Duke | MARGOLIS CENTER *for* Health Policy

February 4, 2022

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

RE: FDA-2021-D-0548 Data Standards for Drug and Biological Product Submissions Containing Real-World Data

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and Drug Administration's "Data Standards for Drug and Biological Product Submissions Containing Real-World Data" (the "draft guidance").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. We hope that our work in this space will continue to be useful and informative to the FDA.

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.

We commend the FDA for its continued advancement of the RWE framework and program. The development of data standards for drug and biological product submissions containing RWD is an important component of appropriate RWE use in regulatory decision making. We have organized our comments by topics areas below. Our primary areas of comment are the following:

- **Improving communication between Sponsors, FDA, and other stakeholders.**
- **Describing the key documentation characteristics desired by FDA for clearly communicating data transformation processes.**
- **Appropriate mapping of RWD to FDA supported submission standards.**
- **Addressing challenges surrounding documentation of data transformations.**

To support FDA's efforts in further clarifying the actions in this draft guidance, we recommend specific steps the Agency could take to build a supported path among the stakeholder community towards the clear and transparent use of RWD sources. Such actions could include convenings, pilot project collaborations, and other types of engagements among the stakeholder community in partnership with the FDA to develop data standards for submissions of study results.

Describing Data Transformations

In addition to our general support for having a multi-disciplinary team, inclusive of data experts, available to discuss data transformation processes, we urge FDA to not yet prescribe specific standards for transformation processes. In lieu of standards, additional guidance is welcomed to help inform the format in which to provide this documentation. Formats might include XML files, data dictionaries, or other types of documentation. One concern we have, regardless of the format, is the broad set of vocabularies included in RWD sources which differ from Clinical Data Interchange Standards Consortium (CDISC)-supported formats. Often vocabularies like SNOMED and RXNorm are used in RWD sources, whereas CDISC standards are specific to MedRA and WHODrug Global vocabularies. We note such differences in vocabularies may result in mapping discrepancies that cause errors in the submitted dataset. Therefore, we suggest FDA support and encourage transparent data mappings across these vocabularies.

We believe more experience is necessary to fully understand the potential impacts of data transformations on the analytic dataset and how to document these impacts. It is beneficial for both FDA and the Sponsor to provide key information on data transformations, including potential impacts, however, this should be done parsimoniously to avoid potential pitfalls associated with providing too much documentation that does not add value to the regulatory review. It would be particularly helpful if the FDA provided an example, possibly in the appendix of the guidance, with a detailed discussion of RWD transformations and the documentation FDA might require as part of the review process. Lastly, we suggest the finalized guidance provide additional clarity on where documentation should be incorporated in the submission, including parameters around the expected rigor of the documentation and best practices for submitting this to FDA.

As experience accumulates across RWD sources, the FDA might also consider providing additional guidance specific to the actions and activities taken by data aggregators and data curators involved with the conduct of data transformations and data mapping to submission standards.

FDA Supported Data Standards for RWD and Considerations for Mapping Study Data

According to the draft guidance, there are potentially a range of approaches that could be applied to transform and map RWD sources to FDA supported data standards. Presently, FDA supported standards, further described in the FDA's Study Data Technical Conformance Guide[i], are primarily developed by CDISC. These standards were developed by industry for purposes of submitting randomized clinical trial results to demonstrate substantial evidence of effectiveness. Given this emphasis on supporting clinical trial data, CDISC standards may define key concepts and terms differently compared to RWD sources.

We appreciate FDA's recognition of the differences in how data elements could be defined and operationalized differently between RWD sources and FDA-supported data standards. For example, definitions like patient visits might be documented differently between a clinical study and within an EHR. In a clinical study, a visit is considered as the clinical encounter based on the schedule specified in the protocol. In an EHR, visits are when patients consult a healthcare provider during a scheduled or an unscheduled visit. Therefore, FDA should carefully consider how its supported standards might fundamentally misalign with the nature of RWD sources and make it difficult to conduct appropriate data mapping.

We acknowledge there are activities underway to improve mapping processes of RWD to CDISC standards. Initiatives such as the CDISC Blue Ribbon Commission[ii] provide helpful resources to the stakeholder community on key challenges and opportunities to appropriately transform and map RWD into FDA supported standards. We applaud this work and encourage more research efforts, and welcome additional guidance that could be disseminated on approaches for data transformation and mapping steps with the goal of improving the stakeholder community's general understanding of how RWE can support regulatory decision making.

There also could be opportunities to evolve the concept and process of how data are submitted to FDA. FDA could prioritize and accelerate the process of updating the data standards catalog with standards outside of CDISC that are specific to and closely aligned with RWD, including the Health Level 7 (HL7) Fast Health Interoperability Resources (FHIR) standard. We are aware of a joint mapping effort between HL7 and CDISC to convert data between HL7 FHIR and CDISC standards[iii], and this mapping tool could serve as an important resource given the flexibility of FHIR to accommodate expanding amounts of digital data from a range of sources potentially not yet envisioned. Any proposed changes to the data standards catalogue should include sufficient time for public comment and transparent due process.

