

March 8, 2022

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

RE: FDA-2021-D-1214 Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

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 “Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products” (the “draft guidance”). We are encouraged by FDA’s commitment to advancing 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 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 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 collaborative (“RWE Collaborative”) with the intent and goal to strengthen the development and potential applications of RWD and RWE (member organizations and representative experts are listed in Appendix I). The RWE Collaborative is guided by an advisory group comprised of leaders from healthcare 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 six major white papers available on our website.

Through this work, Duke-Margolis aims to support collaborative strategies that 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 FDA, the RWE Collaborative, and other stakeholders to move RWE policy development 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 focus on the following areas in the guidance:

- **Protocol development and prespecified analyses.**
- **Understanding suitability of data and data selection.**
- **Documenting methodological decisions and establishing dataset audit trails.**

With these areas in mind, we suggest the FDA and other relevant stakeholders act in the near-term on the following steps as this guidance document is revised and implemented:

- **Leveraging existing initiatives that support the transparent development of protocols that do not favor certain data sources over others.**
- **Engage with stakeholders to continue developing and operationalizing processes that involve the documentation of data selection criteria as well as key decisions or factors that inform data selection criteria.**
- **Facilitate policy discussions to continue building the necessary processes, procedures, and transparent steps Sponsors can take to ensure data reliability and relevance.**

Transparency with Protocol Development and Prespecified Analyses.

Registering Studies

Transparency is foundational to the trust and reliability of the data and results submitted to FDA as part of an evidence package submission. Much progress has been made to strengthen RWE study transparency. The Real-World Evidence Transparency Initiative, a partnership between the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Society for Pharmacoepidemiology (ISPE), Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council (NPC), is one example of such work.¹ This initiative advocates for the registration of non-interventional real-world evidence studies for hypothesis evaluation of treatment effects with the goal of fostering routine reporting of protocol amendments and other changes related to study design and results.

This level of transparency will require both understanding key study details, as well as how and when these details are documented. The Real-World Transparency Initiative suggests that protocols should be sufficiently detailed to describe key study characteristics. Additionally, study elements could be made available to FDA and publicly as part of a study registry that includes protocols and analysis plans prior to study initiation similar to clinicaltrials.gov and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) registry. While these are established protocol registries, however, they are most applicable to prospective observational studies and can be cumbersome to use for retrospective studies such as cohort studies. The collaboration between ISPOR, ISPE, Duke-Margolis and NPC has recently established a “RWE Registry” on the Center for Open Science’s registry platform, Open Science Forum.² It is specifically designed to be fit-for-purpose for retrospective database studies, provides a registration number, date-stamping of revisions, and makes

¹Berger ML, Sox H, Willke RJ, et al. Recommendations for Good Procedural Practices for Real World Data Studies of Treatment Effectiveness and/or Comparative Effectiveness Designed to Inform Healthcare Decisions: Report of the joint ISPOR-ISPE Special Task Force on Real World Evidence in Health Care Decision Making. *Value in Health* 2017; 20(8):1003-1008.

²Willke RJ, Wang SV. Registering Study Protocols: Helping RWE Come of Age. *Value & Outcomes Spotlight*. Nov/Dec 2021.

protocol characteristics available to the public, unless designated to be confidential for some specified period. We recommend this as a registration option in the finalized guidance.

Approaches for Documenting Protocol Development

It is critical to demonstrate that a protocol and statistical analysis plan (SAP) are validated prior to reviewing outcome data of interest. Sponsors need to describe the process used to select data sources and provide detailed information on data source characteristics, benefits, and limitations to show that data were not selected advantageously in favor of an outcome or specific study findings. Currently, ongoing dialogue is often needed between FDA and sponsors to ascertain whether data selection influenced or biased the development of study protocols. The FDA could consider the Real-World Transparency Initiative's recommendation of date-stamping the registered study protocol and the provision of both an attestation about the nature of data exploration (e.g., such as feasibility testing for numbers to support power calculation vs outcome rates by exposure) and rationale for these changes to the protocol. Though we recognize that the application of date stamps can be burdensome, the FDA could clarify in the final guidance what level of revisions to the protocol would warrant a new date-stamp.

While there is no "one-size-fits-all" approach for documenting protocol development, there are potentially some early lessons that could inform this process. One example is a staggered protocol approach that entails two-steps. First, there is a submission of a "data agnostic" version of the protocol for provisional FDA sign-off that does not identify the proposed data source(s). This would potentially include relevant inclusion and exclusion criteria, study measures, and proposed analyses. The second step would consist of reporting a more advanced version of the protocol with the data source(s) identified along with supplemental detail on data provenance, governance considerations, and notes on the curation processes from the databases included. It should be noted in the initial stage of this staggered approach, data sources would only be used to inform sample size estimation and statistical power calculations.

If data agnostic protocol development approaches were acceptable to FDA, then a common understanding of the minimum necessary study parameters, including inclusion criteria based on characteristics of the proposed study population, would be helpful to continue building this type of approach. This minimum necessary could also include general information about the type(s) of data sources under consideration. To help inform more novel approaches, like staggered protocol development, we encourage additional clarification from FDA on the minimum necessary study parameters and potential best practices for protocol development to build trust in the use of RWE for regulatory decision-making.

Understanding Suitability of the Data and Data Selection.

