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Accelerating evidence generation: Addressing critical challenges and charting a path forward

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Abstract

Efficient evidence generation to assess the clinical and economic impact of medical therapies is critical amid rising healthcare costs and aging populations. However, drug development and clinical trials remain far too expensive and inefficient for all stakeholders. On October 25–26, 2023, the Duke Clinical Research Institute brought together leaders from academia, industry, government agencies, patient advocacy, and nonprofit organizations to explore how different entities and influencers in drug development and healthcare can realign incentive structures to efficiently accelerate evidence generation that addresses the highest public health needs. Prominent themes surfaced, including competing research priorities and incentives, inadequate representation of patient population in clinical trials, opportunities to better leverage existing technology and infrastructure in trial design, and a need for heightened transparency and accountability in research practices. The group determined that together these elements contribute to an inefficient and costly clinical research enterprise, amplifying disparities in population health and sustaining gaps in evidence that impede advancements in equitable healthcare delivery and outcomes. The goal of addressing the identified challenges is to ultimately make clinical trials faster, more inclusive, and more efficient across diverse communities and settings.

Introduction

Significant advancements have been made in the development of transformative therapies across medical domains. However, the translation of drug discoveries into tangible benefits for patients is limited, with approximately half of investigational drugs entering late-stage clinical development failing to obtain regulatory approval [1]. Challenges persist in evidence generation, especially after drug approval, such as in circumstances when post-approval data are required to verify the predicted clinical benefit for a drug approved under the accelerated approval pathway or when post-approval data are needed to better understand intervention benefits and risks in diverse populations who may have had comparatively limited presentation in clinical trials, or to assess the value of comparative effectiveness of an intervention compared to standard care [2]. In October 2023, the Duke Clinical Research Institute (DCRI) convened leaders from academia, industry, government, patient advocacy, and nonprofits to explore how incentives can be realigned to accelerate evidence generation in clinical research. The discussions underscored the importance of aligning financial incentives for researchers, clinicians, participants, and sponsors, with a focus on incentivizing prevention and quality care implementation for better outcomes. Key themes emerged, including competing research priorities incentives, an inadequately representative clinical trial patient population, opportunities to better leverage existing technology and infrastructure in trial design, and the need for increased transparency and accountability in research practices. Collectively, the group believes that these factors contribute to an inefficient and expensive clinical research enterprise, exacerbating population health disparities and perpetuating evidence gaps.

Program methods and design

The DCRI Think Tanks are quarterly collaborative forums that bring together leading experts from various sectors, including academia, industry, patient advocacy, nonprofit organizations, and regulatory bodies, to address pressing issues in clinical research, and healthcare innovation. The objective is to focus on identifying and discussing potential solutions to complex problems, advancing methodologies, and shaping policies to enhance the efficiency, quality, and impact of clinical trials and medical research. Topics are selected by DCRI leadership based on collective discussions and agreement within the group, emphasizing the relevance and potential impact of the topics on patient care. Once a topic is chosen, a diverse group of stakeholders is convened to participate in a two-day series of moderated discussions designed to explore the issue from multiple perspectives.

This manuscript summarizes the discussions and key takeaways from the October 2023 session on realigning incentive structures to accelerate evidence generation. The first author identified key themes and actionable items based on the frequency of mention and collective opinion during the meeting, summarized these themes in text, and distributed the summary for review and agreement by all attendees of the Think Tank meeting. A nonsystematic literature review was conducted to identify relevant examples to support key themes.

Barriers to evidence generation

Competing priorities

Efficient evidence generation faces challenges arising from numerous unmet needs and competing priorities across diseases. This fragmentation, paired with a lack of shared clinical trial infrastructure, impedes resource allocation and efficient execution of trials. However, the presence of competing priorities is not insurmountable. The COVID-19 response exemplified both the potential and pitfalls of collaborative efforts and shared infrastructure to advance evidence generation. While most COVID-19 therapeutic trials lacked sufficient power and randomization rates to draw meaningful conclusions [3], the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial was one notable example of effective evidence generation during the pandemic. To investigate multiple treatments for COVID-19 simultaneously, RECOVERY leveraged a pragmatic platform design with adaptive features to add or drop treatment arms. Within 100 days of initiation, RECOVERY demonstrated that dexamethasone could reduce 28-day mortality by up to one-third in hospitalized patients requiring oxygen or ventilation support, and the trial went on to support or refute various purported benefits of several additional COVID-19 therapeutics [4].

