Trials

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Overcoming the barriers to better evidence generation from clinical trials

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Abstract

Clinical evidence generation from and for representative populations can be improved through increased research access and ease of trial participation. To improve access and participation, a modern trial infrastructure is needed that broadens research into more routine practice. This commentary highlights current barriers, areas of advancement, and actions needed to enable continued transformation toward a modern trial infrastructure for an improved evidence generation system. The focus of this commentary is on the development of medical products (e.g., drugs, devices, biologics) and infrastructure issues within the United States, with the aim to have broader, multi-national applicability.

Keywords Clinical trials, Clinical evidence generation, Clinical trial access, Learning health system, Infrastructure

Background

Clinical trials generate critical evidence on medical products but often fail to inform the care of diverse populations in a range of care settings [1]. Clinical trials should efficiently generate reliable and relevant evidence for populations that will use the studied treatments in the real world. The COVID-19 pandemic exposed limitations in the United States (U.S.) to generate evidence efficiently [2].

Current and former leaders of the U.S. Food and Drug Administration have called for changes to the U.S. clinical trial infrastructure to improve evidence generation. Changes include integration of clinical trial conduct into clinical practice, lessening duplication of efforts and resources [3–9] Changes should also include attention to the principles of *quality by design* (i.e., designing a trial to avoid errors that could have a material impact on trial participants or the quality of study results) [3]. These changes will transform trials toward enhanced research access for participants and sites, enable timely and relevant evidence generation, and ultimately, improve the efficiency of therapy development.

Government agencies and groups globally, such as the Medicines and Healthcare Products Regulatory Agency, European Union, G7, and World Health Organization, are likewise calling for modernizing the clinical trial infrastructure and advancing evidence generation [10–14]. Despite heightened attention, progress remains difficult.

While the current clinical trial system is largely designed to answer questions around investigational products without established efficacy or safety, an updated infrastructure should fill evidence gaps and address pertinent, unanswered questions, such as broadening indications and repurposing approved products [15]. This should be done reliably by maintaining critical trial elements, such as randomization [16]; safely by prioritizing the protection of participants; and efficiently by reducing duplicative activities across trial and care

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settings [17]. The infrastructure should help regulators, health systems, trial funders, insurance companies, sponsors, and patients with decision-making; address the burden of common diseases in diverse real-world populations; and respond rapidly to new disease threats in public health emergencies [13, 18].

Internationally, trials successfully integrated into clinical care are helping to fill evidence gaps and demonstrate efficiency [19, 20]. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed how a pragmatic, randomized adaptive trial can promptly produce evidence for regulatory and clinical decision-making, making relevant results available and translating evidence for effective therapies into clinical practice. The RECOVERY design was simple, practical, and built with quality at its core [3]. Design and quality approaches used in RECOVERY are replicable even in systems less integrated than the United Kingdom's National Health Service and for smaller scale studies, such as rare disease studies. The success of RECOVERY paved the way for initiatives and organizations focused on fundamental, yet modern, principles of clinical trials that embrace flexibility, innovation, and community involvement particularly in addressing common diseases [21].

Examples of randomized trials integrated into clinical care within the U.S. have also demonstrated operational feasibility and prompt evidence generation. Two such examples are the I-SPY and Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) trials [22, 23]. Additionally, the National Institutes of Health (NIH) Pragmatic Trials Collaboratory has supported implementing cost-effective large-scale research studies to efficiently generate high-quality evidence to inform medical decision-making [24, 25].

Transforming trials for better evidence generation requires more than just adopting trials integrated into clinical practice. Building from our collective work in this field, this commentary explores current barriers to trial transformation, areas of progress, and steps to enable an improved clinical evidence generation system. While our focus is on the U.S., similar barriers exist elsewhere; thus, our suggestions may have broader applicability to improving clinical evidence worldwide.

Barriers to trial transformation

Inefficient infrastructure and limited supporting resources impede the ability of health care organizations to incorporate research routinely into clinical practice. In turn, this reflects policy gaps that heighten the cost and limit the feasibility and interest of health care organizations to participate in an improved clinical evidence generation system. Figure 1 illustrates current barriers

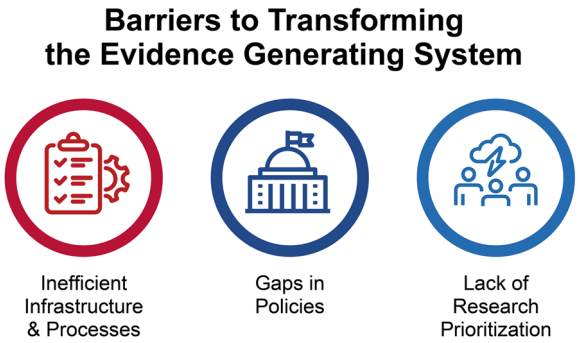

Fig. 1 Barriers to transforming the evidence-generating system

to transforming the evidence-generating system, including inefficient infrastructure, gaps in policy, and a lack of research prioritization. We further address these barriers and note present day solutions below.

