

## 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

### Discussion Guide

#### Background

The desire for rapid modernization of clinical trial approaches, methods, and tools was reinvigorated as a result of the COVID-19 pandemic and has prompted stakeholders across the enterprise to engage on how best to further support innovation in clinical trial design and conduct. In recognition of this surge in interest, **the purpose of this workshop is 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 effectiveness.**

The goals of the workshop are to:

- Identify key challenges or barriers, perceived or actual, that hinder greater adoption of innovative approaches in clinical trial design, conduct, and analysis.
- Share best practices and lessons learned, as well as identify priority areas for improvement in the clinical trial ecosystem.
- Explore ways to expand from conceptual awareness to greater adoption and implementation of innovative clinical trial designs and operational approaches.
- Identify actionable next steps that the Center for Drug Evaluation and Research (CDER), within the U.S. Food and Drug Administration (FDA), can take in concert with other stakeholders to advance the adoption of innovative trial approaches.

The formalization of clinical trial research took shape around the middle of the 20<sup>th</sup> Century as research ethics evolved alongside medical and clinical research advancements. The Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act in 1962 enabled the U.S. Food and Drug Administration (FDA) to require efficacy testing of drugs through “adequate and well-controlled investigations.” The FDA and other global regulatory authorities have also joined together with pharmaceutical industry representatives to solidify regulatory requirements across jurisdictions. In 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established and has developed guidelines on safety, quality, efficacy, and multidisciplinary topics.<sup>1</sup> Chief among these guidelines were standards for Good Clinical Practice (GCP) to be used in processes across the clinical trial lifecycle to facilitate the mutual acceptance of clinical trial data by regulatory authorities across jurisdictions. The most recent update to GCP emerged with the publication of the E6(R3) draft

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<sup>1</sup> International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). <https://www.ich.org/page/history>

guideline.<sup>2</sup> Notably, the updated E6(R3) draft guideline recommends the adoption of a risk-proportionate approach to quality management with adherence to principles of quality by design. This is partly in recognition that clinical trial complexity has vastly expanded over recent decades, creating the opportunity and necessity to determine where innovations and efficiency gains are possible without compromising research participant protection or data integrity.

Clinical care has also benefitted from an expansion in evidence-based medicine emphasizing the use of the most current, practice-based data to improve clinical decision-making. Increased use of the most up-to-date data has migrated towards the creation of a learning health system, which is a pragmatic model for health care systems to drive health care improvements at scale. Advances in data analytics and health informatics have provided meaningful progress; however, data quality and quantity, plus persistent infrastructural and systemic barriers hinder broader integration and adoption across health care systems. While these parallel expansions have been evolving together, further efforts are required to better translate the wealth of knowledge gained from biomedical research advances into routine clinical care.

In helping to advance cutting-edge biomedical research to drug development, CDER supports innovation in clinical trials through the publishing of numerous guidance documents, strengthening those efforts with public workshops, working groups, trainings, and partnerships with both public and private entities. Recent guidance topics and development programs pertaining to clinical trial innovation include the implementation and use of decentralized clinical trials (DCTs), digital health technologies (DHTs), real-world evidence (RWE), master protocols, covariate adjustment, and methods to increase diversity of clinical trial participants, among other topics. Additional programs target areas of need for the clinical trial enterprise including complex innovative designs (CID), model-informed drug development (MIDD), rare disease endpoint advancement (RDEA), patient-focused drug development, and Drug Development Tool Qualifications. While these guidance documents and programs have yielded some traction with improved designs and conduct of clinical studies, the speed and spread of the adoption of innovative clinical trial approaches have not yet matched the shared interest of the FDA, industry sponsors, and additional stakeholders.

## Day 1

### Session 1: Evolution of Clinical Trial Research and the Current State of Trial Innovation

Over recent decades, a variety of efforts have emerged across the clinical trial landscape including increasing the diversity of clinical trial participants; adopting, implementing, and integrating innovative methods and approaches for gaining the necessary safety and efficacy evidence; and developing guidance documents and policies to assure evidence generation with these innovative approaches fulfills regulatory requirements. Decentralized clinical trials are gaining popularity as they permit trial-related activities to occur outside of specialized sites. This was particularly evident during the COVID-19

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<sup>2</sup> International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (2023). Guideline for Good Clinical Practice E6(R3) Draft Version. [ICH E6\(R3\) DraftGuideline 2023\\_0519.pdf](#).

global pandemic.<sup>3</sup> Similarly, research at the point of care facilitates more accessible clinical studies with greater integration to care in usual practice settings, and may improve alignment to financial considerations for clinical care to incentivize the conduct of research.

