selection of research participants. The Belmont Report emphasizes that no one group should be explicitly targeted or excluded from research, without sound scientific or ethical rationale.{22} Institutional and commercial IRBs are responsible for assessing whether the explanation provided is scientifically and ethically sound to achieve objectives of the research study.

TGGD individuals are not considered a traditionally vulnerable population from a regulatory perspective. However, given the documented harm associated with being misgendered in the health setting, among other risks associated with access to general medical care, IRBs should ensure appropriate safeguards and protections as well as reasonable accommodations and assistance for this study population.{23}

Modernizing Data Collection Practices

Sponsors and investigators are encouraged to employ questionnaires and survey instruments that have been validated across gender diverse populations, when possible. If appropriately validated instruments are not available, selected questionnaires should be adapted whenever possible to improve access. When conducting ethical review, an IRB should consider the appropriateness of selected scales in terms of gendered language and intended measurements. A scale might be validated, but that doesn't mean it is applicable to all participants.

Use of Gender Inclusive Language in Participant-Facing Materials

Finally, when designing protocol documents, including any participant-facing materials such as advertisements, consent forms, questionnaires, and other forms, sponsors and investigators should incorporate gender inclusive language as applicable. This means using gender inclusive pronouns, including “they/them,” along with inclusive phrasing. Similarly, binary language should be avoided, unless clinically relevant.

Conclusions

There is an unmet need to identify the root cause of CVD health disparities in TGGD individuals. There are not enough, or sufficient, evidence-based strategies which can be used to improve CVD health in such individuals. To address such disparities, more research is needed. Sponsors, investigators, regulatory authorities, and IRBs all play critical roles in developing solutions to this health disparity. Actionable steps may include the application of community-based participatory research methods in trial development and implementation, but should also encompass ethically and scientifically sound and equitable eligibility criteria.

Providing continuing medical education to healthcare professionals, sponsors, investigators, and research staff regarding specific cardiovascular health disparities in this population, collaborating with patient advocates who are familiar with issues related to TGGD individuals, and actively working to expand the ease of approaches and recruitment for this community will also help. Actions such as these have the potential to improve the representation of this population in clinical research, with specific findings that cascade into the clinical setting. These findings may contribute to evidence-based guidance and new treatment options to positively impact cardiovascular health outcomes in TGGD individuals.

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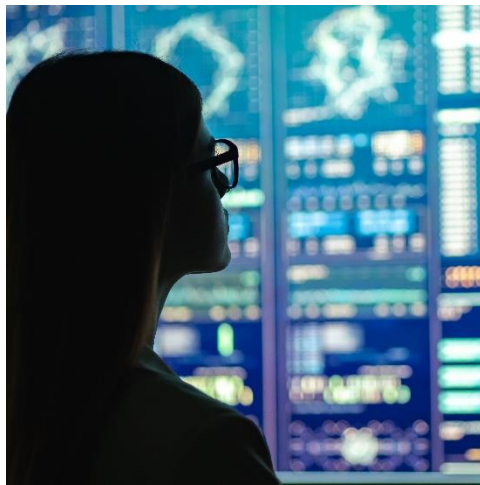
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Disruptive Technologies Redefining the Path of Clinical Trials

Deepika Khedekar, MPharm



This article delves into the critical role of clinical trials in combating major health crises. It elucidates the multifaceted challenges impeding clinical trials, including patient recruitment, funding, and data management issues, while also highlighting the transformative potential of emerging technologies such as artificial intelligence (AI), blockchain, and genomic sequencing. Specifically, it examines the impact of AI in enhancing trial data analysis and patient recruitment rates, the

pivotal role of blockchain in securing data integrity, the dynamic use of wearable devices for continuous patient monitoring, and the cutting-edge application of genomic sequencing in personalized medicine. Furthermore, it addresses the inherent challenges these technologies pose, including data bias, security concerns, and the need for regulatory compliance. Ultimately, the article underscores a hopeful yet cautious outlook towards leveraging these innovations to advance clinical research, emphasizing the importance of ethical considerations and patient-centric approaches in navigating the future of clinical trials.

Global Health Crisis and Clinical Trials Overview

Annually, 67 million lives are lost globally.^{1} Of these, 9.9 million deaths are attributed to cancer^{2} and 18 million to cardiovascular diseases.^{3} It's staggering, isn't it? Clinical trials, essential in battling these diseases, often falter due to an array of challenges, including but not limited to patient recruitment, funding disparities, staff shortage, scaling data analytics capabilities, and more.

Eighty-five percent of all clinical trials experience delays, and each day lost in these trials costs pharmaceutical companies between \$600,000 to \$8 million in U.S. dollars. It's not just about the capital resources. Did you know that less than 4% of the U.S. population participates in these life-saving trials? Moreover, keeping participants engaged is another story, with only 7% of those who start a study seeing it through to the end.{4} However, hope is on the horizon with artificial intelligence (AI), blockchain, and genomic sequencing poised to transform clinical research.

Transforming Clinical Trials with AI-Driven Large Language Models

AI-driven large language models (LLMs) are revolutionizing the field of clinical trials, specifically addressing the challenges of slow patient recruitment and intricate data analysis. Rice University researchers have pioneered the use of these AI models, which are adept at processing and understanding vast amounts of text data, thereby producing synthetic data that mirror the complexity and variability of real-world clinical trial data.{5} This innovation is particularly useful in overcoming the hurdles posed by the need for extensive data in the face of strict privacy regulations like the [Health Insurance Portability and Accountability Act](#) in the U.S. and the [General Data Protection Regulation](#) (GDPR) in the European Union, which rightly limit the availability of sensitive patient information.

The Rice University team's approach is twofold. Initially, it feeds publicly available trial data into a LLM to create artificial yet realistic trial data for deep learning analysis. These data encompass a wide range of inputs, from clinical notes to patient demographics, effectively training the algorithm to recognize and adapt to the nuances of clinical data. Subsequently, the synthetic data are processed by a deep learning algorithm on a secure server, ensuring patient privacy while enriching the model with a comprehensive dataset for nuanced analysis. This method not only mitigates the issues of data shortage and the demand for high precision in patient-trial matching, but also heralds a future where the matching process could become largely automated. This novel approach, recognized by the American Medical Informatics Association, not only promises to enhance the efficiency and accessibility of clinical trials, it also opens the door to a future where the patient-matching process in these clinical trials matching can be

largely automated, significantly accelerating the pace of medical discoveries and the development of new treatments.

While AI has proven instrumental in addressing challenges related to patient recruitment and data analysis, clinical trials also face challenges in ensuring data integrity and security.

Blockchain to Guard Clinical Data

Data form the lifeblood of clinical trials. Data integrity and security are paramount. Any compromise on these fronts can jeopardize the trial's outcomes and, more importantly, patient safety. Here, blockchain technology, with its decentralized and tamper-proof ledgers, offers a powerful solution. Blockchain ensures data security and transparency, making it an invaluable tool in clinical trials.

Several trailblazing programs are already harnessing blockchain's potential. The Mayo Clinic, in partnership with the Dutch blockchain startup Triall, embarked on a mission in 2022 to refine clinical trial design and enhance study data management.{6} In a similar manner, Medidata joined forces with the University of Oxford's Cancer Research U.K. Clinical Trials Unit.{7} Their shared goal? To leverage blockchain technology to amplify the integrity and transparency of clinical trial data.

While blockchain addresses the intricacies of data security and integrity, another challenge looms large in clinical trials: the need for continuous, accurate, and real-time patient monitoring and engagement. With the aforementioned low retention rate for participants in trials, traditional methods for patient monitoring and engagement, often reliant on intermittent check-ins or self-reporting, can miss crucial datapoints, leading to gaps in understanding patient health.

Wearable Devices: Revolutionizing Patient Monitoring

Addressing the gaps left by traditional monitoring methods, wearable devices emerge as the next frontier in clinical trials. These devices, from smartwatches to fitness trackers, provide a solution to the challenges of intermittent check-ins and inconsistent self-reporting. They offer the

advantage of continuous monitoring, capturing an array of health data ranging from heart rates to sleep patterns, ensuring researchers have access to comprehensive, real-time insights.

A testament to the transformative power of wearables comes from an initiative of the Scripps Translational Science Institute,{8} which seamlessly integrated devices like smartwatches and fitness trackers into a clinical trial, allowing for continuous monitoring of patient activity levels and sleep patterns. This innovative approach provided a holistic view of patient health, yielding richer data for analysis.

Further emphasizing the potential of wearables is the Apple Heart Study,{9} a collaboration between Apple and Stanford Medicine. This study utilized the Apple Watch to detect irregular heart rhythms in an impressive cohort of 400,000 participants. This research not only validated the efficacy of wearable devices in large-scale remote monitoring, it also heralded a new era of patient-centric, data-rich, and efficient clinical trials.

While wearable devices address the immediate and tangible aspects of patient health, there's a deeper layer of understanding that remains largely uncharted: our genetic blueprint.

Genomic Sequencing: The Frontier of Personalized Medicine

Our DNA is the blueprint of our existence, holding secrets to our health and lifespan. To truly revolutionize clinical trials and medical treatments, it's imperative to delve deep into this genetic code. Genomic sequencing emerges as a critical technology in this exploration, offering profound insights into an individual's genetic makeup by allowing researchers to pinpoint specific genetic variations or mutations associated with diseases or treatment responses. A prime example is the National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH) trial,{10} which harnessed genomic sequencing to align patients with advanced cancers to targeted therapies based on their tumor genetics.

Similarly, the 100,000 Genomes Project{11} in the United Kingdom aims to decode the genomes of 100,000 individuals. The objective? To unearth disease-causing genetic mutations and pave the way for tailored treatment strategies.

As we harness the power of our DNA to revolutionize treatments, we must also navigate the multifaceted challenges that arise with the integration of cutting-edge technologies in clinical research.