There are proposed frameworks that could inform how sponsors develop their data strategies to demonstrate an analytic dataset is fit-for-purpose. The Structured Process to Identify Fit-For-Purpose Data (SPIFD) is one framework to consider, which provides a systematic process for conducting feasibility assessments to determine whether a data source is fit for decision making.³ This framework builds on FDA's framework for its Real-World Evidence Program and the Duke-Margolis Center's framework on fit-for-purpose data reliability by providing an operational process to assess both data

³ Gatto NM, Campbell UB, et al. The Structured Process to Identify Fit-for-Purpose Data: A Data Feasibility Assessment Framework. Clin Pharmacol Ther. Jan 2022.

relevancy and reliability issues, and how to transparently complete documentation for selecting data sources.^{4,5} We applaud this work and encourage more operational approaches that establish transparent steps sponsors can take to clearly document its process for selecting data sources.

Additionally, as we stated in our RWD Standards guidance comment letter, it is important that FDA encourages dialogue with data aggregators and curators that own the data platforms used in sponsors' drug development programs. These stakeholders can provide the technical expertise necessary to clarify and address data review questions and support a more robust Agency understanding of processes and steps taken to curate RWD sources.

Documenting Methodological Decisions and Establishing Dataset Audit Trails.

The draft guidance requires sponsors to conduct the following to demonstrate the suitability of the data: 1) describe in the study protocol all the data sources accessed when designing the study, 2) describe the results from feasibility evaluations or exploratory analyses, and 3) provide justification for selecting or excluding relevant data sources from the study. FDA could consider clarifying how sponsors should describe those data sources in detail. Given the potentially substantial documentation needed to satisfy these three requirements, the FDA might consider having this documentation included in a separate document apart from the protocol to improve readability and overall clarity of the protocol.

This separate document could include the study feasibility assessment and plan for database options along with the criteria for selection. During selection of an appropriate data source, sponsors may reach approach various data providers, some of whom would provide only a rough estimate for feasibility and would be screened out at an early stage. We request clarification on what level of detail would be needed on "all data sources accessed" as well as on the nature of audit trails for accessing data sets. We suggest that FDA provide more detail on defining feasibility work, so it is clear what steps should be taken and when as to not overlap with other components of the protocol including outcome review.

Finally, programming code and algorithm performance metrics should also be included as key documentation to demonstrate the reliability of the submitted RWD. Any associated programming codes and algorithms should be well-documented, annotated, and sufficient for FDA to replicate the study analysis using the same analytic approach when requested. We hope the finalized guidance will provide information surrounding the expectations of how such programming code and algorithms should be submitted to FDA, including relevant standards or best practices for submission. Simply submitting code, even in a way that respects potentially proprietary issues around software and data analytics, may still not be sufficient for replicating the study without deep expertise for evaluating the code.

Study Population Characteristics

The FDA requests sponsors to document and describe how any potential differences between the study population and the population from which the study population was derived might impact outcomes. We request clarification on how to assess and describe potential impacts on outcomes most relevant for FDA reviewers. This is an important methodological consideration that will require time and resources

⁴ U.S. Food and Drug Administration. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products. December 2021.

⁵ Mahendraratnam, N, Silcox, C et al. Determining Real-World Data's Fitness for Use and the Role of Reliability. Duke-Margolis Center for Health Policy. September 2019.

to document how the sponsor defined and examined different study populations along with an explanation of any resulting outcome differences found across study populations. To support this process, we encourage greater use of databases where pre-existing evidence on study populations could be leveraged to minimize de novo testing on each study population to ascertain potential differences. Additionally, differences in patient characteristics may also be attributable to missingness in the data source, and the FDA might consider in the finalized guidance addressing how to manage data missingness and acceptable proxies when defining study populations.

Reporting Adverse Events

While there is growing sponsor experience reporting adverse events with RWD, more clarification on when to report, including parameters for or potential triggers around off label uses of the medical product under investigation, could support more effective planning for safety assessment. It should also be noted that databases from which analytical data sets are derived are often anonymized and some databases do not contain adverse event data. In such cases, sponsors may not have access to information necessary to identify and report adverse events. More clarification is requested for adverse event reporting requirements when utilizing non-interventional studies.

Duke-Margolis hopes to work with sponsors, data curators, and the FDA to advance the development of standards for providing the information the FDA asks for in this guidance document and any future guidance that will be released by the FDA. We look forward to working with the FDA and stakeholders across the field to continue advancing 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-Sturupp. (rachele.hendricks.sturupp@duke.edu).

Sincerely,

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Appendix

Real World Evidence Collaborative Advisory Group Representatives and their member organizations:

Marc Berger -- ISPOR

Elise Berliner -- Cerner Enviza

Barbara Bierer -- The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital & Harvard

Mac Bonafede -- Veradigm

India Bowman -- PatientsLikeMe

Brian Bradbury -- Amgen

Jeff Brown – TriNetx

Adrian Cassidy -- Novartis

William Crown -- The Heller School for Social Policy and Management at Brandeis University

Riad Dirani -- Teva Pharmaceuticals

Nancy Dreyer -- IQVIA

Andrew Emmet -- Pfizer Inc.

John Graham -- GlaxoSmithKline

Ceri Hirst – Bayer

Stacy Holdsworth -- Eli Lilly and Company

Solomon Iyasu -- Merck & Co.

Brad Jordan -- Flatiron Health

Ryan Kilpatrick -- AbbVie

Lisa LaVange -- UNC Gillings School of Global Public Health

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Lauren Silvis -- Tempus

Michael Taylor -- Genentech

David Thompson -- Syneos Health

Richard Willke -- ISPOR

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