Duke | MARGOLIS CENTER *for* Health Policy

January 24, 2022

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

**RE: FDA-2020-D-2307: Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision- Making for Drug and Biological Products; Draft Guidance for Industry**

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 "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry" (the "draft guidance").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 the FDA, the RWE Collaborative, and other stakeholders to move RWE policy development forward. We thank the FDA for incorporating Duke-Margolis work into the draft guidance. 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 are pleased by the thoroughness of the guidance despite the complex topics under consideration. In particular, we are glad to see that the importance of prespecifying protocols and analysis plans is included in the guidance. The Real-World Evidence Transparency Initiative's registry[1], a partnership between Duke-Margolis, ISPOR, ISPE, and the National Pharmaceutical Council, may provide a useful vehicle for this information in RWE studies. However, we believe there are a few areas that could use further clarification. We have organized our comments by topic area below. Our primary areas of comment are the following:

- **Highlight the unique strengths and limitations of EHR data and claims data, alone and combined.**
- **Develop resources and convenings to advance data validation approaches and expand on the concept of verification.**
- **Consider implementing a risk-based approach to validation and verification of data elements.**
- **Clarify recommendations for evaluation of missing data.**
- **Collaborate with a broad range of stakeholders to ensure responsible and meaningful data linkage.**

With the comments from these areas in mind, we suggest the following action items as near-term steps for the FDA and other stakeholders to consider as this guidance document is revised and implemented:

- **FDA support for convenings on the topic of data quality to promote alignment between FDA, sponsors, and data curators on appropriate data quality benchmarks and standards.**
- **Sponsor and data curator collaboration to develop standard operating procedures that offer transparency around data curation approaches. Both sets of stakeholders should have opportunities to engage with academic researchers and the FDA to vet these data curation approaches.**
- **FDA identification of analytical tools and strategies deemed acceptable to the agency to address bias and confounding due to missing data or misclassification of data.**
- **FDA support for convenings to build consensus on what constitutes acceptable quality for combining data from multiple sources and strategies than can address issues and complexities associated with the use of data linkage to address missing data.**

PDUFA VII commitments[2], especially the proposed Advancing RWE Program, will also provide additional opportunities to advance RWD/RWE, including many of the recommendations described below.

***Highlight the unique strengths and limitations of EHR data and claims data, alone and combined.***

The draft guidance treats claims data and EHR data as similar data sources, but these sources are very different. For example, health plan enrollment is a critical concept used to define observable person-time in claims data sources but cannot be defined within EHR sources. Identification of proxies for observable person-time in EHR sources could be a robust area of research. Additionally, linking EHR data to claims data can help by incorporating enrollment information from claims to the EHR data. In fact, claims and EHR data that are linked can become a valuable data resource. However, claims data are often payer specific, which can introduce issues when attempting to generalize data insights across patient populations. Furthermore, the nature of data elements captured in EHRs may vary depending on many health system factors, such as geographic location, adherence to clinical guidelines, type of health system, patient mix, ontology used and applied (e.g. ICD-10, SNOMED), and operational processes and procedures. For instance, examining data on a national level versus a single health system level may lead to more representative datasets, but might also cause challenges in resolving confounding factors within the data that arise when combining data from multiple sources.

We urge the FDA to consider the strengths and weaknesses of both types of data source, individually and combined, and provide additional guidance specific to other types of relevant or augmentative data sources. As cited in the draft guidance, Duke-Margolis has published white papers that discuss specific considerations for EHR data that might be helpful in providing this additional context[3,4]. Experience with claims and EHR data in the Sentinel Initiative and the Biologics Effectiveness and Safety (BEST) Initiative could also contribute to additional guidance.

***Develop resources and convenings to advance data validation approaches and expand on the concept of verification.***

Identifying ways to validate a variety of variables across RWD sources for different disease use cases can be difficult. One possible strategy to address this difficulty is for the FDA to engage with sponsors and data curators to develop a publicly available list or database of prior successful validation methods and approaches that can be referenced for a variety of unique data sources. Such a list could be based on lessons learned from work under the Sentinel Initiative and the RCT Duplicate[5] project as well as the planned Advancing RWE Program included in the PDUFA VII commitment letter. This list would ideally represent different types of data sources as well as a variety of disease focus areas.