The FDA might also consider developing further guidance on how to appropriately map data standards. Such guidance might address the impact of data mapping approaches on source data, as well as acceptable levels of discrepancies when mapping RWD to submission standards. The latter will be particularly helpful when seeking to address any challenges documenting data transformations and

[i] https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources
[ii] https://www.cdisc.org/about/blue-ribbon-commission
[iii] https://www.cdisc.org/news/cdisc-and-hl7-jointly-release-mapping-guide-facilitate-use-electronic-health-record-data

mappings to submission standards especially when multiple data sources are combined within an analytic dataset.

Addressing Challenges Documenting Data Transformations

The FDA requests information from Sponsors on any challenges encountered during transformations to an FDA-supported data standard in a narrative format. We note there are many validation rules to which Sponsors must comply when mapping traditional clinical trial data to the Study Data Transformation Model (SDTM) standard. Existing validation rules may not apply the same way to RWD sources as traditional clinical trial study results. Additionally, we understand some SDTM validation systems may exclude any data flagged with errors, and this may be a more common occurrence with RWD relative to traditional clinical trials data submissions. More guidance is requested on how to apply SDTM validation rules when utilizing RWD, potentially, as part of FDA's Study Data Conformance Guide.

Communication Between Sponsors, Data Stakeholders, and FDA

Given these challenges and opportunities to leverage RWD sources in support of medical product submissions, we strongly affirm FDA's advice for early industry engagement with the Agency in the development of RWE studies and approaches for submitting study data derived from RWD sources. Of particular interest to the Agency is understanding the processes in place to transform data derived from RWD sources, such as electronic health record and claims data, into an FDA-supported data standard format for submission. The development of such processes requires input from multi-disciplinary teams consisting of methods and technical data expertise. These perspectives could provide key insight across the continuum of data lifecycle stages.

While we support the presence of data technical experts at FDA-Sponsor meetings, the Sponsor should retain its autonomy to make final decisions on who to include in these meetings. The FDA should not prescribe who participates, but it is in the interest of the Sponsor to support the routine interfacing between FDA reviewers and technical data experts who understand the applications of and context around data mappings, transformations, and other curation activities specific to the analytic dataset. As FDA continues to advance the use of RWE in regulatory decision making, it will be important to facilitate communication between the Agency and data aggregators. This collaboration would strengthen review transparency and help ensure the analytic dataset is fit for purpose. Such meetings could be independent of FDA-Sponsor planned review meetings.

Duke | MARGOLIS CENTER for Health Policy

Additional comments and suggested edits

Lines	Current Text	Suggested Change
97-101 101-103 129-131	"…..documentation of these processes may include but are not limited to…." "With adequate documentation of the conformance methods used and their rationale, study data derived from RWD can be transformed…." "Sponsors should also document in their applicable drug submission changes to data to conform to the current FDA-supported data standards…."	It would be particularly helpful to the stakeholder community to have guidance on both what suffices for adequate documentation as well as appropriate transformations and data mappings.
119-121	"Sponsors should discuss early, with appropriate FDA review division, any planned submission of study data derived from RWD sources…."	Sponsors should not be given requirements for who to include in review meetings with FDA. However, there could be opportunities for the Agency to encourage periodic and frequent meetings with Sponsors and data aggregators under the Advancing RWE Program.
168-170	"Sponsors should document data challenges encountered during transformation to an FDA-supported data standard and a justification of their approach to enable the application of an FDA-supported data standard."	In designing approaches to address data challenges, there could be validation rules that help standardize the process. We suggest the Agency provide additional guidance on applicable validation rules for mapping RWD sources to SDTM.
171-174	"….a narrative should be presented in the Study Data Reviewers' Guide, either in the body or as an appendix…."	Given the FDA's intention to review documentation, we suggest the finalized guidance provide additional clarity on where this documentation should be provided in the submission, more parameters around the rigor of this documentation, and best practices for providing this documentation.

Duke-Margolis hopes to work with Sponsors, data curators, and the FDA to advance the development of standards for providing the information FDA asks for in this guidance document and any future guidance that will be released by 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-Sturrup. (rachele.hendricks.sturrup@duke.edu).

Sincerely,

Mark McClellan – Director, Duke-Margolis
Rachele Hendricks-Sturrup, Research Director, Duke-Margolis (rachele.hendricks.sturrup@duke.edu)
Trevan Locke – Research Associate, Duke-Margolis
Adam Aten – Research Associate, Duke-Margolis
Matt D'Ambrosio – Research Assistant, Duke-Margolis

Duke | MARGOLIS CENTER for Health Policy

Appendix

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

Elise Berliner – Cerner Enviza

Marc Berger – ISPOR

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

Mac Bonafede – Veradigm Health

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

Christina Mack – RWE Task Force, ISPE

Elisabeth Oehrlein – National Health Council

Sally Okun – Clinical Trials Transformation Initiative

Bray Patrick-Lake – Evidation Health

Eleanor Perfetto – University of Maryland

Richard Platt – Harvard Medical School

Jeremy Rassen – Aetion

Debra Schaumberg – Evidera

Thomas Seck – Boehringer Ingelheim

Lauren Silvis – Tempus

Michael Taylor – Genentech

David Thompson – Syneos Health

Richard Willke – ISPOR

Marcus Wilson – HealthCore