In the context of the challenges of innumerable unmet needs and competing research priorities, there is a notable lack of consensus within the research community regarding how to determine the most significant public health needs. This determination is vital for optimizing resource allocation and maximizing the impact of investments. The Think Tank group noted that both top-down and bottom-up approaches are needed to shape research priorities and align evidence generation efforts with the most significant public health needs (Figure 1). Top-down approaches involve identifying research priorities from a centralized or authoritative perspective, such as the National Institutes of Health (NIH) setting strategic goals for funding or the Centers for Disease Control and Prevention (CDC) focusing on combating specific public health threats such as opioid addiction or COVID-19. In contrast, bottom-up approaches entail grassroots efforts and community engagement to escalate areas of greatest need that matter most to patients. For example, patient advocacy groups, such as the Cystic Fibrosis Foundation or the Michael J. Fox Foundation for Parkinson's Research, often play a crucial role in highlighting research areas that are most urgent for those living with specific diseases. Elements of both approaches are required to align evidence generation efforts with the most significant public health needs.

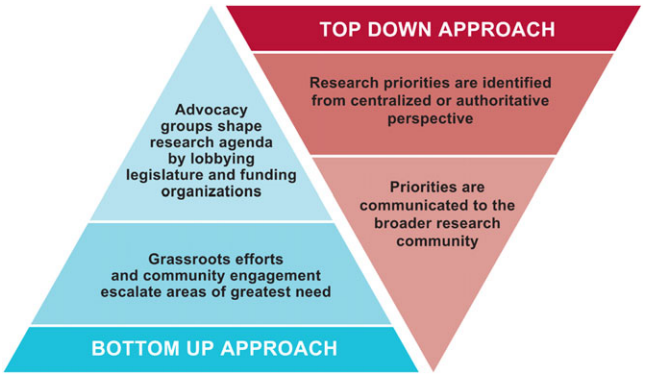


Figure 1. Top-down and bottom-up approaches to determine research priorities.

Competing incentives

The misalignment of incentives in the healthcare system hampers the overarching goal that all stakeholders should share: to improve patient health outcomes and lower healthcare costs. A prime example of this misalignment is the fragmented reimbursement system within the United States (US). Hundreds of private commercial and public payers, such as Medicare and Medicaid, have differing policies regarding services covered and their accessibility for different subpopulations. This fragmentation leads to inconsistencies in patient care and administrative burdens for providers. Moreover, US fee-for-service systems that emphasize volume over value incentivize over-prescription of healthcare services, driving up costs without necessarily resulting in improved patient outcomes. It is estimated that 21%–47% of total healthcare spending in the USA represents wasteful spending, primarily driven by overtreatment and administrative complexities [5].

Therefore, there is a pressing need for a paradigm shift toward sustainable value-based care models where outcomes are intricately linked to financial incentives [6]. Value-based care models, such as accountable care organizations and bundled payment arrangements, focus on rewarding providers for the quality rather than the quantity of care they deliver. This shift can be complemented by data capture aimed at driving improved quality outcomes. For instance, the Center for Medicare and Medicaid Innovation's Enhancing Oncology Model (EOM) is designed to test new payment and service delivery models that aim to improve health outcomes and reduce costs for cancer patients [7]. The EOM focuses on data-driven care coordination and patient-centered approaches, emphasizing the importance of aligning financial incentives with the goal of achieving high-quality, cost-effective care.

Unfortunately, financial incentives for healthcare systems to participate actively in clinical research are lacking. While opportunities exist, private healthcare systems, in contrast to academic or public research organizations, often lack the necessary institutional structures, incentives, and expertise for research [8].

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This is compounded by the resource-intensive nature of research, which may not yield immediate financial returns for private healthcare systems. Similarly, the pharmaceutical industry grapples with reduced profit margins, as evidenced by a decline in the number of new drugs brought through the US Food and Drug Administration in recent years and the failure of the majority of approved drugs to match their research and development costs [9,10]. These financial challenges underscore the critical need to realign incentives to ensure that systems are financially driven to enhance population-level health outcomes and reduce costs.