Challenges on the Horizon

While technological advancements have brought remarkable progress to the field of clinical trials, it is important to acknowledge that they are not without risks and limitations. The adoption of AI in clinical trials, for example, introduces concerns related to the reliability and interpretability of AI algorithms. There is a risk of bias in algorithmic decision-making if the training data used to develop AI models are not diverse or representative of the population under study. Vigilance is required to ensure that AI algorithms are transparent, explainable, and accountable, especially when making critical decisions regarding patient eligibility, treatment allocation, or adverse event prediction.

Similarly, while blockchain technology promises enhanced security and integrity in clinical trials, it also presents several challenges. Its decentralized nature, though ensuring data authenticity, can make updating data records extremely challenging at times. Further, despite its robust security, blockchain is not entirely immune to cyberattacks, which could have severe implications given the sensitive nature of clinical trial data. Additionally, as trial size increases, handling larger volumes of data could lead to scalability issues. Navigating these issues becomes even more challenging when considering compliance with data protection laws, such as GDPR.

As well, the use of wearable devices in clinical trials, though promising for patient monitoring, carries its own set of challenges. Data accuracy can be a significant concern, as the quality of data collected depends on the precision and reliability of the devices. These devices can also suffer from variability in measurements, making data interpretation challenging. Additionally, participants from rural areas may not have access to such devices, which means the trial team will need to provide these devices exclusively to these participants and the corresponding cost and training process will need to be factored into the trial design to ensure these trials are holistically inclusive.

Issues related to patient compliance and comfort with the devices must also be considered. For instance, a participant may forget to wear the device or use it incorrectly, impacting the data collected. Privacy and data security are other crucial aspects, as wearable devices generate large amounts of personal health data that need to be securely managed to prevent unauthorized access.

It is also imperative to address the potential for fraud, misconduct, and Type II errors as these emerging technologies are integrated into clinical trial design and operations. These considerations are essential for maintaining the integrity and reliability of trial outcomes. For example, the use of AI in data analysis and patient selection must be transparent and accountable, with checks in place to prevent bias and ensure fairness. Blockchain technology, while enhancing data security and traceability, requires careful implementation to prevent unauthorized access and ensure the authenticity of trial data.

Since these technologies are dependent heavily on devices and data, if either of those are either knowingly or unknowingly manipulated, the results may represent false and/or fraudulent outcomes hampering the integrity of the trial and raising risks for the health of the participants. Thus, the potential for fraud and misconduct requires stringent oversight and ethical guidelines to prevent manipulation of data or results.

Moreover, Type II errors are also an added concern for these trials. A Type II error occurs when a study fails to detect a true effect or benefit of a treatment or intervention, mistakenly concluding that there is no effect when, in fact, there is. This type of error poses significant risks in trials involving these technologies due to potential technological limitations or incorrect use. For example, if wearable devices are not accurately calibrated, they might fail to detect meaningful changes in a patient's health status, leading to a false conclusion that a treatment is ineffective. Similarly, AI algorithms could miss significant patterns or outcomes if they are trained on incomplete or biased datasets, further compounding the risk of Type II errors.

Therefore, it is essential to establish robust protocols for the deployment of these technologies, such as rigorous testing of wearable devices for accuracy and reliability, and validating AI algorithms against diverse and comprehensive datasets to ensure they are capable of identifying

true effects accurately. Additionally, clear protocols for data validation and result interpretation are essential to ensure that the data collected through these technologies are correctly analyzed and understood. By taking these steps, researchers can minimize the risks associated with integrating these technologies into clinical trials.

The Future of Clinical Trials: Innovations and Ethical Considerations

The integration of emerging technologies such as AI, blockchain, wearable devices, and genomic sequencing into clinical trials heralds a transformative era in clinical research. These advancements promise to enhance patient recruitment, streamline data analysis, secure data integrity, enable continuous patient monitoring, and pave the way for personalized medicine. However, the application of these technologies introduces complex challenges, including the potential for AI-induced biases, data rectification and scalability issues linked with blockchain, data accuracy and privacy concerns related to wearable devices, and the ethical considerations surrounding genomic sequencing.

Addressing these challenges requires a concerted effort to develop robust methodologies that ensure the equitable and unbiased application of AI, as well as scalable and secure data management frameworks that align with regulatory standards. Moreover, ensuring the accuracy and privacy of data collected through wearable technologies, alongside establishing ethical guidelines for the use of genomic information, is paramount. This necessitates a multidisciplinary approach that combines clinical expertise, data science, ethics, and regulatory knowledge, aiming to leverage technological advancements while safeguarding patient welfare and data integrity.

As the clinical trials landscape evolves, the successful integration of these technologies hinges on an unwavering commitment to ethical considerations and patient-centric approaches. The future of clinical research, while promising, demands vigilance, adaptability, and a comprehensive understanding of both the potential and the pitfalls of these emerging technologies. Embracing this future necessitates a holistic approach that not only navigates the balance between innovation and ethical responsibility but also ensures that advancements in clinical trials contribute to the broader goals of enhancing patient care, advancing medical science, and improving health outcomes globally.

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SPECIAL FEATURE

How an Innovative Statistical Methodology Enables More Patient-Centric Design and Analysis of Clinical Trials

Samuel Salvaggio, PhD; Emilie Barré, MSc; Sébastien Coppe, PhD; Marc Buyse, ScD



Clinical trials are critical for assessing new treatments in terms of their potential benefits for patients' health and for their likelihood of financial success if marketed. Yet, the traditional approach focusing on a single primary endpoint may mean lengthy trials that often fail to capture the full spectrum of the treatment effects that are crucial to patient well-being.

Generalized pairwise comparisons (GPC) is an innovative statistical methodology that offers a revolutionary approach to clinical trial analysis,

addressing these shortcomings by allowing the integration of multiple clinically relevant outcomes into a single assessment. This methodology better leverages the large amount of collected data and improves clinical trial efficiency by reducing the required sample size. Multiple case studies have demonstrated the successful application of GPC in regulatory submissions, with notable U.S. Food and Drug Administration (FDA) approvals in cardiovascular disease.

This paper discusses the benefits of GPC, providing a compelling argument for its broader adoption in clinical research to meet modern healthcare challenges, design patient-centric protocols, and approve patient-centered treatments at a faster pace.

Background

Clinical trials stand as the cornerstone of medical advancements, offering critical insights before the commercialization of any new treatment (e.g., a new drug, vaccine, or medical device) which will improve patients' health. Efficacy endpoints in clinical trials are crucial measures designed to reflect the intended effects of a new treatment, encompassing a wide array of assessments from clinical events like stroke and mortality to symptoms such as pain and measures of function. As diseases can affect patients in multiple ways, leading to various clinical events, symptoms, and functional impairments, many trials strive to examine the effects of a treatment on multiple aspects of a disease.

Yet, treatments are often approved based on the results tied to a single primary criterion. This main primary endpoint, while selected for its clinical relevance by medical professionals, may not always resonate with the day-to-day realities and preferences of patients and can overlook broader effects that a treatment might have—such as variations in symptom alleviation, functional improvements, or side effects—which are all critical to patient well-being. This narrow focus can restrict the understanding of a treatment's comprehensive benefits and risks, potentially sidelining important factors that influence patient quality of life and overall treatment satisfaction.

An approach involving a single primary endpoint can be too narrow in scenarios where multiple outcomes are of interest. It does not fully address the complexity of patient needs, especially when evaluating treatments for diseases with multiple symptomatic expressions or functional impacts. This issue is further compounded by the inherent limitations of conventional statistical tests commonly used in clinical trials. These traditional methods are limited to the analysis of a single variable at a time. As a result, clinical outcomes collected during trials are analyzed separately, leading to two significant issues. First, failure to consider the interactions between clinical outcomes. Second, many analyses are considered exploratory and discounted in decision-making processes due to concerns about Type I errors, a statistical technical term meaning that a treatment effect is detected when there is none (e.g., a false positive).^{1} This fragmented approach prevents a comprehensive understanding of how different outcomes of interest collectively influence the efficacy and safety of a treatment.

Another problem related to this way of defining primary analysis is that it may not reflect patient preferences. While patients invest a large amount of time in performing multiple tests at the investigational site or answering different questionnaires, much of the collected data remain unexploited as contributors to decisions about the trial's success. At worst, this single endpoint approach might lead to the wrong "market access" decision.

Imagine a randomized clinical trial in oncology, where a new innovative drug would be compared to the standard of care. Let's take a simple example, where one patient in each treatment arm would have the same overall survival time (i.e., similar values for the primary analysis). These two patients will not play an important role in differentiating the two treatments. Still, one of the two patients may have a much worse quality of life than the other patient. Not being able to leverage this information may prevent some pharmaceutical companies from bringing to market some innovative treatments, which may answer important patient needs, while not being less efficient than the standard of care.

This idea of answering patients' needs in a more holistic way is not an easy one. In some situations, non-inferiority trials have been trying to achieve this objective—to highlight that a new treatment is not much better in terms of efficacy but may bring value to patients when looking to other facets of the treatment's effects.{2}

Non-inferiority trials aim to show that a new treatment isn't importantly worse than an established one. Picture this situation: a new treatment has similar efficacy to the standard of care while reducing treatment burden or side effects. Typically, regulators demand evidence of "non-inferiority." However, non-inferiority trials come with their own set of challenges—among them being the choice of an arbitrary "non-inferiority margin," the requirement for large sample sizes, and the high probability of the trial ending up inconclusive. Moreover, these trials may not always focus on the treatment effects that matter most to patients.

When it comes to helping patients make informed decisions, we need to focus on the big picture—evaluating all the evidence to figure out the net benefit of different treatment options.

Generalized Pairwise Comparisons

As clinical research continues to expand with hundreds of new randomized clinical trials added weekly to public registries like ClinicalTrials.gov, the need for robust, flexible statistical tools becomes ever more apparent. GPC marks a significant evolution in the statistical analysis of clinical trials. GPC, an extension of the well-known Wilcoxon-Mann-Whitney test, offers a robust statistical method to analyze multiple outcomes simultaneously.^{3} Forty peer-reviewed scientific papers were published on the topic over the past 15 years, while the GPC methodology also gained traction in the biopharma industry, with a growing number of protocols approved by the regulatory agencies.

