Duke | MARGOLIS CENTER *for* Health Policy

December 14, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: FDA-2023-D-2318 Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

To Whom It May Concern:

The Robert J. Margolis, MD Center for Health Policy at Duke University ("Duke-Margolis" or "the Center") appreciates the opportunity to comment on the Food and Drug Administration's "Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence" ("the draft guidance") document. We are encouraged by the FDA's commitment to advancing evidence generation including through the use of real-world data (RWD) and real-world evidence (RWE).

Established in January 2016, Duke-Margolis is both an academic research center and a policy laboratory where stakeholders can come together to analyze, propose, and evaluate ways to improve health in the United States and beyond. The Center's mission is to improve health and health care value through practical, innovative, and evidence-based policy solutions. By catalyzing Duke University's leading capabilities, we conduct research and convene activities focused on biomedical innovation and regulatory policy. Thought leadership on the regulatory acceptability of RWD and RWE is a dedicated goal for our team.

Duke-Margolis has two complementary programs dedicated to advancing RWD and RWE science and policy for regulatory use. First, under a cooperative agreement with the FDA's Center for Drug Evaluation and Research (CDER), Duke-Margolis has held several expert workshops and public conferences related to RWE and RWD regulatory acceptability. Second, the Center has formed a multi-stakeholder collaboration ("RWE Collaborative") with the intent and goal of strengthening the development and potential applications of RWD and RWE. RWE Collaborative Advisory Group members and their respective organizations are listed the Appendix and are comprised of leaders from health care industries, academia, and others who are developing practical approaches to support the generation and use of regulatory-grade RWE. To date, Duke-Margolis' RWD and RWE activities have spanned several public and private meetings, the convening of multiple working groups, and the publication of eleven major white papers available on our website.

Through this work, Duke-Margolis aims to support collaborative strategies to advance the effective development and use of RWD and RWE. The comments and considerations below represent the thinking and recommendations of expert Center faculty and staff, which have been informed by RWE

Collaborative activities and expertise. Duke-Margolis looks forward to continuing our work with the FDA, the RWE Collaborative, and other stakeholders to move RWE policy forward.

Duke-Margolis, as part of Duke University, honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important and pertinent issues. The Center's comments herein are informed by RWE Collaborative members but may not represent the opinions of every RWE Collaborative member. This comment letter is not intended to limit the ability of RWE Collaborative members to provide their own comments on behalf of their independent organizations.

Our comments herein focus on the potential role of RWD in generating postmarket confirmatory evidence following approval based on substantial evidence from one adequate and well controlled trial. As FDA noted in this draft guidance document, several guidance documents have been recently released by the agency outlining key considerations for the use of RWD/E to inform regulatory decision making. Based on these guidance documents, several RWD sources could be useful to generate postmarket confirmatory evidence (e.g., registries, claims data, electronic health record data) on a case-by-case basis. We support these guidance documents, both draft and final, and early conversations with the relevant review divisions at FDA must lay the foundation for RWD/E to answer research questions in confirmatory settings regarding medical product safety and efficacy.

However, we also believe FDA could provide more specific guidance on the use and appropriateness of RWD to obtain confirmatory RWE. For example, various pragmatic, decentralized, and point-of-care trial approaches leveraging electronic health records, wearables, or other RWD sources could be implemented in post-market settings to provide real-world insight on the benefits and risks of therapies originally approved using one adequate and well controlled study. Guidance from FDA on how best to leverage these approaches to provide actionable insights on newly approved therapies would be helpful.

Additionally, we recommend the final guidance discuss possible strategies for sponsors to leverage or support the development and use of patient and disease registries that are intentionally designed to capture longitudinal, fit-for-purpose RWD on treatment outcomes and provide ongoing confirmatory evidence for newly approved therapies based on one adequate and well controlled study.

Overall, we believe FDA could provide more specific guidance on study mechanisms that the agency might consider, or may have already considered, in real-world treatment settings without being prescriptive. High-quality RWD may be particularly useful in confirmatory settings to supplement common subgroup analysis constraints that may stem from a lack of clinical trial diversity. Also, and importantly, RWD has the potential to fill knowledge gaps related to assessing long-term treatment safety and efficacy in patient subgroups who, for various reasons, may be at a relatively higher risk of poor treatment outcomes due to comorbidities and/or distinct biological, environmental, social, and/or demographic factors. Therefore, we recommend that FDA acknowledge this and extend practical guidance on strategies to evaluate high-risk subgroups for treatment indications/contraindications and other outcomes that may not be observable in one adequate and well controlled study if factors, such as comorbidities, are exclusionary criteria.

We also recognize these issues are not FDA's alone to solve. We particularly encourage trial sponsors and their partners to disseminate compelling use cases that involve generating or leveraging RWE, whether through the Advancing RWE Pilot Program or through another scientific venue or mechanism We welcome opportunities to collaborate with the FDA in this effort, especially along the use case examples herein and other priority use cases on which we are actively working and engaged (i.e., point-of-care trial implementation; subgroup analyses based on the consideration of RWD; RWD relevance, reliability, and quality considerations; etc.).

As the FDA continues to release and update RWE and related guidance, Duke-Margolis looks forward to continuing the advancement of RWD and RWE. We thank the FDA again for the opportunity to offer comments on this draft guidance. Please send any follow-up questions to Rachele Hendricks-Sturrup at rachele.hendricks.sturrup@duke.edu.

Sincerely,

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Appendix

Real-World Evidence Collaborative Advisory Group (as of April 5, 2023)

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