Inefficient clinical trial design

Randomized controlled trials (RCTs) are the cornerstone of evidence generation to support drug development and regulatory approval. A significant opportunity to improve the evidence generation system lies in optimizing RCT design and integrating real-world data when appropriate. Research protocols that deviate from routine clinical practices pose burdens on both clinicians and participants, contributing to low enrollment and high dropout, hindering the ability to address clinically relevant questions [11]. Moreover, overreliance on rigid and standardized protocols and operating procedures, often driven by perceived risks of regulatory approval failure, exacerbates inefficiency through the overcollection of unnecessary data and application of irrelevant or redundant procedures. Another notable inefficiency lies in the underutilization of preexisting infrastructure. The practice of creating new infrastructure for each study is both inefficient and expensive, diverting resources from potentially more impactful areas.

Inadequate representation of diverse patient populations and patient clinical trial experiences

Inadequate representation of diverse patient populations and their clinical trial experiences remains a significant challenge in evidence generation and leads to poor scientific knowledge of the safety and efficacy of therapeutics in patient subgroups. Despite efforts by the NIH, World Health Organization, and FDA to improve reporting and increase inclusion requirements, minorities and women continue to be underrepresented in clinical trials [12]. Several factors contribute to this issue, including limited access to trial sites, mistrust in the healthcare system, and socioeconomic factors. Overall, patient recruitment is plagued by poor participation and retention rates, with inadequate representation identified as a leading cause for the premature discontinuation of RCTs [13]. Failure to integrate patient experiences into data collection represents a missed opportunity to enhance the clinical trial experience for participants, potentially improving enrollment, retention rates, and ultimately evidence generation [14]. Patient voices and advocacy groups are important forces in driving policy change, maintaining long-term engagement with legislation, and supporting research funding. Leveraging these voices and advocacy groups becomes essential not only for defining priority areas of research but also for understanding how trials can be improved for participants and can support patient recruitment and retention.

Transparency and accountability in research funding allocation and outputs

There is a notable lack of easily accessible data to hold institutions publicly accountable for the quality of their research outputs. Despite well-intentioned initiatives, such as the Blue Ridge Institute for Medical Research (BRIMR), designed to track funding distribution [15], there are notable shortcomings. The BRIMR ranking, while identifying institutions and individual principal investigators receiving the most funding, does not link funding allocations to research outputs, thus failing to ensure that resources are directed toward highly impactful research. The focus on monetarily supporting individual investigators and increasing the number of manuscripts rather than generating impactful research outputs reinforces individualistic approaches.

Another facet of the accountability challenge across the biomedical ecosystem is the continued implementation of underpowered, poorly designed, and poorly executed clinical trials [3]. Alarmingly, an assessment of COVID-19 therapeutic clinical trials showed that 95% of trial arms were not randomized or adequately powered [3]. Underpowered trials not only decrease patient participation but also divert resources from studies with the potential to answer clinically important questions. Conducting or supporting clinical trials with insufficient sample sizes, which are unlikely to yield meaningful results, raises ethical concerns. There must be reevaluation of the research, sponsorship, and funding paradigm, emphasizing the critical need for transparency and accountability to ensure that resources are directed toward research endeavors with the highest likelihood of success in improving healthcare.

Accelerating evidence generation

Define research priorities and align financial incentives with improved population health outcomes

A public health agenda should be developed with input from stakeholders in academia, industry, government, clinical professional societies, patient advocacy groups, and payer organizations, a strategy that incorporates elements of both top-down and bottom-up approaches. For example, the Healthy People 2030 initiative integrated national health objectives with input from local and state health departments to set data-driven core, developmental, and research objectives to improve population health over the next decade [16]. The research priorities identified in public health agendas must be linked to financial incentives that reward improved health outcomes. A critical component of this step is to transition away from fee-for-service based payment models and to choose a value-based payment model that aligns with the identified population health goals and incentivizes value-based care. Additionally, policymakers could implement financial incentives to promote greater participation in research. Alignment between research priorities and financial incentives establishes a symbiotic relationship, wherein the pursuit of better population health is not only made a societal goal but also economically incentivized for stakeholders.