GPC is a statistical methodology that addresses these issues by comparing every possible pair of individuals within a trial to assess the likelihood of one treatment being more effective than another, from a comprehensive standpoint. The GPC methodology stands out as a pragmatic approach that offers unparalleled flexibility, especially in scenarios where multiple outcomes are in play, each with its own priority. Consider the landscape of oncology, where primary outcomes typically revolve around overall survival (OS) and progression-free survival (PFS). However, the traditional focus on just one of these metrics often leads to confusion and inconsistent results. Unlike conventional methods that focus on “time to first outcome,” GPC allows one to focus on the “time to worst outcome.” This nuanced approach addresses the complex trade-offs between OS and PFS, smoothing out the wrinkles of uncertainty. But GPC’s utility extends far beyond oncology. In cardiology, for instance, it has already gained traction, offering a versatile framework for comparing treatment groups across a spectrum of outcomes—be they continuous, time-to-event, binary, or categorical.^{4}

This approach not only accommodates the complexity of modern medical treatments, but also aligns with the growing emphasis on patient-centric research. By allowing outcomes to be analyzed simultaneously and hierarchized based on clinical relevance and patient preferences, GPC facilitates a holistic evaluation of treatment effects, culminating in the calculation of the net treatment benefit (NTB)—the cornerstone outcome of GPC analysis. The NTB serves as a comprehensive measure of treatment’s effects, capturing the disparity between two treatment cohorts: one receiving the experimental treatment and the other the control treatment.

Conceptually, the NTB represents the net probability of observing a superior outcome in the experimental group compared to the control group.

This absolute metric directly correlates with the concept of “number needed to treat” (NNT), wherein the inverse of the NTB yields the NNT value. For instance, if the NTB equals 20%, it implies that, on average, one in every five patients experiences a superior outcome with the experimental treatment over the control treatment. Such clarity in quantifying treatment efficacy empowers clinicians and researchers alike in making informed decisions regarding patient care and trial design. It also helps patients understand easily the outcome of the statistical analysis.

Moreover, it provides a clear breakdown of the contributions of each single outcome in the final NTB value. If three patient-relevant outcomes were chosen, one may see the individual contribution of these three outcomes. For instance, the first outcome may bring a treatment benefit of 10% in favor of the experimental treatment, the second outcome a benefit of 15% in favor of the experimental treatment, and the third outcome a benefit of 5% in favor of the control treatment. Clinicians and patients can therefore easily understand the positive impact of the experimental treatment for the first two outcomes, not especially for the third one.

The GPC methodology not only incorporates outcomes typically used in standard primary endpoints, it can also integrate additional measures such as quality of life and adverse effects, providing a holistic view of a treatment’s impact. This approach allows for the utilization of a broader spectrum of collected data in clinical trials.

One significant advantage of GPC is its capacity to substantially reduce sample sizes. While the extent of sample size reduction may vary depending on factors such as the number of outcomes considered and their relationship, it often leads to notable decreases in sample size requirements. This ability to minimize the number of patients needed for a well-powered clinical trial design is particularly crucial in therapeutic areas such as rare diseases, where patient recruitment is challenging. Achieving reductions in sample sizes without compromising the clinical relevance of analyses is one of the top opportunities for boosting biopharmaceutical research and development productivity.{5}

Leveraging GPC methodology represents a paradigm shift toward more holistic, patient-centered approaches in clinical research. On top of reducing patients' recruitment timelines and study budgets, it provides an efficient approach to listen to a patient's voice and incorporate the most patient-relevant outcomes in the primary endpoint, mirroring the broader transitions in healthcare toward personalized medicine.

Case Studies

Multiple clinical trials have successfully used GPC as their primary statistical analysis for registration clinical trials, mainly for cardiovascular disease. Two of those drug submissions have since received FDA approval for market access, both drugs aiming to treat cardiac amyloidosis. For the first drug, tafamidis meglumine, the primary analysis that led to its regulatory approval used GPC to assess a multivariate hierarchized endpoint. The analysis combined all-cause mortality and the frequency of cardiovascular-related hospitalizations.{6} For the second drug, acoramidis hydrochloride, the GPC analysis was expanded to use four hierarchical outcomes.{7} Alongside all-cause mortality and hospitalization frequency, the analysis also assessed changes in a protein biomarker (NT-proBNP) and the results from a six-minute walk test (to measure one aspect of the patients' quality of life {8}), therefore providing even more layers of understanding of the drug's effects.

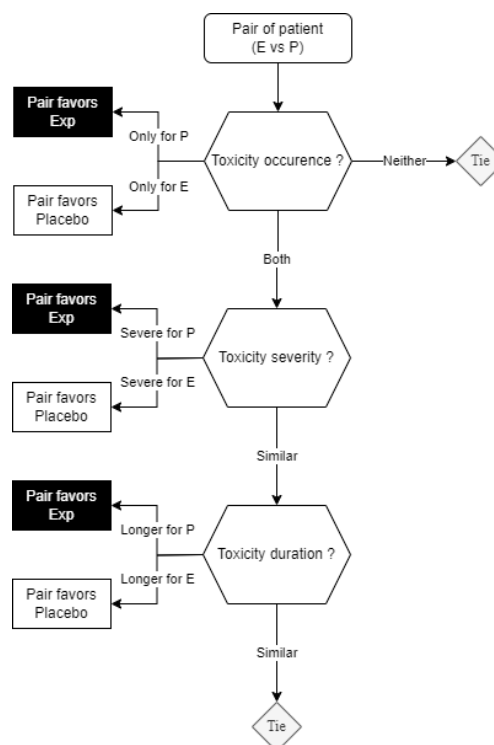
To illustrate the application of GPC, let's examine a real case study from an oncology FDA submission. In this case, the investigational drug was compared to a placebo in a randomized trial, on top of standard of care, to assess its effectiveness in preventing severe toxicity associated with cancer treatment. The primary analysis initially used a traditional approach, focusing solely on the occurrence of severe adverse effects—a mere binary variable. This method underutilized much of the available data, omitting crucial aspects of the toxicity that are significant both to the patient and the overall treatment strategy, such as the severity grade of the toxicity (e.g., whether hospitalization was required) and the duration of the toxicity.

GPC methodology was used to address the shortcomings of the classical univariate statistical analyses by capturing a broader range of outcomes into the evaluation. In the GPC analysis of this oncology trial, multiple dimensions of toxicity were considered: initially, the occurrence of

toxicity at its most severe grade, followed by occurrences at less severe grades, and finally, the duration of the toxicity. To illustrate the analysis process, pairs of patients from the experimental (E in Figure 1) and placebo (P in Figure 1) groups were compared, as depicted below. Each patient from the experimental group was compared to each patient from the placebo group, offering a large number of pairs to be evaluated following this process. This approach allowed for a more comprehensive assessment by comparing treatment effect across different levels of severity and duration of toxicity, providing a clearer picture of the drug's impacts on patient health.

While the univariate statistical analysis narrowly achieved significance with a p -value just below the conventional threshold of 5%, incorporating additional clinically relevant information through the GPC analysis increased statistical power. This led to a more comprehensive and convincing demonstration of the drug's superiority over placebo.

Figure 1: Flowchart depicting the decision process behind a pair classification for a GPC analysis



Note: To compute the NTB, the number of pairs favoring the experimental arm are subtracted from the number of pairs favoring the placebo arm, then the result is divided by the total number of pairs.

Conclusion

In recent years, the clinical research industry has taken significant strides in engaging patients, caregivers, and advocacy groups in the trial design process, gathering invaluable insights into protocols, endpoints, and the overall trial experience. However, despite these commendable efforts, a pressing need remains for a robust methodology capable of synthesizing multiple outcomes into a single, clinically meaningful statistical analysis.

This is precisely where GPC emerges as a transformative solution, seamlessly integrating patients' and clinicians' insights with trial data to create a comprehensive assessment reflective of patient needs. The NTB evaluation offers to both patients and clinicians some easily understandable treatment assessment. By facilitating the combination of all key patient-relevant outcomes, GPC enhances the patient-centricity of clinical research while also optimizing its efficiency and effectiveness. Through its capacity to harness vast amounts of collected data, GPC not only streamlines treatment decisions, but also holds the potential to reduce sample sizes and study timelines, thereby amplifying biopharmaceutical research and development productivity.

As the industry continues to evolve, embracing methodologies like GPC will be pivotal in driving innovation and advancing the pursuit of improved patient outcomes.

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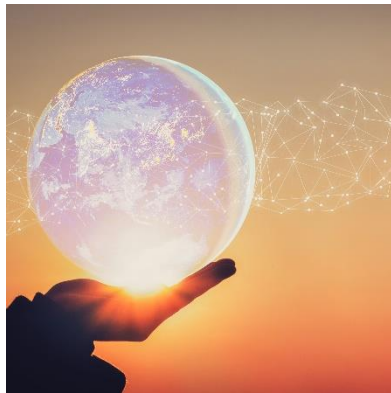


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OPINION

The Illness and the Cure: Technology is Indispensable in Clinical Research, But its Proliferation is Also Creating Friction

Elisa Cascade, MBA



Clinical research is thriving. A recent [report](#) suggests that the U.S. landscape for clinical trials will continue to grow by more than 5% over the next several years. The steady increase is driven by various factors, including the emergence of promising technologies and big data analytics that are creating opportunities to engage in and learn from potentially groundbreaking research.

While growth in clinical research development is expected to yield enormous human benefits, substantial growth can bring challenges, as well. For example, patient recruitment persists as one of the biggest [obstacles](#) to study success. Even as many healthcare providers supplement recruitment via data-driven patient identification and digital advertising, there is still a heavy reliance on site staff to establish a relationship with and qualify the patient referral for screening. At the same time, healthcare workforce levels are at an all-time low. For every one research coordinator seeking work in the U.S., there are [seven jobs available](#) and the ratio of clinical research nurses to potential positions is wider still, with only one nurse for every 10 positions.