As part of the PDUFA VII pilot program, the FDA should also consider sponsoring convenings on the topic of data quality to promote alignment between FDA, sponsors, and data curators on appropriate data quality benchmarks and standards. These convenings could discuss approaches for the validation and verification of key variables or data elements and fit for purpose validation in various contexts.

Furthermore, data de-identification and much of the curation of source data is conducted by data curators versus pharmaceutical industry sponsors. Therefore, it will be incumbent upon such curators to be transparent about their curation approaches and procedures in regulatory submissions. Pharmaceutical industry sponsors need to also be equally transparent about data curation approaches and procedures that may occur further on their behalf. To the extent possible given the diversity of data

sources, these stakeholders should work together to develop standard operating procedures for data curation to support this transparency. As we have discussed in past Duke-Margolis work, maintaining appropriate confidentiality while clearly communicating curation practices is a necessary and shared stakeholder responsibility to support determinations of data reliability[6]. FDA is well positioned to catalyze these conversations across stakeholders.

We also suggest that in the final text of the guidance that FDA provide additional delineation between and clarity around the concepts of validation and verification. The definition included in the guidance for validation aligns well with the definition we have adopted at Duke-Margolis. However, this definition should be carefully distinguished from the definition of verification. We suggest that FDA also align with our adopted definition of verification, which is "assessment of how a data element or variable matches expectations with respect to metadata constraints, system assumptions, and local knowledge"[7]. In EHR's for example, verification might include checks for birth data length not conforming to specifications (conformance), duplicate admissions to the same facility (plausibility), or changes in the denominator of a key variable such as the total number of patients in a database (completeness).

***Consider implementing a risk-based approach to validation and verification of data elements.***

We are supportive of the guidance document stressing the importance of variables being auditable and asking sponsors to be transparent about how data has been processed. Likewise, rigorous assessment of data sources to ensure they are fit-for-purpose and accurate is critical. However, some of the important questions posed in this guidance may be difficult to fully address depending on the data source and expecting RWD characterization that is equivalent to that of clinical trial data may substantially limit use of RWD sources. We therefore suggest FDA consider a risk-based approach that prioritizes the assessment of key variables or clinical concepts as part of its validation and verification processes. This risk-based approach should take into consideration: the clinical question, the regulatory decision, and the contribution of the RWE to the totality of evidence and benefit/risk decision. This risk-based approach could be more stringent for newer and less developed data sources to ensure proper scrutiny and create or augment relevant FDA review protocols and standards. Data sources that are well understood could provide a foundation for developing this risk-based characterization approach.

Overall, a risk-based approach should recognize that, while desirable, complete verification of variables may not be possible, especially when sponsors do not have direct ownership of a given data source. The FDA could also consider requesting data management plans anchored in robust quality assurance and quality control. Further discussion from FDA on the concept of fit-for-purpose data with considerations for flexibility paired with transparent recording of trade-offs and limitations of data sources including documentation of standard operating procedures may also be useful, especially in areas where data options are limited.

A rigid or inflexible approach to validation and verification of data may limit innovation in evidence generation opportunities. Any approach, risk-based or otherwise, should consider the nature of how and why EHR, claims, and other RWD are collected (i.e. generally not for regulatory purposes), the primary requirement for use of the resource should be such that the data used for decision-making mirrors the data found within the source system (e.g., ICD-10 diagnosis codes), data transformations are well

described, and data specialists have developed and applied robust methods to ensure data is fit-for-purpose.

In addition, for data sources that might be used repeatedly, a special certification process that allows sponsors or data source owners to complete validation and verification processes for key data elements, followed by periodic reviews to ensure data standards are maintained, could be one approach to facilitate an efficient review process. This certification process would not only drive transparency around data quality and offer opportunities to reference prior validated work, but also create or maintain data processing efficiencies for evidence generation within critical timeframes. This recommendation contrasts with the proposed processes outlined in the draft guidance. Both this certification process recommendation and the validation approach database described in the previous section are potential approaches to avoid the need to start from scratch each time validation or verification is required. Absent a certification process, it should still be possible for sponsors to leverage prior validation and verification work on a given data source (supplementing with new work as necessary). The ability to build on prior high-quality work where appropriate will help make processes more efficient.