Building a more efficient data and research infrastructure

Our current data infrastructure is inefficient, lacking sufficient reliability and accuracy of clinical data captured in routine practice for trial purposes (e.g., for participant identification or to collect outcomes) [26, 27]. This is due in part to technical issues but also substantial administrative processes and lack of data uniformity.

Limited technical interoperability across medical record systems, digital health technologies, and other real-world data sources creates a fragmented data system. Full adoption of standards and open application programming interfaces (APIs) has yet to be realized, preventing streamlined access, authentication, and auditing of data [28]. Both patient and clinical trial capabilities are thus compromised, inefficient, and uncoordinated due to duplicative or missing data.

Reforms in health care payment and progress in medical record interoperability are contributing to a more robust data infrastructure to support longitudinal clinical care. However, regulatory and payment policies for clinical research complicate its integration [29]. Questions also remain whether longitudinal data that are "good enough" for care are also fit-for-purpose for real-world clinical trials [30]. Administrative requirements create operational challenges that discourage trial activation and participation, especially at locations not accustomed to participating in research [31–34]. These requirements include complex budgeting and contracts and varied expectations from institutional review boards, even for trials that involve approved drugs where there is strong evidence on safety and clinical equipoise between arms.

Solutions to minimize administrative burdens include broad use of reusable protocols, master agreements, and central management approaches that are adaptable

Table 1 Barriers and needed actions to transform the evidence-generating system

Barrier	Needed actions and existing examples	Proposed drivers
Inefficient data infrastructure		
Data protections, integrity, and interoperability	Advance ability to leverage EHR and other RWD sources by: • establishing common ontologies and standard data exchange system (e.g., USCDI + /FHIR) • creating a common data infrastructure usable across unrelated and diverse clinical sites • assessing for impact of missing data through completeness and accuracy checks • developing algorithms to increase trust in data quality • clarifying the distinctions between endpoints constructed from clinical data that have not been acceptable for trials • safeguarding personal health information (PHI) on a common platform when accessed by multiple parties (e.g., TEFCA compliant systems, implementation of tokenization)	• Office of the National Coordinator for Health IT • Regulatory agencies (e.g., FDA) • Data curators and platform developers (including EHR vendors)
Data flow and sharing	Improve data processes to enable: • sponsors and partners to conduct appropriate data queries (e.g., NIH Pragmatic Trials Collaboratory's Data, Tools, and Conduct) • collection of a minimal set of necessary data elements that better reflect routine practice (e.g., RECOVERY trial; REMAP-CAP trial) • data sharing with regulators in an acceptable, appropriate and consolidated format (e.g., Sentinel Initiative)	• National Institutes of Health (NIH) • Data curators and platform developers (including EHR vendors)
Inefficient research processes		
Trial capacity management	Support trial innovation and site readiness to: • establish a continuous pipeline of trials so that research is sustainable • maintain trial capacity for efficient response to health emergencies	• Funders (NIH, ARPA-H, FDA, BARDA) • Health system leadership • Medical product developers
Master agreements	Streamline administrative processes by: • establishing master agreements that enable reusable infrastructure, appropriate data sharing and reduced start-ups costs • leveraging central coordinating centers and single institutional review boards (IRBs) to allow for a broader range of sites to engage in trial opportunities (see NIH's sIRB policy; CTTI sIRB and Trials in Clinical Practice resources)	• Health system leadership • Medical product developers • NIH
Policy reform to support transformation		
Appropriate risk-proportionate regulatory pathways	Embrace risk proportionality and trial oversight clarification while maintaining protection of patients, to: • enable a risk-based monitoring approach • delineate and standardize principal investigator oversight at the whole-institution level to reduce bureaucracy (e.g., Form 1572 revision) • simplify reporting of drug dispensation and consider allowing tracking through EHR • adjust training expectations for participating providers based on risk and support systems	• FDA • Office for Human Research Protections • Health system leadership
GCP renovation	Update GCP standards through international guidance to: • drive principle-based approaches (e.g., ICH E6 R3) • better account for flexibility	• International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use • FDA

Table 1 (continued)