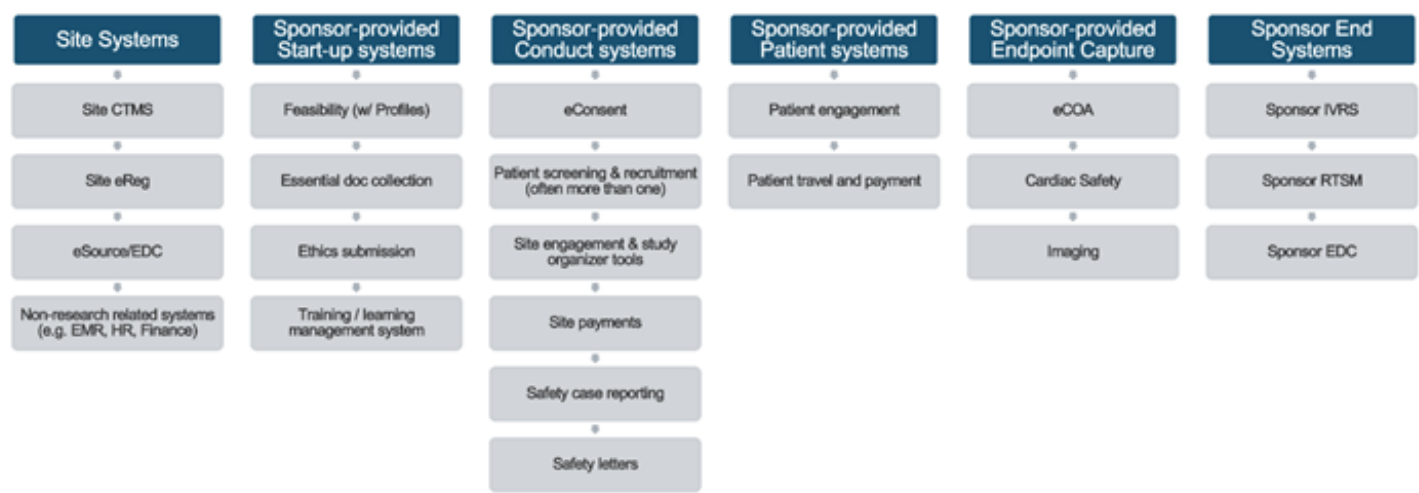
In addition to the steady demand for patients and the site staff to screen them, research itself is more complex. Nuanced protocol designs for personalized medicines are adding heavy burdens, including stricter inclusion and exclusion criteria as well as federally mandated requirements for population representation. Biomarker-driven trials, which add both logistical and patient recruitment complications to trials, are becoming mainstream with [half of all oncology trials and nearly 20% of all trials using biomarkers](#) today. Further, the number of datapoints generated in Phase III trials is [three times](#) the data collected in late-stage trials a decade ago—at an average of 3.6 million datapoints.

Technology to the Rescue...Sort of?

To compensate for today’s mounting trial complexity, sponsors are turning to technology to improve efficiency and streamline workflows. Technology is having an important positive impact on trials—from accelerating the collection of higher quality data to driving more real-time data monitoring and much more. Yet, despite technology’s abundant benefits, the introduction of disparate point systems into clinical trial settings has resulted in unforeseen burdens on sites. The wide range of site- and sponsor-based systems has created a patchwork that can be difficult to navigate.

Based on feedback from [Advarra’s 2023 Study Activation Survey Report](#), and validated through discussions with 10 experienced sites, a typical oncology study now uses about 22 different systems. For many studies, this number can be even higher with the use of wearable technologies, which are increasingly leveraged in diverse trial applications with [more clinical certifications](#) since the start of the pandemic. This massive proliferation of technology adds to site managers’ already substantial administrative burdens. In fact, nearly two-thirds of respondents in Advarra’s survey said that the burden caused by technology is greater than it was just five years ago (see Figure 1, which displays the various systems that a site would need to access in a sample oncology trial).

Figure 1: Technology Systems Accessed by Sites in an Oncology Clinical Trial



Source: Advarra discussions with 10 experienced oncology clinical trial sites representing a mix of academic medical centers, hospital systems, and site networks.

Interviewed site staff indicated that they have their own organization-wide systems (i.e., human resources, finance, electronic medical/health records), and technology-enabled sites would typically add three more tools such as a clinical trial management system (CTMS), electronic regulatory system, and electronic data capture (EDC) system. Beyond these site systems, sponsors often ask sites to use licenses of their systems for study start-up, study conduct, patient support, endpoints capture, plus some home-grown sponsor systems for randomization and supply chain management.

Given this web of technology, it is not surprising that set-up and training for sponsor-provided technology systems is now the most burdensome site activity, overtaking such traditionally arduous activities as contracting and budgeting. Unfortunately, there's no slowdown in sight, as technology expands. Even as modern technologies have made a measurable impact on U.S. Food and Drug Administration inspection findings by reducing the number of protocol deviations and improving the overall quality of the research, sites are underwater. Worse, the more time site staff spend logging into and navigating disparate systems, the less time they have to work directly with patients and support vital patient recruitment and onboarding efforts.

Sign in Once, Access All

One solution to streamline the site staff's experience is to enable single sign on (SSO) to all site technologies—site practice systems, site research applications, and sponsor-provided tools—through one set of login credentials. More than 80% of respondents in the 2023 Advarra site survey said that being able to use their own site credentials to log in to sponsor-provided systems was “extremely valuable” or “very valuable.”

Recognizing that the challenge of multiple systems and passwords extends more broadly than just sponsor-provided technology, it is not sufficient to centralize on a single vendor's credentials. Fully streamlining the site's experience across all their systems requires SSO capabilities that leverage the site's own credentials. SSO frees site staff from managing and juggling dozens of passwords and increases focus on participant qualification and enrolled participant engagement.

“Large academic medical centers are conducting hundreds of trials for dozens of different sponsors, and this comes with a myriad of systems each with individual login credentials. Many staff require spreadsheets just to keep track of all their different passwords,” said Brian Sevier, PhD, chief operating officer at Yale Center for Clinical Investigation. “Not only does this complexity burden staff and slow trials, but it can also be a security issue such as when working with temporary consultants.”

SSO using an organization’s own credentials has the potential to impact security in several ways. First, it eliminates the need for maintaining a centralized spreadsheet tracker that would provide a threat actor with access to credentials to all site systems in a single location. SSO also enables the automated propagation of employee account deactivation across all site and sponsor systems used on a study at exit. Automated log-in deactivation saves time and reduces staff burden since this is typically a manual process, with a potential time lag. Further, there’s risk for user error in manual system deactivation, opening the site up to potential future security risk.

SSO is a critical step toward achieving a fully connected clinical trial ecosystem, but it’s also just the beginning. Sites can navigate this increasingly complex landscape by identifying the systems that offer the greatest benefit and integrating them seamlessly. Today, different processes and systems often require duplicative effort, making collaboration and real-time decision-making difficult for all stakeholders. In contrast, integrating systems via application programming interfaces (APIs) enables frictionless flow of data and documents across platforms, minimizing duplication of effort and providing a reliable, singular view of all study activities.

Sites, pharmaceutical companies, and technology providers all recognize the value of the connected ecosystem, however, achieving this goal will take time due to variances in the underlying data structures of individual systems. Working with technology providers that have multiple connected components and open APIs for integration with other site and sponsor systems should be prioritized when making technology purchase decisions.

Connect the Disconnect for a Better Future

Technology has had a transformative effect on clinical research but has also brought challenges. Site staff are using spreadsheet trackers to manage lists of systems and passwords across all their

studies. Rather than reduce the number of systems, which would take the industry backwards, improve the technology. Implement SSO using a site's own credentials to streamline the user experience while preserving important technology advantages in areas like data capture, study compliance, information transparency, and more.

Technology is here to stay, so the focus needs to remain on streamlining the site experience. The industry already has the technical capability to align on a single standard for site access to clinical research systems, and that standard should leverage their own credentials, not yet another externally created identity. With more systems coming online regularly, the time to act is now. Without properly corralling and managing this growing ecosystem, we stand to curb clinical research's promising growth.



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SCIENCE & SOCIETY

The Future is Now: Clinical Trials Must Keep Up in the Age of Precision Medicine

Rohit Nambisan, MS, MA



Precision medicine brings about transformational advances in how we treat and prevent disease. As our understanding of biology progresses, we advance our ability to precisely target therapies to individuals with specific variants of broad diseases. The continued evolution of biomarker-driven therapeutics has given rise to unique, novel clinical trial designs that are largely focused on complex rare conditions and indications. This is a level of precision and complexity

that is helping us take important steps forward in our ongoing battle against the most vexing clinical needs.

While this development is overwhelmingly positive, especially for patients, it creates unintended challenges. As clinical sciences rapidly progress, the processes and technologies that are used to run trials have not kept pace. As a result, we endanger critical advancements in patient care.

Evolving Dynamics of Growing Complexity

The complexity of clinical trials has dramatically increased in recent years. Today, more than [3.5 million datapoints](#) are collected for each late-phase trial, which is three times the number that were collected in similar trials just a decade ago. Moreover, these datasets include a growing number of primary and secondary endpoints—averaging 26 for late-phase trials—as well as the specific biomarkers, which are required in half of all oncology studies and in about one in six of other trials.

Additionally, new studies are increasingly focused on niche sub-indications, driven by the need for sponsors to show improved efficacy over existing treatments. As a result, nuances that are often found in rare disease trials are becoming more prevalent across a broader range of trials, increasing operational complexity, especially in patient-finding. For example, in a recent oncology cell therapy [study](#), eligibility was based in part on expression of human leukocyte antigen (HLA)-A*02:01. A *Precision for Medicine* analysis found that prevalence of this antigen varied in different parts of the world, ranging from 38.5% to 53.8% in Europe to 16.8% to 47.5% in North America.

