Duke | MARGOLIS INSTITUTE for Health Policy

Enhancing Adoption of Innovative Clinical Trial Approaches

Hybrid Public Meeting • Kellogg Conference Hotel • Washington, D.C.

March 19, 2024 | 10:00 am – 5:00 pm ET

March 20, 2024 | 12:30 pm – 5:00 pm ET

Meeting Summary

Background

The clinical research community seeks to improve innovative clinical trial methodologies to advance efficiency and ultimately lead to better patient outcomes. The generation of evidence to support approvals of investigational new drugs continues to be complex, with lengthy and costly traditional registration trials, despite decades of work on innovative approaches. Risk aversion and comfort with traditional approaches are reasons that drug developers, contract research organizations, regulators, and others steer away from innovative approaches. However, fit-for-purpose innovative clinical trial approaches can efficiently produce robust evidence that drives the development of critical therapies, especially in cases where traditional clinical trial designs are less feasible. Many initiatives from the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER)—as well as industry and academic partners—have explored the use of pilot studies to foster the utilization of innovative approaches. With the current surge to modernize clinical trial conduct, design, and analysis, parties must work together to move beyond pilot studies toward widespread adoption of innovative approaches. An important step is for adopters of innovative clinical trial approaches to showcase lessons learned, success stories, and opportunities for improvement so that others can benefit from these experiences. Working toward this larger goal of widespread adoption of innovative approaches, on March 19 & 20, 2024, CDER and the Duke-Margolis Institute for Health Policy convened a public workshop to hear perspectives from across the clinical drug development ecosystem. Workshop discussion aimed to better understand shared opportunities for communication and cooperation to enhance the development and adoption of innovative approaches in clinical trials to promote timely and reliable evidence generation on drug safety and efficacy.

Key Themes from Public Workshop

Promoting Change Management to Address Risk Aversion with Innovative Clinical Trials Approaches

Across all sessions of the two-day event, participants expressed that many individuals within their organizations want to use innovative clinical trial approaches, but that risk aversion can be difficult to overcome internally. To address this challenge, organizations can facilitate a culture of consistent transparency and trust. Regulators acknowledged continued efforts—across review divisions and inspectorates—to engage thoughtfully with industry, academic, and other clinical research partners towards aligned expectations for clinical drug development programs. Participants expressed how regulators can further support change management with forward-thinking guidance documents that emphasize core principles without being prescriptive. Drug developers, contract research organizations, and others in clinical research can aim to generate fit-for-purpose evidence rather than to think about compliance with Good Clinical Practice guidelines as a box-checking exercise. Shared examples highlighted successfully developed and applied innovative approaches, where adherence to core principles of a guidance document and clear illustration of the regulatory interpretation might be applied to other drug development programs. Panelists also recommended further distribution of lessons learned from other innovative initiatives created by FDA—including the model-informed drug development and complex innovative trial programs—to bolster clinical development. Increased knowledge and greater transparency on submissions to these programs may help spur interest from potential partners. Another way to support clinical trial design innovation is to adopt concepts fundamental to building quality management into clinical studies, i.e., quality by design. Overcoming risk aversion will take a collective, multi-party effort. Each organization within the lifecycle of a clinical trial can address inertia to change within their own work processes while guided toward common goals to maintain patient safety and data integrity.

Parties hope to learn from others about what innovations worked and what did not work as they consider implementing innovative clinical trial approaches. Panelists discussed specific trials and the contexts that made these trials successful. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial began during a public health emergency, where rapid generation of evidence on potential treatments was needed. Clear and relevant endpoints, streamlined trial procedures, and a culture of collaboration to kickstart the study quickly contributed to the adoption of an innovative approach. This approach was designed to fit into routine clinical care and the trial could recruit large numbers of

patients to consistently and systematically assess potential therapies. The Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis or I-SPY trial was also able to foster a shared, collaborative culture of providers participating in research. Clinical care teams were encouraged to reengineer their workflows to support the research activities, which was critical to the success of the trial, while maintaining high-quality care for the patients involved. Omaveloxolone to treat Friedreich's Ataxia (FA) was another recent successful story of innovation in clinical research. The drug was approved during the pandemic and the situation presented challenges to obtain the necessary confirmatory evidence. The FA Research Alliance, a patient organization, worked with the sponsor and the Critical Path Institute to leverage natural history data as the external control arm of the study. This well-matched control group made the external efficacy data useable.

Sharing experiences and lessons learned from successful and unsuccessful innovative approaches is not simply about replicating successful designs and dismissing the unsuccessful ones. Instead, it aims to develop core principles and constructs in clinical trial innovation that can be applied across various contexts and stimulate further adoption of innovative approaches in drug development. A change in the clinical research culture from private and public parties is needed to foster pre-competitive environments for knowledge-sharing while protecting intellectual property. In addition, the potential remains for more decision-making transparency within an organization when clinical trial innovation is implemented and downstream implications for drug development exist. Sharing reasons that these decisions are accepted or rejected by either their organizations or regulators can help to guide other organizations to improve future innovative study designs.

