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Re: Comment Letter on Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice [Docket No. FDA-2024-D-2052]

Dear Dr. Cavazzoni, Dr. Marks, and Dr. Pazdur:

The FasterCures team at the Milken Institute is honored to provide its response to the Request for Comments on Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice [Docket No. FDA-2024-D-2052].

As a nonprofit, nonpartisan think tank, the Milken Institute believes in the power of capital markets to solve urgent social and economic challenges to improve lives. At the heart of the Institute's work is the idea that societies prosper with an educated, healthy workforce, open and efficient capital markets, and effective social institutions. FasterCures is driven by a singular goal: to save lives by speeding scientific advancements to all patients. For the last 15 years, FasterCures has advanced health equity by advocating for systemic patient engagement in biomedical research by bringing together diverse stakeholders to assess gaps, identify solutions, and develop the tools and resources to support the decision-making of policy stakeholders.

FasterCures applauds the FDA's leadership in issuing a series of guidance documents aimed at enabling innovative approaches to clinical trials. These approaches can improve the speed and quality of evidence generation for medical product evaluation and approval and enable participation by a larger and more diverse pool of populations.[1] The current draft guidance is a welcome step toward progress that the clinical research ecosystem has articulated for years but struggled to achieve—making rigorous research opportunities possible in routine clinical practice and, therefore, accessible to more patients.

For several years, FasterCures has worked to realize the vision of community-based clinical research infrastructure, from a federal perspective to commercial organizations and health systems to the role of data in supporting a participant-centric infrastructure.[2] As outlined in our previous comments on research infrastructure to the White House Office of Science and Technology Policy[3] and in our comments on decentralized trials to the FDA,[4] we

believe clinical research should be accessible and familiar to the people most affected by the diseases or conditions in question, regardless of where they live. A distributed network is necessary to participate in trials and study new medical products with the everyday people who will ultimately use them. This approach increases the ability for treatments to reach communities and community practices more quickly after approval since the innovation is already known to them. It also gives health-care providers confidence in treating their patients with new products since they were tested in populations reflecting real-world settings.

Drawing from years of experience engaging stakeholders advocating for community-based clinical research infrastructure, we want to share the following recommendations for the agency's consideration to strengthen the draft guidance and advance the integration of clinical research and trials in routine clinical practices.

Summary of Recommendations:

1. Ensure the alignment among all guidance documents relevant to conducting clinical trials as part of routine clinical practice and clearly state their relationships.
2. State that sponsors are responsible for designing trials in order to maximize opportunities for the most efficient integration of the trials into routine clinical practice.
3. Clarify how risk-informed quality management defined within the quality by design principle could enhance greater engagement by providers and patients.
4. Emphasize the overarching importance of person-centric research throughout the draft guidance.

Recommendation 1. Ensure the draft guidance is well aligned with related guidance documents and clearly states their relationships.

The FDA has established multiple guidance documents that apply to conducting trials as part of routine clinical practice, enabling broader participation and innovative data collection models.

A few that are most immediately related to the current draft guidance include "Conducting Clinical Trials with Decentralized Elements,"[5] "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products,"[6] and "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products."[7] While none of the guidance documents seem to conflict with one another, it is not easy to consider them together. It would be helpful for stakeholders if these guidance documents were presented as a package, with some discussion of how they are interrelated.

For example, the "Conducting Clinical Trials with Decentralized Elements" guidance specifies a broad range of activities that are considered decentralized elements, such as home testing, remote sensor monitoring, tests conducted by or with local labs and provider offices, or electronic informed consent.[8] It also entrusts a more active role for local health-care providers (HCPs). The guidance acknowledges potential challenges with HCP participation but broadens the venues and activities to include local clinical laboratory facilities, local health-care facilities, mobile research units, visits to trial participants' homes, and direct distribution of investigational products. It also enables the use of telehealth visits to supervise tests that participants conduct at home. Many of these concepts apply to HCPs in the context of trials as part of routine clinical practice as well, and we believe that this level of creativity for HCPs' role could also benefit the current draft guidance.