Regulatory guidelines add yet another layer of complexity. For example, the Consolidated Appropriations [Act](#) 2023 (H.R. 2617) recently signed into law now requires sponsors of many trials to submit a diversity action plan to the U.S. Department of Health and Human Services to address the representation disparity that has plagued clinical trials for decades. Patient demographics vary across each disease, making it especially critical for sponsors to effectively represent those disease-specific demographics in their studies. Misrepresentation increases the risk of commercial failure due to low awareness from minority populations, or worse, adverse reactions since the therapies were not rigorously tested across the appropriate patient demographics. Yet, while it is crucial to ensure population representation in trials, it is also difficult to achieve, as it requires sponsors to recruit from a narrower demographic pool.

Heightened complexity also means that trials take longer and are more expensive. Between 2008 and 2019, Phase III participant recruitment timelines [jumped by 39%](#), requiring, on average, a total of 18 months to complete. Recruitment challenges also [commonly](#) lead to delays and can often derail trials entirely.

More Data, More Challenges

The industry's need for more precise data adds to today's clinical research challenges. Sponsors, contract research organizations, and sites struggle to integrate the multitude of disparate datasets from a variety of institutions and systems. A 2023 [survey](#) of trial sites punctuates how the proliferation of systems increasingly burdens trial operations. More than half the respondents indicated that setup and training on sponsor technology is their biggest challenge during a trial,

with 70% of respondents reporting that each of their studies requires six (or more) unique system logins to have access to all the required data.

Inevitably, the industry's collective challenges are increasing costs without commensurate gains in efficiency. Between 2012 and 2022, inflation-adjusted research and development spending [increased by 44%](#), from about \$170 billion to \$247 billion. Yet, during this same period, the number of U.S. novel drug approvals remained flat.

Out With the Old: New AI-Optimized Approaches

Today's obstacles represent an existential threat to our continued ability to engage in effective clinical research. The pharmaceutical industry is naturally driven to follow tightly controlled processes—which, on the one hand, yield repeatable, reproducible performance. Moreover, these ingrained processes are difficult to change without significant upheaval in change management. However, science has progressed and is demanding new approaches from trial operations. What worked in 1990 will not yield the same performance today.

It's time to reconceptualize operations to tackle modern clinical science's complexities, otherwise novel therapies for specialized diseases will remain out of reach for patients in need.

In the past two years, artificial intelligence (AI) has upstaged all technology applications in its ability to transform multiple industries, regardless of domain. Now, AI-optimized approaches can address the substantial challenges facing global clinical research as well.

For example, sponsors can leverage AI-based feasibility analysis that incorporates real-world data, amongst other critical data sources, to make informed and accurate enrollment predictions for their trials. An [analysis](#) by consulting firm McKinsey notes that such tools could result in trial recruitment that is accelerated by as much as 20%. AI-optimized approaches can also help to predict optimal trial sites, troubleshoot problems that might arise before becoming too late to mitigate, and even evaluate latent risks before a trial is launched.

While it impacts change management, utilizing real-world, patient-level data to drive site identification and study forecasts can drive better outcomes. Given the increasing complexity

and costs associated with clinical trials, we should leverage the best possible information on where highly niche patient populations are receiving care, informing recruitment projections and opportunities to access and enroll participant populations. In much the same way that biotech leaders extol the virtue of “failing fast” when it comes to experimental therapies, assessing trial sites for their likelihood of recruiting appropriate participants beyond the scope of investigator feasibility surveys, which typically measure investigator motivation instead of enrollment potential, can save critical time and resources.

Further, consider conducting feasibility analyses regularly during a trial rather than just one time, before the study starts. Automated data tracking solutions can surface accurate insights throughout study conduct so teams can dynamically reassess the trial plan and course-correct at any time. For instance, each time a new country opens, a new site starts recruiting, or there is a market change (i.e., a competitor suddenly goes to market), continuous feasibility analysis identifies how these events impact the trial timelines and budgets. Prescriptive or causal AI models can empower trial managers by recommending scenarios to ameliorate trial performance and explain why the recommendations will produce desired outcomes.

Conclusion

We should no longer force yesterday’s one-size-fits-all approach onto biotech’s third wave of advanced drug development. As precision medicine effectively makes every trial today a rare disease trial, the operations of these trials must keep pace or else we squander today’s most promising clinical advancements. By embracing AI-optimized approaches, we can improve operations and ensure that decades of scientific innovation achieve the ultimate goal: improving the human condition.



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DATA & DEVELOPMENTS

New Big Data Strategies Will Drive Improvements to Personalized Medicine

Stephan Ohnmacht, PhD



The potential of personalized medicine presents an opportunity for life sciences to leverage big data to target therapies to specific patients better. With artificial intelligence (AI) and machine learning technologies continuing to develop, research and development teams can finally bring this vision of personalized medicine to life, provided that the data they are using are clean, standardized, interpretable, and secure.

Understanding a treatment's potential for a specific patient requires biopharmaceutical companies to bring together data from multiple disparate sources. Some sources, like patient demographics, electronic medical records, and quality-of-life scores, will be consistent across all therapeutic areas. However, most of these data sources—including genetic information, imaging, and activity data from wearable devices—will be unique to each individual. With personalized treatments, clinical effectiveness and safety profiles will vary from patient to patient, so relevant stakeholders must be able to trust the data to make medical and business decisions confidently.

A new approach to quality, ownership, and interoperability will ensure the data are useful, even when working with millions of datapoints. Biopharmaceutical companies are also rethinking existing ways of working to get to first-time-right submissions. With access to a clean data foundation, they can identify which functional areas are most important in accelerating time to market so that patients get the innovative treatments they need sooner.

Getting Treatments to Patients Faster

In the past, data collection initiatives have been broad in scope and ambition, ranging from sequencing, imaging, and electronic health record data to text-based data, such as interactions with health authorities and conference abstracts. These initiatives strived to achieve data completeness, but the scale of datapoints collected made it challenging to develop useable insights.

Now, the go-to-market and approval requirements for personalized treatments are highly complex. Biopharmaceutical companies are looking to use their study data appropriately earlier in the process, shifting focus from data collection to governance and ownership. This shift in control and oversight will change the companies' relationships and contracts with third parties. In turn, connected technology is becoming critical, as it allows relevant stakeholders to maintain constant visibility into the data rather than waiting for data to be shared in specific meta-data formats or final text-based documents.

With clean data, biopharmaceutical companies can more easily pinpoint the inefficiencies most detrimental to the clinical development phase—a vital step in lessening time to market so that personalized medicines remain commercially viable. Analyzing data on the cycle times between two critical clinical milestones could determine where inefficiencies and operational challenges typically arise, whether during protocol design, site selection, or elsewhere. With a single source of accurate data, companies can gain a competitive advantage by improving decision-making on patent filings, patient recruitment, or efficiency gains in outsourcing, procurement, or portfolio rationalization.

While analytical and data science capabilities have improved, limitations remain. Raw data are not standardized, and limited reference models exist. However, if common pain points around cleaning, ownership, and standards can be resolved, data will be more plentiful and accessible. Establishing a data model with stringent user access controls is essential to address privacy and cyber-security concerns.

Clean Data are Useful Data

When prioritizing data initiatives, clarity of purpose is key. Suppose the primary goal is significantly reducing the time from “first patient, first visit” to database lock. In that case, selecting a group of experts before data are collected and cleaned to decide the approach and exact use cases is the best approach. Data scientists, subject matter experts, and even external experts (e.g., healthcare professionals, key opinion leaders) could all take part in these decisions and test hypotheses for this key clinical development milestone.

For many organizations, the problem is not assembling the right talent and technology, but rather effective governance. Solving this may require collaboration between functions that typically don’t interact, such as research and information technology, and certainly requires commitment from leadership. Testing different working models can help narrow the options to one that best suits the company’s culture.

Once roles and responsibilities are established, align people, processes, and technology to the broader corporate goals, problem statements, and hypotheses. Ensuring resource flexibility is key. For example, an urgent drug safety issue might have immediate clinical and downstream commercial repercussions for a company, meaning that the right experts must be available to tackle it. Having clean data from a single source is critical so that all the stakeholders, from statisticians to chemists, can work efficiently to get back on track.

As the use cases for big data are defined and executed, collaboration between teams within organizations will improve as they all work toward the goal of effective, personalized medicine. The result will be higher-quality documentation, reduced cycle times, and more right-first-time submissions. The growing need for direct data application programming interfaces with regulatory and health authorities, contract research organizations, and other third parties could lead to more cooperation and faster regulatory decisions. That’s good news for biopharmaceutical organizations and patients who stand to benefit from the treatments.

The Wide Reach of Smarter Data Use

Developing personalized medicines challenges even the most efficient research and development functions due to the associated costs and risks. Smarter data use will help organizations better manage the complex drug development journey and identify which issue to solve first.

Personalized medicine isn't the only area that stands to benefit from big data that are clean, standardized, and interoperable. Other possibilities include finding novel biological targets or new patient populations. Eventually, a centralized approach to data management could support the long-held ambition of connecting real-world data—such as patient data, electronic medical records, and digital therapeutics—to clinical development, improving the patient experience. Fundamentally, these advances with big data move us toward the shared goal of providing life-enhancing medicines to patients who need them.

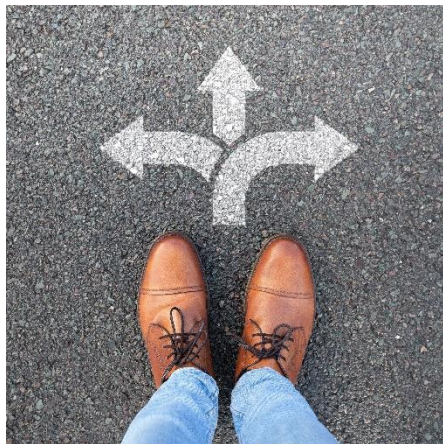


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GOOD MANAGEMENT PRACTICE

Does Risk-Based Quality Management (RBQM) Actually Improve Quality?

Steve Young, MA



Over the past 10 years we have seen a lot of progress in risk-based quality management (RBQM) adoption across the industry. This has rightly led to questions about its impact.

Is RBQM working? Is it supporting the primary mission of improving quality in clinical trials?