Streamline clinical trial design

Streamlined clinical trial design is critical to ensure that trials provide reliable answers to important questions while minimizing participant and clinician burdens. This approach aims to align clinical trial protocols with routine care when possible by simplifying participant experiences, minimizing enrollment barriers, and reducing duplication of data collection already occurring in routine care settings. The concept of quality by design (QbD) was first applied to clinical trials around 15 years ago. In the context of clinical trials, "quality" can be defined as the absence of errors important to decision making. QbD aims to systematically reduce errors by directing attention to crucial elements of trial

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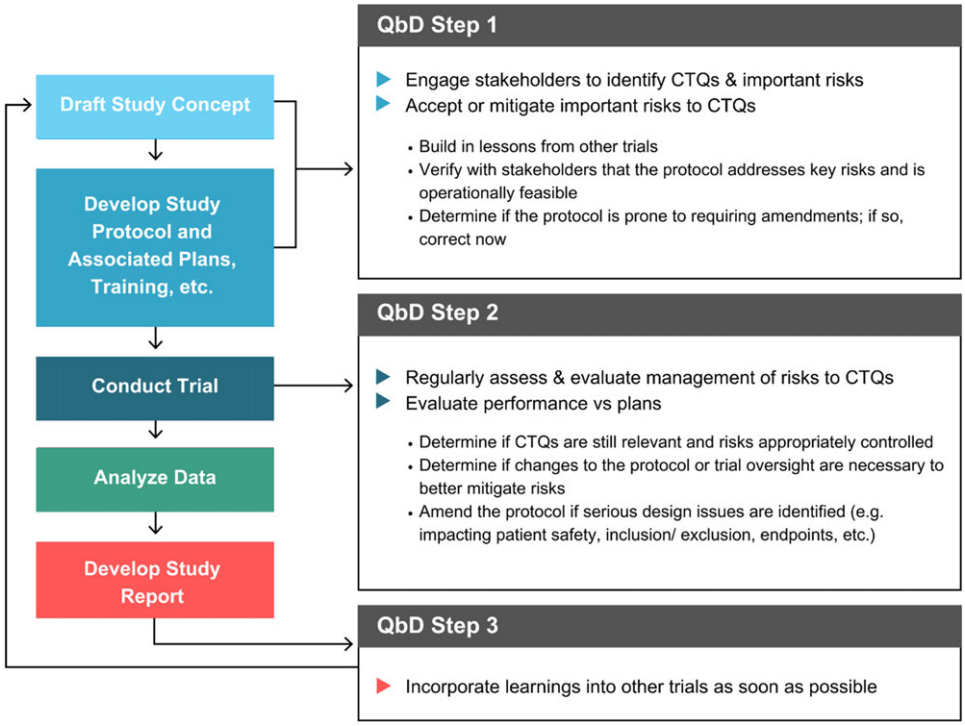


Figure 2. Application of quality by design principles in the clinical trial life cycle. CTQs indicates critical-to-quality factors; QbD = quality by design. Figure reproduced with modifications from Meeker-O'Connell A, Glessner C, Behm M, et al. Enhancing clinical evidence by proactively building quality into clinical trials. Clin trials 2016; 13: 439-444. 20160420. DOI: 10.1177/1740774516643491.

design and oversight while eliminating unnecessary procedures that may divert focus from critical components [17]. It emphasizes the benefits of considering steps to enhance trial quality proactively (i.e., avoiding errors that matter) rather than merely relying on post hoc monitoring (i.e., looking for faults after they have already occurred) (Figure 2) [17]. It is time for a profound change in our approach to clinical trial design. Instead of focusing on which aspects to remove from existing designs, we should begin with a clean slate, guided by QbD principles, to pinpoint only the essential components necessary to address the clinical question.

Additionally, advances in technology and artificial intelligence could play important roles in streamlining clinical trial processes. First, when real-world data are appropriate, electronic health record data could be leveraged as outcomes in pragmatic clinical trials conducted at the point of care, as the volume of data amassed in everyday clinical practice surpasses what can be collected through clinical trials. Second, technology should be leveraged to facilitate more efficient enrollment and diversity in clinical trials. This should be done with careful consideration to avoid inadvertently excluding underrepresented populations with overuse of technology. Initiatives such as the Patient and Provider Assessment of Lipid Management (PALM) study, which employed video-based consent, underscore the potential of technology to recruit a more diverse participant demographic, including older, Black, and less health-literate individuals [18].