Sponsors, contract research organizations, patient groups, regulators, and other leaders have also sought to increase patient input in the design and conduct of trials from very early stages, partly in an effort to increase feasibility, lower burden, and improve recruitment and retention. This focus on patient-centricity and efforts to improve the patient experience are partially responsible for the use of DCTs and DHTs. DHTs can capture different indicators and metrics for patients thus reducing the time, effort, and burden of trial participants who may no longer need to make as frequent trips to a clinical trial site. Remote assessments may also help encourage participation of rural populations who otherwise would have been excluded due to the distance to and frequency of trial visits.<sup>4</sup> Stakeholders have also long been interested in using real-world data (RWD) and RWE to gain a better understanding of how different interventions perform in everyday clinical care. Using RWE, when appropriate, may answer research questions in a more rapid and generalizable manner than traditional clinical trials. To reduce costs and more rapidly identify problems across clinical trial sites and settings, sponsors and other clinical trial vendors have turned to remote and/or centralized monitoring of trial-related activities for many years.

#### *Discussion Questions*

1. How have milestones in drug development, regulatory guidance, digital health, real-world data, and other areas led to greater innovation in clinical trials? What examples best illustrate the advancements?
2. What new emerging technologies, tools, or methods to implement trials have the potential to make sustainable differences in health care? How are these innovations impacting the design and conduct of trials?
3. How can the continued push to improve representation in clinical trials synergize with enhanced adoption of innovative approaches?
4. Where have innovative approaches made the most progress and how can we best transfer learnings to build upon these successes?
5. Building on existing public-private partnerships, how can stakeholders continue to promote lasting clinical trial advancements?

## Session 2: Regulatory and Compliance Considerations

Regulations form the foundation for clinical trial study design and conduct. With the evolution of the clinical trial enterprise outpacing updates to existing regulations, guidance on regulatory interpretation and additional supporting mechanisms are needed to account for the increasing variety of clinical trial approaches. Guidance documents are important for understanding FDA's interpretation of regulations

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<sup>3</sup> U.S. Food And Drug Administration. (2023). The evolving role of decentralized clinical trials and digital health technologies. <https://www.fda.gov/drugs/news-events-human-drugs/evolving-role-decentralized-clinical-trials-and-digital-health-technologies>

<sup>4</sup> Mittermaier, M., Venkatesh, K. P., & Kvedar, J. C. (2023). Digital health technology in clinical trials. *NPJ digital medicine*, 6(1), 88. <https://doi.org/10.1038/s41746-023-00841-8>

and set expectations for clinical development. Recently published and updated guidance documents have been informative but further work is needed to operationalize the principles in the current clinical trial landscape. A non-exhaustive list of recently updated FDA guidance documents related to clinical development are available in the Appendix. Trials have unique designs, endpoints, and infrastructure considerations that often cannot be detailed in guidance or regulations, which understandably have to be more generally applicable. The roles and responsibilities of sponsors, principal investigators, sub investigators, other trial staff, service vendors, and local health care practitioners have been cited as areas that need more clarity with non-traditional clinical trial approaches.

While there are numerous benefits to the increased use of multiple innovative approaches, there are additional considerations needed to account for the increasing complexity of operationalizing multiple innovations and the number of data sources used in these approaches and their impact on patients, investigators, and investigative sites. Assuring data quality and integrity will require, among other things, modernizing data standards to ensure data are fit-for-purpose and interoperable. FDA programs and initiatives have provided guidance and entry points for conversations to address regulatory uncertainty, however, further efforts and more detailed advice are needed so guidance can be incorporated into research activities. More experience with RWD and RWE submitted as part of applications for marketing approval may lead to additional understanding on when such approaches are fit-for-purpose.

#### *Discussion Questions*

1. How have stakeholders been implementing the principles from recently issued guidance documents on Good Clinical Practice, decentralized trials, digital health technologies, real-world data/evidence, etc.?
2. What are some promising practices for traditional and non-traditional clinical trial stakeholders to effectively engage with regulators early in the process to ensure innovative approaches achieve regulatory objectives?
3. How can risk thresholds across industries be communicated and aligned to overcome perceived and real barriers to innovation?
4. What lessons have we learned from continued efforts to incorporate a variety of data sources, care settings, health systems, and patient groups into clinical trials?