To answer these questions, we need to understand the limitations of traditional approaches to quality and explore the latest evidence which demonstrates how the components of centralized monitoring are helping to find the errors that matter.

Traditional Approaches to Quality Management

We know traditional approaches to quality management have been largely ineffective and inefficient. A 2014 analysis of clinical data from 1,168 trials found that only 1.1% of all data entered into electronic data capture (EDC) systems by sites was corrected as a result of 100% source data verification (SDV).^{1} All quality reviews combined resulted in corrections to 3.7% of EDC. This included EDC auto-queries (1.4%) and all other reviews—data management, medical/safety monitoring, biostatistical reviews, etc. (1.2%).

This does not mean these approaches do not add value; however, it does raise questions as to whether we have been finding the errors that really matter.

In the past, we were using very visual, unguided manual reviews. Today, RBQM allows us to leverage the advanced analytics of centralized monitoring, which is much more effective at spotting potential issues more quickly.

The Key Components of Centralized Monitoring

Centralized monitoring ideally consists of three key components—statistical data monitoring (SDM), key risk indicators (KRIs), and quality tolerance limits (QTLs). SDM is an unsupervised analysis running statistical tests across all of the clinical data to expose systemic risk patterns your study team may not even have thought about in a pre-study risk assessment. KRIs monitor pre-specified (anticipated) risks at a site or country level while QTLs monitor pre-specified critical risks at the trial level.

Crucially, experience over hundreds of studies has shown that SDM generally finds issues which are more impactful to the potential reliability of study results because they are systemic in nature. Statistical tests can and have been designed to run across all of the clinical data in a study. Those tests generate p -values—a measure of how different a given site is on each parameter than all other sites in the trial. The lower the p -value, the more unlikely the observed value of the parameter for the given site.

Hundreds of p -values can be generated for each site on a suitably designed platform. All those scores are then converted into a single site-level score, which is referred to as the site's data inconsistency score (DIS), ranging between 0 and 10. This allows sponsors to quickly identify any sites they should be concerned about, and is simply the negative log of the p -value, so that the higher the score, the more unusual or at-risk your site is for the given test and variable.

Site DIS Progression as a Measure of Quality Improvement

To explore whether SDM is improving quality, we used site DIS progression as a measure of quality improvement. Once you decide to follow up on a site with a high DIS (i.e., at-risk site), the DIS becomes a real marker of quality rather than just an indicator of risk. In particular, you would generally expect follow-up remedial actions to result in a lower DIS score because the site has corrected its behaviors.

For this analysis, we looked at sites that went above the threshold of risks and had risk signals which were followed up by the study team. This could include multiple issues requiring investigation and possibly action. We then compared the DIS when risk signals were opened to the DIS when they were all closed.

We measured two outcomes for this analysis. The first was the proportion of sites with improved quality—the finishing DIS score is lower than it was at the start of the study team follow-up. The second measurement was how much that DIS score improved. For example, if Site A had a DIS of 1.57 when risk signals were opened and 1.04 when all signals were closed, that is a 34% improvement in its DIS (i.e., 1.04 is 34% closer to a perfect score of 0 than 1.57).

The analysis incorporated 159 studies, across a whole range of therapeutic areas and phases. This included 1,111 sites with significant DIS (> 1.3), investigation of 3,651 risk signals, and 7,576 significant observed values. We were also given access to two large studies which had never used SDM, so these were pre-RBQM studies, to use as a comparison.

We found 83% of the sites using SDM had a lower DIS at the point when all risk signals were closed compared with only 56% for all sites in the two comparator studies. Data quality improved by 46% in sites using SDM compared to only 17% in those not using SDM. For sites which were using SDM, similarly positive results were repeated across all therapeutic areas and phases. This provides quantitative evidence that SDM is improving quality.

What is interesting about the two comparator studies is that, if you are not doing anything to address the risk signals found via SDM, you would expect around a 50/50 chance of the DIS improving vs. not improving over time (i.e., random drift), and that is essentially what we observed in this sample.

To give an example from one site among the hundreds we analyzed, the DIS was above the threshold when risk signals were first opened. Two individual risks of interest were surfaced, both of which were real issues which required correction. The first was that half of the study participants had a very high disease response score. Investigation revealed an error in data entry—this was corrected and no additional atypical scores were observed.

The second risk signal was a low volume of drug dispensed for the first two patients at the site. A clinical research associate checked the weighing technique and scale calibration and identified an issue due to a misunderstanding of reporting requirements. This was resolved and there were no additional erroneous results. These corrections meant the individual test scores improved, along with the overall DIS for the site.

Of course, not all risk signals represent an actual issue once they are investigated by the study team. In those cases, you are not necessarily going to get an improvement. It is statistically anomalous, but we have plenty of examples of where that has occurred. That is why we would not expect to see 100% of sites with a lower DIS when risk signals are closed and why 83% is so significant.

Analyzing Key Risk Indicator Outcomes

SDM is not the only component of centralized monitoring helping to drive quality improvement. A similar analysis was conducted on the impact of KRIs using data from the same platform as described earlier. The analysis focused on nine commonly used KRIs, representing categories including safety, compliance, data quality, and enrollment and retention. More than 20 organizations contributed data, allowing analysis of 212 studies and 1,676 sites with KRI risk signals.

Two quality improvement metrics were used for assessment—one based on *p*-value, and one based on a KRI's observed value. Both metrics showed improvement in a vast majority of sites (82.9% for *p*-value, 81.1% for observed KRI value). Additionally, there was a 72.4% improvement toward expected KRI value on average.^{2}

To illustrate what these improvements mean in practice, I have two specific examples.

At one site, the standard KRI of visit-to-electronic case report form (eCRF)-entry cycle time had increased to more than 30 days. The study team opened a risk signal, followed up, and talked to the site, and subsequently the site team members improved their behavior. When the signal was closed, the site's average eCRF entry cycle time had dropped to less than five days.

Another site was not reporting any adverse events when the signal was opened. After the risk signal was followed up, the adverse event reporting improved dramatically, and the site was near the study trend.

Centralized Monitoring Works

The examples shared provide clear, compelling evidence that the use of central monitoring—both KRIs and SDM—is leading to improved behaviors and improved quality outcomes. They contribute to the growing body of evidence demonstrating how RBQM approaches which harness centralized monitoring can improve quality.

Risks detected via SDM and KRIs result in successful remediation and improved quality. This enables site metric values to improve toward nominal expected behavior and sites to become statistically less atypical or at risk.

Central monitoring is a critical component of effective quality oversight. It allows us to detect systemic issues in study conduct—the errors that matter—and identify issues typically missed by traditional methods like SDV or transactional data reviews.

All of this demonstrates how RBQM is an important new weapon in quality oversight.

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INTERNATIONAL INTERLUDE

The Evolution of Access: A Pathway to Multiple Markets

Piety Rocha



As companies seek ways to bring their products to multiple markets, understanding those markets and their regulatory approval process is imperative. Choosing the most appropriate pathway can reduce the burden on both the sponsor and on the health authorities, and potentially expand access to more patients.

One such pathway is the Access Consortium, which was formed in 2007 by four health authorities: Australia's Therapeutic Goods Administration (TGA), Health Canada, Singapore's Health Sciences Authority (HSA), and Swissmedic.^{1} In 2020, following Brexit, the United Kingdom's Medicines and Healthcare products Regulatory Agency joined the Access Consortium.

The Access Consortium was established amid increased globalization and, with it, a growing push toward greater harmonization by aligning regulatory policy approaches, providing joint scientific advice and work-sharing, reducing duplication and the burden on health authorities, and accelerating access to high-quality medicines.^{2,3}

Access Consortium Developments

While the Access Consortium has been in place for 17 years, there are signs that interest in the pathway is gaining momentum. According to the TGA, the first two submissions to all five agencies were approved through the New Active Substances Work-Sharing Initiative (NASWSI) in 2022–23.^{3} In 2023, the TGA approved seven new medicines through the NASWSI. As of June 2023, NASWSI had approved 25 applications.^{4}

In recent years, there have been a number of developments to further strengthen the process. Access now has several active working groups in place to support a range of activities across active substances, generics, information technology architecture, and, most recently, a group dedicated to advanced therapy medicinal products (ATMPs).{5}

In late 2023, Access created the Promise Pilot Pathway to establish a common approach to the criteria for priority review. The pathway applies to products that treat a serious, life-threatening, or severely debilitating condition or where no other treatment is registered or marketed in participating regions. The pathway will be further reviewed after the pilot. Assessment of an application is carried out by one agency with peer review by all participating agencies.{6}

The Agency Review Process

The way the agencies manage work-sharing is to have different agencies than the originating one review each Module within the electronic [Common Technical Document](#) (eCTD) submission, depending on capability, experience, and capacity. The other agencies will review and discuss the assessment reports for these modules and a consolidated list of questions, which are then sent to the marketing authorization holder (MAH) for Modules 2 to 5.{4} The country assigned to specific modules will evaluate the responses and, if necessary, the agencies may prepare an additional list of questions for further clarification, and any remaining country-specific questions will be treated on a national level.{6,7}

Differences between Modules 2 to 5 are accepted, though MAHs are asked to outline any differences in the information they provide to each authority. These will be discussed by participating members to determine if the application is suitable for a work-sharing arrangement.{5}

Module 1 (not part of the CTD) will be reviewed separately by each participating agency, given that it contains country-specific administrative information. At the end of the review period, each authority issues its decision on marketing authorization independently.{4}

Sponsors also can take advantage of predictability of evaluation timelines, which arise agreed to by all participating health authorities before commencing the evaluation.{8} This, together with

a consolidated set of questions, provides MAHs with a clearer timetable of the process from start to finish, helping teams to plan and prepare their organizational strategy.

The Access pathway also gives companies the potential to consider submission to the five markets concurrently with submissions in other markets, which our experience has found would otherwise put too great a burden on busy global pharmaceutical teams that are often faced with competing deadlines, making prioritization challenging.