Diversify clinical trials and prioritize patient-centric approaches

Enrolling more diverse patient populations in clinical trials and prioritizing patient-centric approaches are essential for creating more inclusive trials with generalizable results. Initiatives to educate patients about their role in research design and conduct are essential. Conveying the broader benefits of participation beyond individual health outcomes engages participants and illustrates how their contribution advances medical knowledge. Moreover, actively soliciting feedback from participants and including patient representatives in trial design are vital to improve the patient experience and address barriers to enrollment and retention.

Decentralized clinical trials (DCTs) and mobile technology present promising opportunities to enhance patient engagement in research. DCTs offer several advantages over traditional trials, including reducing the burden of in-person visits, thereby improving recruitment and retention, especially for underrepresented groups such as elderly individuals, low-income populations, and ethnic minority groups. Moreover, research-oriented platforms that incorporate consent, surveys, and other customizable modules provide an infrastructure for conducting remote mobile-based research trials. These mobile methods can expedite research enrollment rates, as exemplified by Stanford researchers in the MyHeart Counts Cardiovascular Health Study, who used a mobile application to collect informed consent from 48,968 participants between March and October 2015, a level of enrollment unattainable through traditional methods [19].

Enhance accountability in research participation and transparency in research progress

A key strategy to enhance accountability in research participation and transparency involves investing in public reporting mechanisms that measure the quantity and quality of research outputs. One existing metric is the NIH's relative citation ratio for publications, which assesses the scientific impact of articles by normalizing their citations per year against those received by NIH-

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Table 1. Key themes and calls to action to accelerate evidence generation

Key Themes	Call to Action
Competing priorities and incentives	• Develop a public health agenda with input from stakeholders in academia, industry, government, clinical professional societies, patient advocacy groups, and payer organizations • Link research priorities to financial incentives that reward improved health outcomes
Inefficient clinical trial design	• Minimize participant and clinician burdens to participation in research • Allow QbD principles to guide clinical trial design and pinpoint only the essential components necessary to address the clinical question • Leverage electronic health record data as outcomes in pragmatic clinical trials when appropriate • Leverage existing clinical trial infrastructure whenever possible
Inadequate representation of diverse patient populations and patient clinical trial experiences	• Prioritize patient-centric approaches through active solicitation of feedback from participants and patient representatives • Engage patients and patient advocacy groups in trial design • Adopt elements of decentralized trials and mobile technology to reduce participation burden
Transparency and accountability in research funding allocation and outputs	• Invest in public reporting mechanisms that measure the quantity and quality of research outputs • Share organizational experiences, both positive and negative, to facilitate vicarious learning within the research community • Hold institutions accountable for timely reporting of clinical trial results

QbD = quality by design.

funded papers in the same field and year [20]. Enhanced adoption of such metrics, along with public reporting of clinical trial elements such as patient recruitment numbers, retention rates, diversity, randomization rates, and statistical power, can encourage the conduct of high-quality trials while discouraging underpowered or poorly designed studies.

Another important aspect of accountability and transparency involves sharing organizational experiences, both positive and negative, to facilitate vicarious learning within the research community. By openly discussing the challenges and successes encountered during the research process, organizations contribute to collective knowledge, promoting continuous improvement. Finally, the timely reporting of clinical trial results is essential to improve transparency. Without comprehensive and timely reporting of both negative and positive findings, the ability to make informed decisions about patient care and future research directions is severely compromised. This multifaceted approach aims to create a transparent and accountable research ecosystem that maximizes the impact of clinical trials in advancing medical knowledge.

Conclusion

Significant challenges impede the seamless translation of scientific innovation into tangible patient benefits. The prevailing state of evidence generation and clinical trial research is marked by critical issues, with a fragmented system at its core, driven by misaligned incentives and individualistic priorities. By addressing the identified challenges, all stakeholders can improve this process so that clinical trials may become faster, more inclusive, and more efficient across diverse communities and settings (Table 1).

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