***Clarify recommendations for evaluation of missing data.***

Evaluating the impact of missing data is a critical step in the selection of real-world data sources. However, we are uncertain about how the draft guidance describes missing data. The guidance refers to two broad categories of missing data: 1) "when the information was intended to be collected…, but is absent from the data sources" and 2) "when the information was not intended to be collected…and is therefore absent." Determining intent in this instance is difficult if not impossible and it is not clear why this delineation in types of missing data would be necessary. Perhaps a better framing for missing data might be unsystematic absence of data vs. systematic absence of data vs. unavailable data. Systematic missing data might arise when a health system does not collect a certain variable despite having the data infrastructure capacity to do so, thus biasing or skewing datasets at a significant level, while unsystematic missing data would be more random and may not introduce confounding bias into analytic findings. Unavailable data are data missing due to lack of data infrastructure capacity or data collection protocols, policies, or procedures.

Further clarification from the FDA would be helpful in a couple areas. First, the guidance states that "the protocol and the statistical analysis plan should be developed and based on an understanding of reasons for the presence and absence of information. Descriptive analyses should be included to characterize the missing data." Additional clarification from FDA on what the agency would like to see in these descriptive analyses, especially as it relates to our proposed categories of missing data, would be welcome. Also, it would be helpful if FDA could reference analytical tools and strategies deemed acceptable to the agency to address bias and confounding due to missing data for the three categories or missing data described above. This is an area the FDA has considered before and may be worth revisiting as the RWE program at FDA continues to evolve[8]. These analytical methods may also extend to evaluation of the impact of data misclassification.

***Collaborate with a broad range of stakeholders to ensure responsible and meaningful data linkage.***

FDA also notes that data linkage can serve as one way to address missing data. While this is true, data linkage can introduce additional complexity, particularly for longitudinal studies where it may be difficult to appropriately link variables to specific time points. Further, it is important to recognize that linkage, although highly desirable, presents challenges in balancing patient privacy with the desire to be able to reidentify records for validation. Certain transformations must often be made to protect privacy, for example providing age in bands rather than by year to limit the likelihood of reidentification.

Through the RWE Collaborative and other avenues, Duke-Margolis has driven thought leadership on the development of a robust health data infrastructure in the United States that would support data linkage to address this and related data issues[9]. We have urged the FDA to work closely with other federal agencies, drug and device sponsors, data providers, and other key stakeholders to ensure responsible and meaningful data linkage. This collaboration will help further FDA's recommendation in the present draft guidance that sponsors demonstrate "whether and how data from different sources can be obtained and integrated with acceptable quality, given the potential for heterogeneity in population characteristics, clinical practices, and coding across data sources."

It may be useful to hold multistakeholder convenings to 1) build consensus on what constitutes acceptable quality for combining data from multiple sources and 2) discuss and share methods and strategies than can address issues and complexities associated with the use of data linkage to address missing data.

***Additional comments and suggested edits***

| Lines | Current Text | Suggested Change(s) |
|---|---|---|
| 54-55 | "Selection of data sources that appropriately address the study question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key ***covariates"*** | "Selection of data sources **that have the greatest potential to** appropriately address the study **or research** question and sufficiently characterize study populations, exposure(s), outcome(s) of interest, and key covariates **with limited or controlled bias and confounding."**<br><br>Also, it would be helpful for FDA to offer specific approaches, perhaps like the target trial framework[10] and estimand thinking process (as described in the ICH E9 Addendum[11]), that can be useful for assessing the suitability of a data source for addressing a 'study question,' especially in instances where the causal effect of a drug on an efficacy or safety variable are of particular concern. |
| 99-100 | "…sponsors should submit protocols and statistical analysis plans before conducting the study." | Clarify what processes should be used to submit and discuss plans with the FDA. Consider developing a meeting format that will allow data providers to meet with FDA on study design topics outside of sponsor-led meetings on specific drug applications. |