However, it is important to consider the approach carefully, since as our experience shows, some authorities, for example Singapore's HSA and the TGA, have in the past rejected applications through Access for products approved in the European Union (EU), choosing instead to use other reliance (whereby one national authority takes into account assessments performed by another authority) or comparable overseas pathways.{9}

Therefore, companies should take time to understand what is expected. In addition to an Expression of Interest submitted to each participating health authority, companies interested in the Access pathway can take advantage of technical and logistical pre-submission meetings with the health authorities to clarify expectations.{6}

Planning the Regulatory Pathway

We have seen examples where different evaluation outcomes by each regulator can significantly delay approval when an MAH submits national applications in each country, rather than through the Access Consortium. For example, a pharmaceutical company obtained registration from one of the Access regulators with a post-approval commitment to submit impurity-related information once it became available. However, for the same product, another regulator put a stop clock on the submission until the data were generated, resulting in an 18-month delay to approval. Had the application gone through the Access Consortium, experience would suggest the likelihood of the health authorities coming to an agreement, for example on post-approval commitment, therefore reducing the delay to approval in one Access market.

For the sponsor or MAH, another advantage of the pathway is it reduces the burden on global teams. If applying separately, each team—chemistry/manufacturing/controls, clinical,

preclinical—will face different sets of questions from each jurisdiction, which can result in a constant flow of questions throughout the year, depending on the submission plan. By way of example, one large pharmaceutical company that took a combination product through the Access pathway found that the reduced burden on the global teams—in terms of not having to respond to multiple identical requests for information—allowed them to focus their attention on other priority products. This provided predictability in relation to their internal resourcing needs.

For small companies that don't have large teams, being able to answer just one set of questions can be hugely advantageous.

Companies should understand that Access is a work-sharing initiative, not a harmonized process like the Centralized Procedure in the EU, where there is an agreed assessment report to which all EU member states must adhere. Rather, Access facilitates the review process in the five countries, or however many countries members participate in a given application. Ultimately, each regulator will make its own decision. Indications and final product labeling could be slightly different in each country, but the core evaluation is common.{6} This has similarities to Europe's Decentralized Procedure, where one agency acts as a reference regulatory agency and will evaluate Modules 2 to 5.{10}

Companies considering the Access pathway will also need to allow for the preparation time. While, overall, the process can reduce the burden on global teams, there is an administrative burden to consider since potential applicants will first need to seek permission to begin the process through an Expression of Interest application to participate in work-sharing.{6} The form will need to be sent simultaneously to at least two Access members for their approval in order to adopt the Access pathway.{11} Although Modules 2 to 5 might be harmonized, MAHs may also need to meet country-specific requirements before initiating the process—for example, obtaining an establishment license from Swissmedic to distribute a product in Switzerland or a Good Manufacturing Practice clearance from the TGA for all sites involved.{12,13}

A Triple Advantage

A recent survey found that MAHs that did participate in the Access pathway were largely satisfied with the experience. Participating affiliates surveyed cited several benefits to the process, with 76% saying it

helped them gain experience with a work-sharing pathway, 73% saying it led to near simultaneous approval in multiple countries, 61% saying the review process was shorter compared to national timelines, and 61% saying there were fewer overall questions from the health authorities.{4}

While most health authorities now have reliance programs in place, these are not work-sharing initiatives.{9} It is this work-sharing approach with the potential for simultaneous assessment and approval timelines to allow access to all the markets involved—potentially five different jurisdictions—that separates Access from the reliance programs. This is an advantage both to the individual health authority, reducing workload, and to the MAH, by way of being able to submit one version of the dossier to all participating countries.

This can lead to a vast time saving for busy regulatory affairs teams, which would otherwise have to adapt multiple country-specific dossiers—a process that experience shows can take several months.

Besides the work-sharing benefits, data from the Centre for Innovation in Regulatory Science shows that the median submission gap and median approval time for new active substances approved through Access was faster than for those approved by the individual health authorities.{14}

Conclusion

Work-sharing is a clear benefit to the health authorities, helping to reduce resource pressures. Additionally, products are becoming more complex, which requires specific expertise to handle more innovative biologics and ATMPs. Being able to leverage expertise from other health authorities can help to address some of the skills and staffing gaps.

Most importantly, Access benefits patients by giving them earlier access to medicines that otherwise might take longer to get to the relatively smaller markets that make up the Access Consortium.

Disclaimer

The information provided in this article does not constitute legal advice. PharmaLex and its parent Cencora, Inc., strongly encourage readers to review available information related to the topics discussed herein and to rely on their own experience and expertise in making decisions related thereto.

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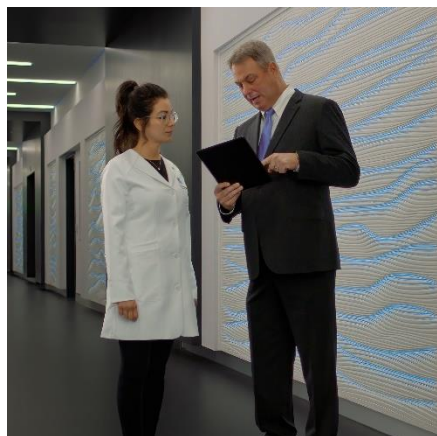


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PRESCRIPTIONS FOR BUSINESS

Establishing Early Efficacy in Depression Clinical Trials

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The most common pathway for developing a new molecular entity (NME) for approval by the U.S. Food and Drug Administration (FDA) is a well-defined process.

The first step is defining a substantive unmet medical need such as COVID-19 or a long-recognized condition like major depressive disorder (MDD). Approximately 30% to 35% of patients with MDD have a form that is not responsive to most currently available oral antidepressants.

The next step is for the biopharmaceutical sponsor to have reason to believe it has discovered a new treatment that may be a significant improvement over existing therapies.

The third step is to apply for patent approval, but in such a way that the filing is recognized by the government even though additional research must be conducted before the patent can be approved. This approach provides the sponsor with protection while the patent is being finalized and allows them additional time to work on the drug without burning through the patent exclusivity.

Preclinical studies must often be conducted before the new treatment can be given to human subjects. These preclinical studies may include *in vitro* (e.g., test tube) or animal research.

If these studies sufficiently demonstrate to the FDA that the investigational product can safely be given to study volunteers, then human testing can begin. It generally, but not always, involves three phases, aptly named Phases I, II, and III.

Phase by Phase

Phase I is usually conducted in healthy volunteers (i.e., they do not have the disease of interest). These studies help determine the pharmacokinetics or concentration of the drug in the body for the doses administered, as well as the safety of the drug in healthy volunteers. However, these studies do not always predict the safety of the drug in patients with the disease of interest. The reason is that participants with the medical condition may be more or less tolerant of the drug, so that different doses could be required.

Phase II trials are generally the initial studies that determine whether the drug has efficacy in the target illness. Everything from preclinical to Phase II studies is termed the “learning phase” of the drug development process.

Phase III trials are large-scale, multisite studies that either confirm what was learned in the early-phase work or demonstrate problems in translating the earlier findings regarding tolerability, safety, or efficacy. Depending on the degree of any issues discovered in Phase III, the drug may advance into regulatory review and possible approval for commercialization, more development work may be needed, or the drug’s development may be halted.

Each step in the above process costs more money and consumes patent life. Both may seriously impair the sponsor’s ability to continue developing the drug. This background is critical to understanding why establishing whether the investigational product is likely to have efficacy as early as possible is so important, as discussed in the rest of this article.

Aiming for Efficacy

There are multiple approaches to establishing a signal for earlier efficacy. Considering the sponsor’s need for volunteer study subjects, many clinical research sites have potential participants in their databases available with known inadequate response to current therapy. These sites can enroll such eligible patients quickly. Further, even a small number of enrolled subjects can test the efficacy of a mechanistically new treatment. The study design should minimize placebo response without compromising the detection of an efficacy signal.

One of the authors of this article conducted a study for an NMDA antagonist with only 15 subjects in each of the two arms of the study: the investigational treatment versus the placebo control.^{1,2} This study provided a blueprint for the successful development of intranasal esketamine for patients with a form of MDD not responsive to biogenic amines (essentially all currently oral antidepressants).

The success of a new drug is ultimately judged by its ability to meet the predefined primary endpoint. In the context of clinical trials for depression treatments, early efficacy refers to evidence indicating that an investigational product shows promise in improving symptoms. This preliminary assessment of efficacy is crucial for gauging the potential effectiveness of the treatment before proceeding to the later stages of the drug development process.

Researchers use rating scales, like the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression-17, to assess how patients respond to the treatment. This endpoint is a specific, measurable outcome chosen by clinicians to determine the treatment's antidepressant effectiveness. Clinical trials typically rely on the MADRS to obtain primary endpoint data in depression studies. The MADRS asks research participants questions about their mood, sleep, appetite, and concentration, providing a standardized assessment of core depression symptoms.

Rater variability, in which different clinicians administering the MADRS score the same depression symptoms differently, can significantly compromise the quality of collected data. To control this risk, psychiatric trial clinicians must first undergo extensive training to ensure consistent and reliable scoring of the various ratings scales among other raters at their own organization and at participating research sites.

Another approach is to use biomarkers as a surrogate for efficacy. For example, all serotonin transport (or re-uptake) inhibitors must inhibit this transporter by 70% to have an antidepressant response.^{2} This biomarker has been successfully used to determine the dose needed in depression efficacy clinical trials.

Further Considerations

Beyond these examples, there are other biomarkers as well as other study designs. These can be used to test whether an investigational drug in early-phase trials will likely be able to show efficacy in the large-scale, multisite Phase III trials needed to obtain regulatory approval.

The neurobiology of underlying MDD has become better defined, resulting in the availability of more biomarkers as well as the potential for earlier efficacy signals. These studies require knowledge of the biology of MDD, the biomarkers that can be used as signals for efficacy, the optimal study design, and the availability of a study population that meets the protocol-specified inclusion and exclusion criteria.

Together with sponsors and sites, we can facilitate the successful development of new and effective treatments for MDD in a time- and cost-efficient way.