Meeting participants also wanted more opportunities to engage with regulators on innovative trial approaches. Early touch points for communication provide the opportunity for drug developers to present proposed trial designs, metrics, and key outcomes. Patient organizations, digital health technology developers, and other clinical trial service providers wanted more forums available for their groups to interact with regulators. Implementation of innovation extends beyond the clinical trial sponsor and regulators, with continued spaces needed to bring all parties to the table.

Lastly, FDA and CDER can continue to promote innovation across review divisions, inspectorates, and offices. Enhancing collaboration across the Center; producing thoughtful, practical guidance; and building clear communication pathways to ensure parties are receiving consistent feedback can help mitigate risk aversion and promote innovation.

Expanding Inclusion of the Patient Community

Throughout the meeting, the need for better bidirectional engagement with patient communities was a common thread. Parties were encouraged to ensure that research participants understand how the information collected during the trial will be used, how they can receive results from the clinical trial, and how they can learn of opportunities to participate in future studies. To design clinical research studies that measures outcomes most meaningful to patients, researchers were directed to proactively seek community input to ensure specific barriers to clinical trial participation—including childcare, transportation, technology for remote participation, internet access—are addressed. In addition, parties emphasized the importance of informed consent but suggested moving beyond the one-size-fits-all informed consent document to an approach that better addresses patient needs and concerns, especially as clinical trial designs evolve. This might include the way in which the information is discussed, simplified informed consent documents for studies with minimal potential risk, or new tools or processes to promote greater understanding of the research and better aid in patient decision-making. Promoting ongoing and active research engagement, rather than a limited "one-and-done" approach, can improve the patient experience and help to ensure efficiency in research.

Even with the best intentions for community involvement in research, those conducting clinical trials can place undue burden on communities that are frequently asked to participate in studies. Working to ensure that community research is not too burdensome is critical to respecting communities while still gathering their valued input. To avoid overburdening communities with research activities or leaving them feeling "used," researchers can ensure community relationships care built and well-established before trying to use community resources to fill enrollment quotas. In addition, any technologies used in trials need to be intuitive and accessible, with technical support provided to minimize burden on patients, providers, and community researchers. Enrolling a population that accurately represents the patients intended to be treated with the product is important for building confidence in the data the trial will generate. For research participants, clinical trials may provide an opportunity to access cutting-edge treatments and help these individuals reach a standard-of-care that was not previously available to them. As efforts continue to integrate clinical research with clinical care, a person-centered care framework can reassure patients that the conduct of research will not interfere with meaningful care. Person-centered care focuses on respecting patients as individuals and working to continually integrate patient perspectives and goals, which may include participating in clinical research. Working to ensure

that the patient's goals and preferences are heard is important when discussing research as a component of high-quality clinical care.

Thinking and Working Globally to Harmonize on Innovation

With clinical development programs stretching across borders, the workshop dedicated time to discuss working towards global harmonization on innovative clinical trial practices. Adoption of innovative approaches is uneven globally and there is space for greater alignment across jurisdictions. Leveraging existing forums such as the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) working groups to encourage global alignment on these research priorities continues to be critical to global harmonization. In particular, adaptive clinical trials are one innovative approach where regulatory guidance currently differs across regions. While global harmonization might not always be the immediate or only goal, it is important to think of clinical trial innovation as a global issue given the global nature of data needed for quality evidence generation. Global guidance should be broad enough to be used long term while still meeting the needs of parties and not inhibiting innovation. Continued investment in collaboration is needed to handle complex topics like Artificial Intelligence (AI)/Machine Learning (ML) to avoid silos and ensure patient safety is maintained in the face of new technologies.

Panelists also discussed different priorities for global collaboration alongside the priorities for their regulatory authorities. Health Canada is leveraging the ICH M15 Model-Informed Drug Development General Principles Guideline and is working to adopt risk-based approaches for the assessment of innovation as it applies model-informed drug development. The goal is to use a risk-based framework that enhances communication and uses better criteria to assess risk in innovative approaches. Integrating these newer risk approaches can be challenging but ultimately should permit more innovations being used in trials that regulators oversee. The Pharmaceuticals and Medical Devices Agency, or PMDA, in Japan specifically mentioned looking at decentralized clinical trial innovation for new drugs, selective safety data collection, and the use of registry data for investigational drug studies. The response to the COVID-19 pandemic demonstrated the use of these different trial designs, how they can be appropriately leveraged, and how these lessons should be used for other applications. In the European Union (EU), the ICH E20 working group is focusing on adaptive clinical trial designs. Currently these guidelines can vary by region. As a result, the EU hopes to standardize these guidelines to simplify them for researchers and regulators. Participants emphasized the benefits of conducting international

clinical trials for researchers and patients, and stressed the importance of global collaboration in developing guidelines for newer, innovative trial designs.