#### **Session 3: Patient-Centric and Recruitment Considerations**

Patients have been rightfully viewed as the primary stakeholder of clinical studies; however, many patients are still not reached by the existing clinical trial ecosystem, and the patient perspective is not effectively integrated into all trials. FDA recognizes that patients can use their own lived experiences to inform the therapeutic context for drug development and evaluation. In 2012, FDA established the Patient-Focused Drug Development (PFDD) initiative to more systematically obtain the patient perspective on specific diseases and their currently available treatments. PFDD meetings are designed to gain patient input on the most significant symptoms of their condition, the impact of the condition on daily life, and the current approaches to treatment. FDA is also developing a series of methodological PFDD guidance documents on the collection of patient experience data and the use of such data and related information in drug development and decision-making. Entities like the Patient-Centered Outcomes and Research Institute (PCORI) have also strived to help patients feel more informed about their health care decisions. PCORI seeks to empower patients and others with actionable health care

choices, in part through being the leading funder of comparative clinical effectiveness research in the U.S. Since its creation in 2010 by Congress, PCORI has led with a well-rounded approach to centering patient needs in generating and using evidence from clinical studies.

Trust and buy-in from patients come downstream from their early engagement in clinical trial design and conduct. There also needs to be clear communication around the process for informed consent and transparency on what's being done with data acquired from the patient. Engagement may be helped by technological advancements but also requires accounting for the human factors that go into deciding whether or not to participate in a trial. Bringing trials to the patient through the use of telemedicine, mobile units, retail health, wearables, patient-reported outcomes, and ensuring no out of pocket costs all may contribute to a greater patient-centric design. Recruitment for trials is also bolstered by prioritizing diversity with the end goal being an enrolled patient population that best matches the use of a product after marketing approval.

#### *Discussion Questions*

1. How can patients be engaged earlier in clinical trial design to ensure trials address the most relevant outcomes and concerns?
2. Where have patient-centric solutions using digital technology, home trial services, and other mechanisms improved patient recruitment and retention? And what are some key factors in creating a seamless experience for participants, from recruitment through to follow-up?
3. Beyond recruitment, enrollment, and retention what are best practices for patient engagement throughout the lifecycle of innovative clinical research? Are there specific times within the trial design and conduct where patient input can be most impactful?
4. How has the informed consent process evolved to address new considerations with the introduction of innovative trial designs and approaches?
5. What unique patient considerations are inherent when conducting master protocol designed studies with multiple targeted therapies for a single disease?

#### Session 4: Infrastructure and Organizational Considerations

Implementation of new clinical trial approaches and innovations in the clinical trial workflow from site selection, patient recruitment, and data collection, to analysis and reporting relies on the technical infrastructure and organizational culture throughout the clinical trial enterprise, which exists in the broader health care ecosystem. Diversification of trial settings through decentralized trials, use of digital health technology tools, and other innovations have showcased the opportunity to expand organizational capacity. This is well aligned with the goal of increasing the participation of underrepresented patients in clinical research by advancing community-centric approaches. Community-based practice involvement in clinical research is being boosted by pilot projects such as the Equitable Breakthroughs in Medicine Development (EQBMED),<sup>5</sup> which seeks greater partnerships between academic medical centers and community leaders to bring clinical trial sites closer to patients.

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<sup>5</sup> Johnson, T., Nunez-Smith, M., Suttiratana, S., Lew, S., Linnander, E. & Curry, L. A. (2024). Equitable Breakthroughs in Medicine Site Maturity Assessment. New Haven, CT: Yale School of Medicine. <https://medicine.yale.edu/ycci/researchspectrum/collab/equitable-breakthroughs-medicine-development/>

A greater understanding of the infrastructural and organizational needs of these community-based sites are vital for assuring data quality and integrity are maintained, as well as participant safety. All of these factors drive the risk management of clinical trial sponsors and participating organizations that can be thoughtfully implemented with quality by design and risk-based monitoring principles. In addition, organizational culture shifts fostered by effective change management are needed to facilitate innovative approaches sustainably implemented at scale.