Barrier	Needed actions and existing examples	Proposed drivers
Consent modernization	• Evaluate optionality and adequacy of consent methods in trials that leverage pragmatic, decentralized and point-of-care approaches (see CTTI Planning Decentralized Trial recommendations, MRCT IRB considerations for DCT) • Address concerns related to waiver or modification of informed consent and broad consent	• Medical product developers • Office for Human Research Protections • Institutional review boards/independent ethics committee • Patients
Reviewer and inspector collaboration	Align reviewer and inspector expectations	• Regulatory agency leadership
Addressing the lack of research prioritization		
Value of research	Align research questions and clinical care interests to support evidence generation. Support: • continuous learning and decision making (see CTTI Trials in Clinical Practice recommendations) • patient and participating health care provider input into research questions and study design • a shared understanding that knowledge generation is a continuous process informed by research and care	• Health system leadership • Medical product developers • Patients
Cost	Invest in building a sustainable, reusable clinical research infrastructure by supporting: • additional provider time • trial management activities • data collection and validation efforts (e.g., U.S. Veteran's Affairs Health System)	• Health system leadership • Government agencies • Medical product developers
Lack of incentives	Align incentives by: • enabling quality improvement supports • providing protected research time for providers and patients • leveraging technology to minimize provider and patient burden (i.e., automated data processing where possible) • moving away from "fee for service" and toward accountability to improve outcomes and equity, and reduce health care costs	• Centers for Medicare and Medicaid Services • Health system leadership • Medical product developers • Data and technology providers

CTTI Clinical Trials Transformation Initiative, *EHR* electronic health record, *FDA* United States Food and Drug Administration, *GCP* Good Clinical Practice, *RECOVERY* Randomized Evaluation of COVID-19 Therapy, *REMAP-CAP* Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia, *RWD* real-world data

for future studies. Current trends in health care policies and practices offer solutions toward a data infrastructure that better captures accurate and complete data along a patient's health care journey. The Health Information Technology for Economic and Clinical Health (HITECH) Act and ensuing actions by the Office of the National Coordinator for Health IT (ONC) and Center for Medicare and Medicaid Services (CMS) are driving efforts to increase adoption of interoperable standards in electronic health records (EHRs) [35, 36]. The U.S. Core Data for Interoperability (USCDI) and USCDI + are building on Health Level 7 (HL7) and related standards to create "use cases" that cover an array of clinical care and public health activities, and CMS is increasingly requiring EHRs to support these standards [37].

The CMS, private insurance payers, and states are shifting their payments and care models away from "fee for service" and toward accountability for improving outcomes and equity. These models aim for reducing costs with attention to key clinical and patient-reported outcome measures [38, 39]. The enhanced longitudinal primary care and specialty care integration required to succeed in these models is supporting investments in a more reliable, interoperable health data infrastructure that can power research integrated with care [40].

Policy reform to support transformation

Regulatory policies and reform guidelines should support modernizing trials for efficient evidence generation [41].

The U.S. Food and Drug Administration (FDA), MHRA, and other organizations are modernizing clinical trial guidance aligned with reforms to the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) [11, 42, 43]. ICHE6(R3) initial draft revisions provide a strong start, but additional efforts are needed to ensure focus on principles and purpose rather than process, with an emphasis on generating actionable information about the effects of an intervention [44].

International efforts that focus on the fundamental scientific and ethical principles underpinning randomized trials while embracing flexibility and innovation are critical to these efforts [10, 41, 45, 46].

Further clarification around areas of regulatory flexibility with case examples that support efficient risk–benefit management would also be useful. For example, there are opportunities to clarify investigator oversight requirements and essential record documentation. In the U.S., the FDA Form 1572 Statement of Investigator is commonly used to delegate authority and track information on investigators, sub-investigators, and clinical facilities used in trials [47]. Such attestation is unlikely to materially reduce risk for clinicians who are practicing in organized health systems that are implementing trials through common electronic record and practice support systems. In such cases, Form 1572 is likely more appropriate at the health system level, building from the various codes of practice already in place, such as good documentation, data privacy training, and mentoring. Regulatory clarifications could better delineate the role of providers and staff involved in trial-related work, especially trials integrated at the point of care [26], and standardize this role across whole-institution settings. In addition, clarifications around essential record documentation with an emphasis on fitness for-purpose and proportionality, could support the reduction of unnecessary documentation and reduce burden.

Addressing the lack of research prioritization

While frontline health care providers have a strong interest in assuring that their patients receive well-informed care, incentives to participate in trials are often limited and/or misaligned with clinical care activities.

The lack of participation in trials is partly due to overly complicated trial designs and the burden to conduct them [48, 49]. Additionally, this lack of participation is due to a culture that does not decidedly value high-quality clinical trials as an important component of a high-quality clinical care system and evidence development [50].