Closing the Gap Between Clinical Care and Clinical Research

Effective adoption of many innovative approaches will require integration of clinical research into existing and future clinical care settings. Considerations for clinical research can account for how provider education, physical and data infrastructure, staffing needs, financial resources, and other elements of clinical care will interplay with trial design, conduct, and analysis. Barriers and opportunities exist to bridge the divide between clinical care and clinical research to realize greater adoption of innovative approaches. Barriers to integrating clinical care and research include workforce shortages, tasks that are time-consuming and minimally beneficial, education needed on research methods and insufficient financial support. Simplifying parts of the clinical research process can support more effective integration of research into care, while maintaining emphasis on integrity, ethics, and safety. One example is reducing the burden of adverse event documentation through selective safety data collection. A modernized clinical research infrastructure can also promote collection and potential repurposing of data, where appropriate, to support the efficient use of personnel, resources, and technology. Investment in key components, such as data collection, adjudication, and/or validation of extraneous data to reduce redundancies and re-engineer workflows, can support research tasks in clinical care settings. Finally, creating more opportunities for the existing and future clinical workforce to learn about research opportunities may help address workforce shortages and provide feedback from frontline workers for refining clinical workflows.

Another concern discussed was the challenge of ensuring clinicians and sites are not overburdened by clinical research conduct. Many clinicians—especially in primary care—are overworked and asking them to participate in research is not feasible without additional support or accommodations. Sites may want to position research as a care option to their patients but the barrier to entry is too high. Participation in research often entails extra time and costs, such as hiring and training additional staff, making changes in EHR systems, and engaging with insurers to navigate the line between clinical and research activities. Finding innovative solutions to reimburse for research activities and reduce the administrative research burden can help widespread adoption of community trials. For example, one opportunity to consider is to engage payers to support infrastructure that is necessary to conduct trials.

A Roadmap for Wider Adoption of Clinical Trial Innovation

Opportunities to promote wide adoption of clinical trial innovation include building upon FDA's existing work, such as its real-world evidence (RWE) and complex innovative designs programs, to institutionalize innovation across review divisions and inspectorates and contribute to a culture of innovation. This includes creating a "connective tissue" for innovation within CDER and between FDA and other government agencies to support the drug product lifecycle both upstream (e.g., National Institutes of Health [NIH]) and downstream (e.g., Centers for Medicare & Medicaid Services), coupled with consistent messaging about goals regarding innovation in clinical trials. To help communicate these messages, workshop participants said they would like to have product-agnostic listening sessions for public engagement hosted by FDA and other agencies. Creating these pathways of communication between FDA and drug developers to discuss potential innovations and receive feedback from FDA was an ongoing theme throughout the sessions. The opportunity to have early input from regulators can help parties mitigate the risks of different innovations and can make investing resources and time into new innovations more advantageous.

The NIH announced its plan to build out a clinical trials network, which increases research opportunities for both clinicians and patients. This also provides a potential learning opportunity for others to pilot and scale innovative strategies for incorporating research into clinical care. Successful collaborations like those seen in the Friedreich's Ataxia community can serve as an example for fostering partnerships to innovate clinical trials. Another effort highlighted included continued work on building out Diversity Action Plans and ensuring they complement other efforts to promote diversity and representativeness, including through the inclusion of innovative approaches aimed to reduce the burden of participating in clinical trials. Participants agreed on the need to simultaneously leverage AI/ML tools to support research innovation while also maintaining patient safety and privacy.

Looking to the future, clinical trial innovation is sparking continued interest in drug development and requires sustained communication and collaboration that will transcend single groups of parties. This meeting showcased the need for buy-in from different groups across the clinical development spectrum to create sustainable innovation in trial design, conduct, and analysis. Further forums, both public and private, can facilitate the continued development of a roadmap to promote innovation across the clinical trial enterprise. This future roadmap for clinical trial innovation will involve sustained

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communication and collaboration across parties. It is crucial to build on the FDA's existing pilots and programs to move from proof-of-concept to implementation at scale, and thoughtfully further integrate these efforts across therapeutic areas and drug development programs. While more work needs to be done and the success of clinical trial innovation relies on cross-sector collaboration, this workshop provided a foundation for where to start pursuing changes. CDER will be using its new Center for Clinical Trial Innovation as a hub for this collaboration and encourages others to move in this direction as well.

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