Considerations in characterizing real-world data relevance and quality for regulatory purposes: A commentary

Cynthia J. Girman1 | Mary E. Ritchey2 | Wei Zhou | Nancy A. Dreyer4

1 Patient-reported Outcomes and Real-world Evidence, CERobs Consulting, LLC, Chapel Hill, North Carolina
2 Epidemiology, Medical Devices, and Real-World Evidence, RTI–Health Solutions, Research Triangle Park, Durham, North Carolina
3 Department of Pharmacoepidemiology, Center for Observational and Real-world Evidence, Merck & Co., Inc, North Wales, Pennsylvania
4 Real-World & Analytic Solutions, IQVIA, Cambridge, Massachusetts

Correspondence
C. J. Girman, CERobs Consulting, LLC, 107 Turtleback Crossing Dr, Chapel Hill, NC 27516.
Email: cindy.girman@cerobs.com

1 INTRODUCTION

The 21st Century Cures Act of 2016 provided a framework to the US Food and Drug Administration (FDA) to rapidly move treatments to patients. The increased acceptability of real-world data (RWD) sources allows for innovative ways to study products and has the potential to reduce trial costs. Published papers provide guidance regarding data quality issues, reproducibility, and validity assessment. Rapid evolution of electronic health records (EHRs) encourages greater consideration of their use in research. For years, the FDA has relied on epidemiological studies of postapproval product safety using RWD (eg, administrative claims and EHR) and for device effectiveness studies; however, regulatory use for evaluating drug effectiveness has been rare. As part of the Prescription Drug User Fee Act (PDUFA VI), use of RWD is being considered for potential contributions to evaluating effectiveness and safety of new indications for approved products and to satisfy postapproval study requirements. Recently, the Duke Margolis Center for Health Policy held workshops and issued two paper on this topic. The first paper focused on defining RWD as data routinely collected pertinent to patient health status and/or delivery of care, and the use of RWD in regulatory and clinical contexts.

The second white paper from the October 1, 2018, workshop focused on data relevancy and quality, including cleaning, transforming, and linking RWD to characterize RWD sources as “fit for regulatory purpose.” These papers offer a practical “commonsense” high-level view of primary data and methods considerations for RWD use from a regulatory perspective, facilitating discussion around regulatory uses of RWD within the research community and industry. However, salient points are missing from the papers and the RWD discussions among FDA, researchers, and industry. Here, we provide a commentary on the data considerations discussed in the white papers and highlight pertinent considerations with respect to RWD in the context of whether data are relevant, representative, and robust.

1.1 Data relevance

The recent white paper defines data relevance dimensions including representativeness of the population of interest, critical data field availability, accurate linking at the patient level with multiple data sources, and adequate sample size and follow-up time to demonstrate expected treatment effects. Guidance from FDA on how to ensure RWD are fit for purpose and adequate to support regulatory decisions would be helpful on each dimension.

Determining if RWD is fit for regulatory purpose is a “contextual exercise” where the specific research question, regulatory use, and data characteristics drive what meaningful conclusions can be drawn. Covariates may be critical for one research question but not another. Exposures and outcomes should be well defined when part of the research question but may not be critical for natural history studies. There is no "one-size-fits-all" approach, and critical data components should be evaluated for each research question and regulatory use. A framework is needed to guide choice and evaluation of critical data elements for specific research questions for regulatory use.

Representativeness of the population of interest is gauged in many ways. Recent FDA guidance on Patient Focused Drug Development suggests a statistical sampling approach be used to obtain...
Data quality should be considered in terms of validity, conformance, plausibility, and consistency. The acceptability of various degrees of accuracy and completeness depends on the specific research question and regulatory purpose. The white paper refers to data verification procedures, minimizing missing data, and consistency with source, often impractical given the anonymized nature of accessible data. RWD have proven valuable for specific purposes despite known limitations, when due attention is given to the adequacy of data elements, study design, and analysis. RWD used to support regulatory decisions must be of sufficient quality to ensure that it can be transformed to adequate and well-controlled real-world evidence.

Evaluations of data quality should be focused on fit-for-purpose design and methods, applying sensitivity analyses to support robustness and interpretation. It is highly desirable to use a set of validated codes or algorithms (computable phenotypes) for critical fields, depending on study purpose. Decades of validation work in administrative claims have evaluated such algorithms relative to manual chart review. Now that the chart and data for research may be the same (ie, EHR), we need to understand how and when such validation should be conducted. Even if all available processes and SOPs for cleaning, transforming, and linkage are followed, overall data adequacy in the context of study and regulatory purpose should be assessed, preferably by a researcher experienced with RWD sources for regulatory decision making.

Missing data should be considered in the context of the impact on validity and generalizability of results. Whereas follow-up data can be critical for certain purposes such as use of RWD as a comparative arm or concurrent/historic control group, missingness may be less critical for other purposes (eg, missing health outcomes may be less likely to affect results of a product utilization study than an outcomes study). That said, US RWD sources often are systematically missing follow-up data due to turnover in health insurance plans and the US health care system’s transient nature. Thus, a key consideration for any real-world evidence research question is how much systematic loss of follow-up data or other missing data would influence study conclusions.