The guidance on "Real-World Data (RWD): Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products" discusses in depth the aspects of data collection that can be supported through electronic health records (EHRs).[9] Many sections address topics relevant to Routine Clinical Practice guidance, including data capture, distributed networks, unstructured data, or missing data. While the RWD guidance is generally referenced in the current draft guidance, a more direct link, and thoughts on how

data are collected in clinical practice—primarily envisioned through EHR prompts and forms to minimize the burden on HCPs—would be helpful to navigate the complexity of this issue.

"Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" does not call out the role of HCPs, yet when trials are part of routine clinical practice, HCPs will likely contribute a large portion of the RWD used to support a trial.[10] The current draft guidance references this in some ways; however, stitching together how these two guidance documents interact—or do not—would help enable sponsors' confidence to take the perceived risk of conducting trials in a new way.

Recommendation 2. State that sponsors are responsible for designing trials in a way that maximizes opportunities for the most efficient integration of the trials into routine clinical practice.

In Section III.A.1, "Role of Sponsors in Engaging Health Care Institutions," we encourage the FDA to add language to the sponsors' role, clearly stating that they should endeavor to design trials in ways that maximize opportunities to conduct trial-related activities in the most convenient locations for participants and ensure that trial-related activities can be conducted in a streamlined, low-burden way whenever possible. These ideas appear in Section IV, "Using a Quality by Design Approach." Still, it would be important to link this directly to the sponsors' roles and responsibilities in the earlier section. Considerate trial designs can support the trial integration into clinical practice.[11]

Recommendation 3. Clarify how risk-informed quality management defined within the quality by design principle could enhance greater engagement by providers and patients.

The draft guidance strongly advocates that sponsors take a "quality by design" (QbD) approach,[12] devoting one of the two major sections to it. A key principle of QbD is risk-informed quality management. Still, the guidance invokes this idea explicitly only once, in the section introduction, line 267: "Remote (including centralized) and/or onsite monitoring should be risk-based and should address the critical-to-quality factors that are needed to generate reliable results and ensure the safety of participants." The draft guidance might be missing opportunities to clearly call out instances where taking risk-based approaches could facilitate greater engagement by HCPs—and, therefore, by patients—in research.

Recommendation 4. Emphasize the overarching objective of increasing patients' access to research.

A critical reason for integrating trials into routine clinical practice—or any other decentralized and innovative model—is to enable more patients to participate in and benefit from clinical research.[13] Patients can weigh in on more products to improve their relevance, enhance their engagement in their health, and ultimately improve their health. Participating in clinical research and trials might offer an opportunity for many patients to access high-quality care in a way they might not be able to otherwise. This broad level of access also enables more inclusive evidence generation. It allows providers and others to confidently know how to use products in real-world settings for their specific patients.[14]

In the current draft guidance, patients are mentioned only briefly in the introduction. The FDA should seek opportunities to tie the specific trial design suggestions back to one of the cornerstones of this work—enabling access, representation, and relevance of clinical research for everyday people.

For example, the FDA could strengthen Section III.A., "Role of Sponsors, Health Care Institutions, Clinical Investigators, and Local Health Care Providers in RCTs Integrated Into Clinical Practice," by highlighting that sponsors, institutions, and providers have opportunities to more broadly engage patients by integrating patients' priorities and community insights, building familiarity with health and research concepts, and understanding the effects of research in the context of each patient's individual experience. Section III.B., "Streamlining RCTs to Align With Clinical Practice," could incorporate the patient experience of the trial in addition to outlining trial procedures and HCP responsibilities.

We recommend that the FDA emphasize the central importance of person-centric research throughout the draft guidance rather than merely mentioning it without reflecting on the necessary actions that sponsors, institutions, and providers should take in this type of research.

FasterCures welcomes the FDA's draft guidance in advancing clinical trials to be better integrated into routine clinical practice, which is essential to making the trials more inclusive and representative, hence making medical products safer and more effective for the populations they are intended to treat. As long-term advocates and leaders in building community-based clinical research infrastructures, we are deeply committed to promoting the FDA's efforts for more effective and inclusive research and trials.