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Clinical Development of Preventive Antimicrobials

Brian Finrow, JD



The antimicrobial therapy world is undergoing a pivotal shift toward prevention.^{ 1 } Preventive antimicrobials—in the past, an underexplored concept—are a promising solution to the antibiotic resistance problem. This also represents a paradigm shift in healthcare management—better for patients, payers, and healthcare service providers alike.

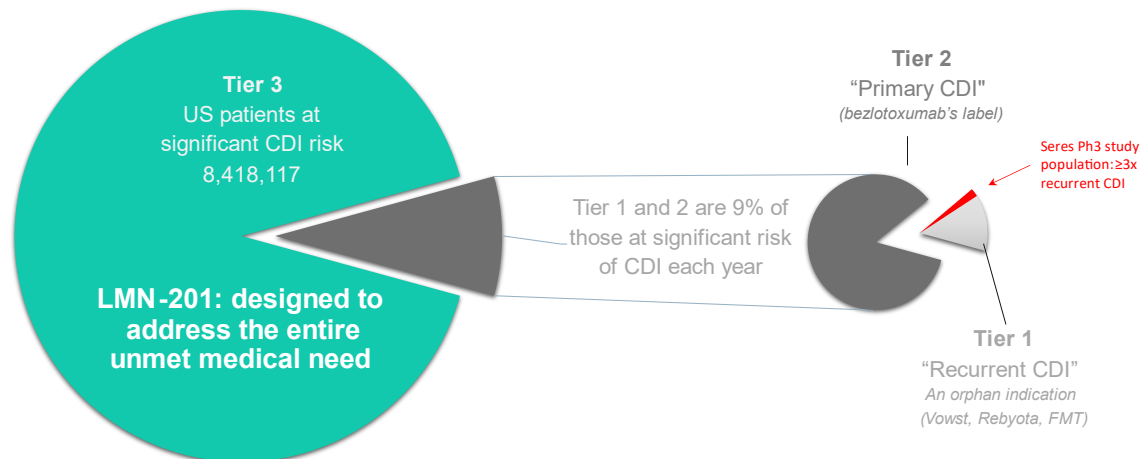
This shift is driven in part by recent advances in cell engineering technology^{ 2 } and the important safety advantages of biologic drugs over their small-molecule cousins. However, not all of the barriers to wider adoption are scientific or biological—this novel therapeutic modality has important clinical, regulatory, and patient recruitment implications.

Commercial Advantages of Preventive Antimicrobials

The market dynamics of preventive antimicrobials differ significantly from conventional treatments (antibiotics, in most cases). This is a good thing for would-be drug developers, as the market incentives for developing novel antibiotics are famously broken.^{ 3 }

In any given disease, the preventive market invariably outstrips the treatment market in size. This is due to the broader base of potential users—essentially, anyone at risk of contracting the disease. The larger total addressable market (TAM, in Silicon Valley’s jargon) for preventive drugs means a broader scope for revenue generation, and a healthier investment case to attract the capital needed to fund development. A larger TAM goes a long way to solving the broken incentives faced by conventional antibiotics (see Figure 1).

Figure 1: The market for a CDI preventive is sensitive to the product’s price, safety, and ease of administration



Key sources: Third-party research commissioned by Lumen Bio; Kazakova, et al. 2020; NHANES 2000-2018 data; Rodrigues, et al. 2017. Model source code and full bibliography available to researchers on request.

Preventive drugs also offer second rationale to support investment, in that they are generally a superior value proposition for patients. This is for obvious reasons—everybody would prefer to avoid a disease in the first place than receive life-saving care after symptom emergence. Since many infections require hugely costly healthcare services to manage, prevention can also generate savings for the healthcare system itself. These are not small numbers—dealing with just one hospital-associated disease, *C. difficile* infection (CDI), is estimated to comprise 2.3% of all U.S. hospital spending.^{4} This amounts to billions of dollars lost to the U.S. economy annually. If you also factor the indirect costs of CDI (premature mortality and morbidity, burden on caregivers and family), the total costs are far larger.

In short, the potential financial rewards for preventive antimicrobials are superior to the daunting economics facing conventional antibiotics. This creates an encouraging opportunity to create a new generation of antimicrobials without undue reliance on public subsidies.

Regulatory and Clinical Development Considerations

These improved commercial prospects do create some unique challenges for regulatory and clinical development, however. Most importantly, the larger TAM comes from the fact that

preventive drugs, by definition, are given to people *at risk* of the disease, which is always a larger number than the number *actively suffering* the disease. In turn, this implies larger clinical trials. Trial size is a major driver of development costs, so this must be confronted honestly when building a business case for a preventive antimicrobial.

There are also regulatory implications. Statistically, the preventive approach involves treating many to benefit a few, raising the bar for safety. Put into health economics terms, the larger TAM translates directly into a higher “number needed to treat” (NNT in the jargon of health economists). The NNT for any preventive drug will always be larger than for an analogous treatment for the same disease.

In turn, a higher NNT effectively raises the bar for safety and tolerability since the product will be used by many healthy people who have not (yet) contracted the disease. Regulators therefore scrutinize these drugs more stringently, necessitating comprehensive trials to demonstrate a favorable risk-benefit ratio. Such trials must be designed meticulously to balance the need for robust data against ethical considerations and practical feasibility. Relatedly, if the TAM and NNT get too large, this can generate concerns about Good Manufacturing Practices production costs, since so many doses must be delivered for each avoided harm.

Resolving the Contradictions

Addressing these challenges requires clear thinking, but fortunately, straightforward solutions do present themselves when looking at certain scenarios.

High-Risk Periods

For example, there are known high-risk periods for many infections, and it’s not hard to identify patients during these times through existing disease surveillance tools. CDI is a great example—it is by far the most common healthcare acquired infection and in most cases is caused by antibiotics. Usually prescribed for something completely unrelated (post-operative infection, for example), many antibiotics kill off the commensal bacteria in the gastrointestinal tract that ordinarily protect us from CDI. This well-documented, close relationship to certain antibiotics makes it very easy to identify the high-risk period from billing codes, since the diagnosis code

predictably follows the codes for certain antibiotics prescriptions. This makes it relatively straightforward to find and enroll patients who stand to benefit. Identifying the risk period for traveler's diarrhea is even easier: one can simply recruit travelers to regions endemic the major pathogenic enteric bacteria, especially enterotoxigenic *E. coli* and *Campylobacter jejuni* (Africa, India, and Central America).

In short, it is not necessary to recruit randomly. Most infections have known risk periods, and it is usually straightforward to recruit individuals because they (or their physicians) are often fully aware of that fact.

Trial Enrichment Opportunities

The U.S. Food and Drug Administration's (FDA's) trial guidance document on trial enrichment is a second good source for inspiration for preventive drug trial design. Again, *C. difficile* is instructive. CDI incidence varies by antibiotic, the nature of the preceding infection for which the causal antibiotic was used, and the health status of the patient.

For example, clindamycin prescribed for an unrelated infection carries a >10% risk,{5} whereas the risks can exceed 50% in the case of antibiotics prescribed for CDI itself in individuals who have experienced multiple prior CDI recurrences.{6} To a first approximation, this translates into a five-times smaller trial in the latter population while holding statistical power constant. While label negotiations are a distinct activity, the FDA's guidance makes clear that enriching the study population in this manner will not necessarily limit the scope of the label if the underlying biological mechanism is understood.

Seres Therapeutics recently pursued exactly this strategy in developing Vowst, its fecal microbiota transplant product for CDI recurrence prevention. Seres' pivotal trial enrolled individuals with at least *three* prior CDI recurrences, enriching their primary endpoint event rate by double (from a more typical CDI recurrence rate of 25% percent to something closer to 50%). Nevertheless, the FDA approved a label for the somewhat broader universe of patients suffering their *first* recurrence.{7}

This idea can be taken too far, however. While increasing statistical power, enrichment can also shrink the recruitable trial population so far that it becomes impossible to find enough patients. If taken too far, it can affect the external validity of the study results and therefore the breadth of the market label that the FDA is ultimately willing to approve.

Nevertheless, the general principle is sound—by focusing on individuals at heightened risk during a defined period, trials can yield more meaningful data while simultaneously decreasing costs and minimizing the number of patients exposed to the investigational drug, delivering a triple win.

Clinical Trial Efficiency

A third area for creative thought is clinical trial efficiency, particularly in terms of designing clinical studies that prioritize participant and clinician experience. This involves treating these stakeholders more like customers in the normal world—ensuring smooth study logistics, building easy-to-use data collection tools, and leveraging decentralized trial techniques. Such an approach can enhance participant engagement, reduce dropout rates, and ensure more representative and robust data collection. All of these expedite trial cadence and cut costs, sometimes dramatically. Where enrichment strategies hit their statistical limits, or concerns about external validity or label breadth limit recourse to enrichment, a focus on trial efficiencies may be essential to affordability.

Fortunately, COVID-19 sparked a significant culture shift in how these tools are viewed by important stakeholders in the clinical trial process. Many essential tools for lower-cost, decentralized trials—including video completion of informed consent, remote collection of patient-reported outcomes data, and virtualized clinical visits—are more now widely accepted by regulators and clinicians than before the pandemic.

While these efficiencies can improve productive for nearly all disease areas, they hold particular promise for preventive drugs. As noted above, these products already have higher standards for safety and tolerability, which makes them a natural fit for decentralized trial techniques given the reliance on less direct means of patient supervision. Further, because distributed trials rely less heavily on in-person site visits, they expand the number of eligible and willing patients. This is

good for enrollment velocity (and therefore, ultimately, trial affordability), but it can also improve study diversity, which in turn improves the external validity of study results. Trial diversity is also an important issue for the FDA and other regulators for reasons of equity and statistical validity, so this represents another important way to improve study affordability while simultaneously improving data quality.

Conclusions

Preventive anti-infective biologics drugs are a significant advance in healthcare, offering a promising solution to the antibiotic-resistance crisis. By shifting the focus from treatment to prevention, they are poised to transform patient care and the economics of healthcare. The challenges in market dynamics, regulatory considerations, and clinical trial design are substantial, yet surmountable with the straightforward application of a few simple techniques.

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