### 1.3 Research framework

A fit-for-purpose framework starts with a well-defined research question and an assessment of relevance and quality of specific critical data elements within the RWD source (Table 1). This might include assessing whether the population, outcomes, and treatments, as part of the PICOT definition of a well-defined research question, can be validly and reliably defined using structured data (eg, diagnosis and procedure codes, laboratory tests, and pharmacy data) contained in RWD. If the critical data elements for a specific research objective can be defined in the RWD source, researchers might consider sample size and follow-up time given the expected effect size, whether validation is needed for critical data elements, and what level of missing data can be tolerated (Table 2), given the specific research question and regulatory use. With data linkage, these considerations would be applicable to the separate data sources and the linked data.

Preliminary data extraction may be performed to crudely determine number of patients and median follow-up time in the specific RWD source. Very small effect sizes may be difficult to address with precision in RWD sources due to potential for bias. Research with larger expected effect sizes can often be addressed with RWD, with careful attention to appropriate design and methods. At a very high level, one can apply the crude estimate of disease or exposure prevalence (whichever is smaller) to the number of lives covered in a database to better understand adequate sample size.
A framework to assess usefulness of RWD in the context of specific research questions and intended regulatory purpose, along with published reporting guidelines,\textsuperscript{9,14,15} could significantly help identify major components of well-designed studies in RWD to support specific product effectiveness and safety research questions for regulatory purposes.

2 | CONCLUSIONS

Recent papers on use of RWD for regulatory purposes have initiated discussions among regulators, industry, and researchers on practical considerations of RWD relevance and quality. Beyond availability of data fields, valid definitions of components of research questions are crucial. More guidance is needed on what constitutes acceptable evidence of validation for critical data elements given the clinical research question and intended regulatory use. Besides FDA, other agencies are also exploring the appropriate usage of RWD in regulatory decisions. Understanding how to use RWD and whether they are “fit for purpose” is helpful for regulatory agencies, industry, and researchers around the world.

ACKNOWLEDGEMENTS

Authors acknowledge Nicole Mahoney and Molly Aldridge for assistance with review of the manuscript. No specific funding for this work was provided, and no specific product is involved.
REFERENCES

1. Energy and Commerce Committee. 21st Century Cures Act. Retrieved 01OCT 2018 https://energycommerce.house.gov/cures

2. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to improve reproducibility and facilitate validity assessment for healthcare database studies V1.0. *Pharmacoepidemiol Drug Saf*. 2017;26(9):1018-1032.

3. Center for drug evaluation and research. Prescription Drug User Fee Act (PDUFA)—PDUFA VI: fiscal years 2018–2022. U.S. Food and Drug Administration. Retrieved 01 October 2018. http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm

4. U.S. Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. Guidance for Industry and Food and Drug Administration staff. Center for Devices and Radiological Health (CDRH). Retrieved 12 October 2018. https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

5. Berger, M, Daniel, G, Frank, K, et al. A framework for regulatory use of real world evidence. Retrieved 06SEPT2017. https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf

6. Daniel G, Silcox C, Bryan J et al. White paper: characterizing RWD quality and relevancy for regulatory purposes. Retrieved 01OCT2018. https://healthpolicy.duke.edu/sites/default/files/atoms/files/characterizing_rwd.pdf

7. Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. *Clin Pharmacol Ther*. 2018;103(2):202-205.

8. U.S. Food and Drug Administration. Patient focused drug development: collecting comprehensive and representative input. Guidance for Industry, Food and Drug Administration Staff and Other Stakeholders, 2018. Retrieved 27Aug2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610442.pdf

9. Dreyer NA, Schneeweiss S, McNeil B, et al. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. *Am J Manag Care*. 2010;16(6):467-471.

10. Girman CJ, Faries D, Ryan P, et al. Pre-study feasibility and identifying sensitivity analyses for protocol pre-specification in comparative effectiveness research. *J Compar Effect Res*. 2014;3(3):259-270.

11. Kahn MG, Callahan TJ, Barnard J, et al. A harmonized data quality assessment terminology and framework for the secondary use of electronic health record data. eGEMS (Generating Evidence & Methods to Improve Patient Outcomes). 2016;4(1):1244.

12. Funk MJ, Landi SN. Misclassification in administrative claims data: quantifying the impact on treatment estimates. *Current Epidemiology Reports*. 2014;1(4):175-185.

13. Richardson WS, Wilson, MC, Nishikawa, J, Hayward, RSA. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995;v123:A12-A13.

14. Morton JB, McConeghy R, Heinrich K, Gatto NM, Caffrey AR. Consensus of recommendations guiding comparative effectiveness research methods. *Pharmacoepidemiol Drug Saf*. 2016;25(12):1354-1360.

15. Morton SC, Costlow MR, Graff JS, Dubois RW. Standards and guidelines for observational studies: quality is in the eye of the beholder. *J Clin Epidemiol*. 2016;71:3-10.

How to cite this article: Girman CJ, Ritchey ME, Zhou W, Dreyer NA. Considerations in characterizing real-world data relevance and quality for regulatory purposes: A commentary. *Pharmacoepidemiol Drug Saf*. 2019;28:439-442. [https://doi.org/10.1002/pds.4697](https://doi.org/10.1002/pds.4697)