Sincerely,

Esther Krofah
Executive Vice President, Health
Milken Institute

[1] "Integrating Clinical Research and Clinical Practice," Clinical Trials Transformation Initiative, accessed December 6, 2024, https://ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/integrating-clinical-care/.

[2] "Enabling Networks of Research Infrastructure for Community Health through Clinical Trials (ENRICH-CT)," Milken Institute, accessed December 6, 2024, https://milkeninstitute.org/health/fastercures/improving-rd-environment/community-based-research-infrastructure/enabling-networks-research-infrastructure-community-health-through-clinical-trials-enrich-ct; "Community-Based Research Infrastructure," Milken Institute, accessed December 3, 2024, https://milkeninstitute.org/health/fastercures/improving-rd-environment/community-based-research-infrastructure; Esther Krofah, Freda Lewis-Hall, and Annalisa Jenkins, *Community-Based Infrastructure for Inclusive Research: Democratizing Access to Research* (Milken Institute, November 2024), https://milkeninstitute.org/content-hub/research-and-reports/reports/community-based-infrastructure-democratizing-access-research; Kristin Schneeman and Amanda Wagner Gee, *Community-Based Infrastructure for Inclusive Research: Engaging the Private Sector* (Milken Institute, March 2023), https://milkeninstitute.org/content-hub/research-and-reports/reports/community-based-infrastructure-inclusive-research-engaging-private-sector; Alisha Sud and Kristin Schneeman, *Building Community-Based Infrastructure for Inclusive Research: Lessons from the Pandemic for Federal Action* (Milken Institute, May 2022), https://milkeninstitute.org/content-hub/research-and-reports/reports/building-community-based-infrastructure-inclusive-research-lessons-pandemic-federal-action.

[3] Esther Krofah, "OSTP RFI on Clinical Research Infrastructure and Emergency Clinical Trials," Milken Institute, December 27, 2022, https://milkeninstitute.org/content-hub/government-affairs/comment-letters/ostp-rfi-clinical-research-infrastructure-and-emergency-clinical-trials.

[4] Esther Krofah, "Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials," Milken Institute, May 12, 2023, https://milkeninstitute.org/content-hub/government-affairs/comment-letters/advancing-clinical-and-translational-science-through-accelerating-decentralization-clinical-trials; Esther Krofah, "FDA Draft Guidance on Decentralized Clinical Trials for Drugs, Biological Products, and Devices," Milken Institute, July 31, 2023, https://milkeninstitute.org/content-hub/government-affairs/comment-letters/fda-draft-guidance-decentralized-clinical-trials-drugs-biological-products-and-devices.

[5] "Conducting Clinical Trials with Decentralized Elements," U.S. Food and Drug Administration, September 2024, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements.

[6] "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products," U.S. Food and Drug Administration, July 2024, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory.

[7] "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products," U.S. Food and Drug Administration, August 2023, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug.

[8] "Conducting Clinical Trials with Decentralized Elements."

[9] "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products."

[10] "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products."

[11] "Integrating Clinical Research and Clinical Practice"; Alex Hellman and Kirsten Bibbins-Domingo, *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups* (Washington, D.C.: National Academies Press, 2023).

[12] Lawrence X. Yu, "Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control," *Pharmaceutical Research* 25, no. 10 (July 2008): 2463–2463, https://doi.org/10.1007/s11095-008-9667-3.

[13] Annaleise R. Howard-Jones and Steven A. Webb, "Embedding Clinical Trials within Routine Health-Care Delivery: Challenges and Opportunities," *Journal of Pediatrics and Child Health* 57, no. 4 (March 2021): 474–76, https://doi.org/10.1111/jpc.15354.

[14] Vindell Washington, Joseph B. Franklin, Erich S. Huang, Jessica L. Mega, and Amy P. Abernethy, "Diversity, Equity, and Inclusion in Clinical Research: A Path toward Precision Health for Everyone," *Clinical Pharmacology and Therapeutics* 113, no. 3 (December 15, 2022): 575–84, https://doi.org/10.1002/cpt.2804.