| Lines | Current Text | Suggested Change(s) |
|---|---|---|
| 184-185 | "A description of prescribing and use practices in the health care system (if available), including for approved indications, formulations, and doses." | Clarify the intent and purpose of providing such a description. This description is likely to vary even within a single health system for factors related to time, geographic location, insurer policies, health care provider protocols and procedures, and other contextual factors. Most notably, health system prescribing/dispensing patterns may vary by provider and may even conflict with insurer coverage policies, authorizations, and other restrictions.<br><br>A more meaningful alternative would be to focus on whether the research question and corresponding methods are appropriate or reasonable for a given cohort based on prescribing/dispensing patterns across data sources. |
| 204-205 | "… given that patients often enroll and disenroll in different health plans when they experience changes in employment or other life circumstances." | "… given that patients often enroll and disenroll in different health plans when they experience changes in employment, **relocate across health systems,** or other life circumstances." |
| 270-271 | "…whether and how data from different sources can be obtained and integrated with acceptable quality, given the potential for heterogeneity in population characteristics, clinical practices, and coding across data sources." | "…whether and how data from different sources can be obtained and integrated with acceptable quality, given the potential for **significant** heterogeneity in population characteristics, clinical practices, and coding **practices** across data sources **or systems**." |
| 356 | *Computable Phenotypes* | FDA should support or encourage the development of an ontology for computable phenotypes, which can be publicly available and complementary to existing initiatives like the eMERGE Network.[12] The ontology could include information around the intended use of the phenotype (outcome, cohort definition, exclusion criteria), intended sensitivity or specificity, the appropriate data source for implementation, and links to prior implementation. This approach could address heterogeneity, for example, in the use of terms used to describe a single diagnosis for a variety of purposes (e.g., setting exclusion criteria, conducting safety assessments, examining outcomes, etc.). |

| Lines | Current Text | Suggested Change(s) |
|---|---|---|
| 391-392 | "…, whether the algorithm was supervised (i.e., using input and review by experts) or unsupervised,"… | In the context of artificial intelligence and machine learning, supervised and unsupervised refer to types of ML methods. It is not clear if this section is referring to those methods or to whether execution of final algorithm is overseen by humans. |
| 473 | "FDA recommends assessing the performance of operational definitions in an adequately large sample of the study population…" | Define "adequately large" |

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 will provide comments on the related RWD/RWE draft guidance that have been and 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
Trevan Locke – Research Associate, Duke-Margolis
Adam Aten – Research Associate, Duke-Margolis
Matt D'Ambrosio – Research Assistant, Duke-Margolis
Rachele Hendricks-Sturrup, Research Director, Duke-Margolis (rachele.hendricks.sturrup@duke.edu)

Duke | MARGOLIS CENTER *for* Health Policy

## Appendix

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

**David Apfel** -- Janssen

**Marc Berger** – Retired/ISPOR

**Elise Berliner** – Cerner Enviza

**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** -- CTTI

**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

Duke | MARGOLIS CENTER for Health Policy

## References


[1] "Real-World Evidence Transparency Initiative," Default, accessed November 18, 2021, https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative.
[2] "PDUFA VII Commitment Letter," accessed December 6, 2021, https://www.fda.gov/media/151712/download.
[3] "Characterizing RWD Quality and Relevancy for Regulatory Purposes," accessed November 29, 2021, https://healthpolicy.duke.edu/sites/default/files/2020-08/Characterizing%20RWD%20for%20Regulatory%20Use.pdf.
[4] "Determining Real-World Data's Fitness for Use and the Role of Reliability," accessed November 18, 2021, https://healthpolicy.duke.edu/sites/default/files/2019-11/rwd_reliability.pdf.
[5] "RCT DUPLICATE," RCT DUPLICATE, accessed December 6, 2021, http://www.rctduplicate.org/.
[6] "Determining Real-World Data's Fitness for Use and the Role of Reliability."
[7] "Determining Real-World Data's Fitness for Use and the Role of Reliability."
[8] Timothy L. Lash et al., "Quantitative Bias Analysis in Regulatory Settings," *American Journal of Public Health* 106, no. 7 (July 2016): 1227–30, https://doi.org/10.2105/AJPH.2016.303199.
[9] Trevan Locke et al., "Building a Modern Health Data Infrastructure:," n.d., https://healthpolicy.duke.edu/sites/default/files/2021-10/Cures%202.0%20Shared%20Evidence%20Data%20Infrastructure_0.pdf.
[10] Miguel A. Hernán and James M. Robins, "Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available," *American Journal of Epidemiology* 183, no. 8 (April 15, 2016): 758–64, https://doi.org/10.1093/aje/kwv254.
[11] "E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials," accessed December 6, 2021, https://www.fda.gov/media/148473/download.
[12] Ning Shang et al., "Making Work Visible for Electronic Phenotype Implementation: Lessons Learned from the EMERGE Network," *Journal of Biomedical Informatics* 99 (November 1, 2019): 103293, https://doi.org/10.1016/j.jbi.2019.103293.