Supported by government efforts to address infrastructure and regulatory modernization, health system leadership can play a critical role in driving culture change. Organizations increasingly use electronic data, quality improvement, and safety initiatives to improve care models; therefore, contributing to a "learning health system" is a natural complement to improving patient health and avoiding unnecessary health care costs.

Health system and policy leaders should align around goals to increase access to and expand the conduct of randomized clinical trials integrated into routine clinical care. Health care insurance payers, purchasers, trial sponsors, and health systems should collectively support key clinical questions to fill evidence gaps. Sponsors should engage health care providers and patients early in trial design to ensure that the research question is important and that participation in the trial would not unduly complicate patient care. Regulatory organizations should focus on good trial principles, participant safety, and trial integrity while allowing for flexibility. There should be alignment in and facilitation of efficient, appropriate research training and education that will support research participation. Current initiatives, such as ENRICH-CT, ACT@POC, and the U.S. FDA's C3TI, show promise to address these needs [51–53].

Moving from shared goals for improving evidence generation to practical actions requires recognition of the constraints facing clinical practice today. Health system staff turnover is high [54, 55], creating challenges to devote limited staff time and effort to clinical research even as learning health care concepts spread. However, if the costs of participation are low and the research questions are relevant to their patients, health system executives should strengthen the connection between evidence development and the quality of care in their health systems.

Policies, such as the Patient Protection and Affordable Care Act (ACA) and the CLINICAL TREATMENT Act [56, 57], are enabling action by requiring coverage of routine care related to clinical trial assessments. Additionally, CMS has taken important steps, such as considering participation in a COVID-19 clinical study to be a Quality Improvement activity for the Merit-based Incentive Payment System (MIPS) [58].

While policy changes are underway, more actions and collaborations are needed to enable transformation.

Enabling trial transformation

The technological capabilities, regulatory momentum, and trial design innovations exist to improve the data infrastructure and mitigate administrative, operational, and participation burdens. Yet, strategized efforts and resources will help harness these capabilities toward implementation.

Collaboration, pilot projects, and case examples can address remaining gaps and the challenges highlighted in this commentary [15, 23, 52, 59].

Government agencies can continue to advance policies and reimbursement opportunities. Quality improvement programs, such as MIPS or other Medicare payment initiatives, can support providers who participate in well-designed point-of-care trials that address key questions for Medicare beneficiaries [3]. CMS can also further clarify its support for covering the cost of innovative technologies in well-designed studies in its Coverage with

Evidence Development (CED) program and Transitional Coverage for Emerging Technologies (TCET) initiatives [60, 61].

Health care systems and their practicing clinicians can help build public understanding, trust, and engagement in research to foster better evidence generation.

Sponsors should design trials with a greater focus on quality of data and processes rather than quantity [62]. Particularly for approved drugs with known side effects and interactions, trial data collection should focus on an essential set of data elements, such as major patient risk factors, meaningful endpoints, relevant and serious adverse events, and key concomitant medications [63].

An extensive, guided set of actions are suggested in Table 1. We propose priority actions at the top of each section of the table, specifically around improving trial capacity management, the value of research, data protections, integrity and interoperability, and appropriate risk-proportionate regulatory pathways. With that said, we should strive to address all of the barriers listed to improve our capacity to efficiently generate high-quality, practical evidence from trials.

Conclusion

The time is now for a broad range of stakeholders, including patients, to build the clinical trial enterprise of the future and improve our evidence generation system. More reliable and higher-quality evidence can be generated with the creation of a sustainable system-wide infrastructure, simplified, quality by design trials that integrate with clinical care and reduce duplication of activities, regulatory clarity, and coordinated leadership.

It is imperative that we aim for modernization and do not slip into the way trials were approached pre-COVID-19 just because those paths are easy. Concerted action by health care systems, policy leaders, and industry can accelerate the implementation of integrated clinical trials, with substantial implications for the quality of evidence and health care. We owe it to patients and their providers to work together to transform our trial infrastructure and build a clinical evidence generation system that is responsive to public health needs and ensures that innovation reaches patients safely and efficiently.

Abbreviations

ACA	Affordable Care Act
API	Application programming interface
CED	Coverage with Evidence Development
CMS	Center for Medicare and Medicaid Services
EHR	Electronic health record
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G7	Group of Seven
HITECH	Health Information Technology for Economic and Clinical Health
HL7	Health Level 7
ICH	International Council for Harmonisation
MIPS	Merit-based Incentive Payment System
NIH	National Institutes of Health
ONC	Office of the National Coordinator for Health IT
RECOVERY	Randomized Evaluation of COVID-19 Therapy
REMAP-CAP	Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia
TCET	Transitional Coverage for Emerging Technologies
U.S.	United States
USCDI	United States Core Data for Interoperability
VA	United States Department of Veterans Affairs

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