#### *Discussion Questions*

1. What operational approaches, digital technologies, data standards, and other human factors are needed to broaden the adoption of innovative clinical trial designs to community-based sites?
2. How can the technical, operational, and organizational changes needed to support innovative approaches to clinical trials be best communicated across a variety of sites and settings?
3. What lessons have been learned from the implementation of digital tools and technologies for remote data acquisition and monitoring?
4. How can we best measure and evaluate the performance of community-based sites based on site readiness preparations, study and data management, and quality and ethical oversight?
5. What actionable steps can be taken to assist in promoting an organizational culture that is conducive to adopting innovative clinical trial approaches?

## Day 2

### Session 5: Global Regulatory Collaboration on Clinical Trial Innovation

Recognizing the benefits of innovations in clinical trials, regulatory authorities have made significant efforts to provide guidance and programs to encourage further development and adoption. For example, advances in guidance regarding the conduct of decentralized trials have been issued across the European Medicines Agency, the Pharmaceuticals and Medical Device Agency, the FDA, and other authoritative bodies. Noting that clinical trials are generally conducted across clinical sites spanning multiple geographical areas and countries, alignment among regulators will need to be considered to support advancements in clinical trials due to the various laws, regulations, and jurisdictional differences involved. Global harmonization and collaboration by regulators and pharmaceutical industry representatives in organizations like ICH is possible and has enabled greater efficiency, diversity, and consistency in regulatory standards and practices.

The importance of working together across jurisdictions is heightened by the vast evolution of the clinical trial approaches. Adherence to updated GCP guidelines may involve working together on how to approach the modernization of clinical trial designs and data standards. Harmonization efforts like the Pharmaceutical Inspection Co-operation Scheme (PIC/S) have developed common standards in Good Manufacturing Practices.<sup>6</sup> Additionally, it may take working across jurisdictions to realize improved opportunities for alignment on the use of complex and innovative designs, digital health technologies, artificial intelligence, and machine learning. Building on previous international collaborations and forging stronger relationships among regulatory bodies worldwide will be essential to facilitate the

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<sup>6</sup> Gouveia, B. G., Rijo, P., Gonçalo, T. S., & Reis, C. P. (2015). Good manufacturing practices for medicinal products for human use. *Journal of pharmacy & bioallied sciences*, 7(2), 87–96. <https://doi.org/10.4103/0975-7406.154424>

widespread acceptance and adoption of advancements in clinical trials, ensuring that innovative methodologies and technologies can benefit patients globally.

#### *Discussion Questions*

1. How have existing guidance documents been updated in response to the innovative designs and conduct of clinical studies?
2. What value has been realized by international collaborations to advance and harmonize innovative trials across jurisdictions?
3. How have initiatives within your organizations sought to address perceived and real barriers most present in your jurisdiction?
4. How has collaboration between regulators and clinical trial sponsors contributed to international harmonization? What forums and mechanisms have been utilized to maximize public feedback?
5. Where do you anticipate seeing the greatest progress and challenges with global regulatory collaboration in the next few years?

### Session 6: Collaborations Across Industries to Leverage Innovation

There have been numerous examples of clinical trial innovation in action that have been facilitated by stakeholders from different sectors working across boundaries. The Veterans Health Administration has pioneered the use of point-of-care trials within their integrated system.<sup>7</sup> The Foundation for the National Institutes of Health utilized an adaptive, platform trial to evaluate several therapeutic agents against COVID-19.<sup>8</sup> Flatiron Health has leveraged digital solutions and fit-for-purpose RWD via a community-based research network to optimize study management, site selection, and patient identification. Friends of Cancer Research has explored improvements to oncology clinical studies through leveraging novel biomarkers, supporting use of AI/ML, and including pragmatic trial elements. The Critical Path Institute has successfully developed multiple tools for use in drug development programs in disease areas with unmet needs including Alzheimer's Disease, kidney transplantation, and other therapeutic areas. In addition, organizations such as the Clinical Trials Transformation Initiative (CTTI), TransCelerate BioPharma, and the Reagan-Udall Foundation for the FDA are just a subset of collaborative industry, government, and non-government shared collaborations that have developed recommendations, tools, and best practices.

#### *Discussion Questions*

1. How have industry collaborations served as the cornerstone for your successfully enacted point-of-care, platform, decentralized, and pragmatic trial approaches?
2. How have real-world data helped to optimize clinical trial execution?

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<sup>7</sup> D'Avolio, L. W., Ferguson, R., Goryachev, S., Woods, P., Sabin, T. P., O'Neil, J., Conrad, C. H., Gillon, J., Escalera, J., Brophy, M., Lavori, P. W., & Fiore, L. D. (2012). Implementation of the Department of Veterans Affairs' first point-of-care clinical trial. *Journal of the American Medical Informatics Association*, 19(e1), e170–e176. <https://doi.org/10.1136/amiajnl-2011-000623>

<sup>8</sup> Currier, J. S., Moser, C., Eron, J. J., Chew, K. W., Smith, D. M., Javan, A. C., Wohl, D. A., Daar, E. S., Hughes, M. D., & ACTIV-2/A5401 Study Team (2023). ACTIV-2: A Platform Trial for the Evaluation of Novel Therapeutics for the Treatment of Early COVID-19 in Outpatients. *The Journal of infectious diseases*, 228(Suppl 2), S77–S82. <https://doi.org/10.1093/infdis/jiad246>

3. Where have innovative clinical trial approaches demonstrated benefit in rare disease therapeutic development? And therapies for common, chronic conditions?
4. How have public-private collaborations helped translate innovative clinical trial ideas into action?
5. What have been the biggest stumbling blocks limiting the broader implementation of these innovative approaches, and how do you suggest we overcome them?

## Session 7: Future Directions on Clinical Trial Innovation

The future of clinical trial activities stems in part from harnessing of new and emerging technology to improve the ability of clinical trials to adjust to a variety of settings and conditions aligned with the ever-changing demands of health care. The landscape of clinical trial innovation has been rapidly evolving, driven in part by patient-centered, technologically integrated approaches, and advances in methodology. Furthermore, the necessity for innovation stems from the evolving nature of biomedical science innovations, which are bringing forth new treatment modalities, enabling the targeting of previously undruggable pathways, fostering greater precision medicine approaches, and facilitating the development of truly disease-modifying agents such as cell and gene therapies. New trial approaches incorporating digital tools have the potential to broaden participation to be more inclusive of diverse representation while enhancing the implementation and conduct of fit-for-purpose clinical trials for a wider range of novel treatments and emerging post-approval questions. It is hoped that the integration of advanced technologies can more fully streamline trial processes, patient engagement, and provide more accurate and timely data. However, the successful adoption of these innovative technologies and methodologies will rely in large part on collaboration among all stakeholders, including regulatory bodies, the biopharmaceutical industry, health care providers, and patients. This collective effort will be essential to address challenges related to incorporating new technologies and methodologies, ensuring appropriate ethical considerations, and further advancing clinical research. This final session will focus on priority next steps.

### *Discussion Questions*

1. How can insights from this workshop further advance efforts by CDER and other regulators to promote adoption of innovative clinical trial approaches?
2. What incentives may be leveraged to enhance communication and collaboration among stakeholders across the clinical trial enterprise?
3. How do we best engage new or different clinical trial contributors (e.g. tech companies, non-traditional sites, new third-party vendors) in order to advance novel approaches to the design and conduct of clinical trials, while ensuring rigorous standards that maintain data integrity and quality?
4. Where can more innovative trials be most impactfully used for evidence generation?
5. How can pre-competitive spaces be best designed to facilitate open dialogue on current and future considerations for clinical trial innovation?



Appendix

A selection of recently updated guidance documents pertaining to clinical trial design, conduct, and analysis.

Guidance Title	Draft/Final	Date
<a href="#">Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry</a>	Final	November 2019
<a href="#">Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry</a>	Final	November 2020
<a href="#">Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products</a>	Final	Jan 2021
<a href="#">Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability</a>	Draft	April 2022
<a href="#">Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments</a>	Draft	June 2022
<a href="#">Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making</a>	Draft	April 2023
<a href="#">E8(R1) General Considerations for Clinical Studies</a>	Final	April 2023
<a href="#">Decentralized Clinical Trials for Drugs, Biological Products, and Devices</a>	Draft	May 2023
<a href="#">Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products</a>	Final	May 2023
<a href="#">E6(R3) Good Clinical Practice</a>	Draft	June 2023
<a href="#">Digital Health Technologies for Remote Data Acquisition in Clinical Investigations</a>	Final	December 2023
<a href="#">Master Protocols for Drug and Biological Product Development</a>	Draft	December 2023