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Assessing Real-World Data Quality: The Application of Patient Registry Quality Criteria to Real-World Data and Real-World Evidence

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Abstract

The use of real-world data and real-world evidence to inform health care decisions is increasing. Yet, the variable quality of these data and the lack of widely-accepted criteria by which to assess quality create uncertainty about how and when to use these data and the associated evidence in decision making. Patient registries are an important source of real-world data and real-world evidence. The good practices and evaluation criteria developed for patient registries are highly relevant to real-world data and real-world evidence and offer a foundation for a unified set of quality criteria that can be applied across sources of real-world data and real-world evidence intended for use in medical product evaluation.

Keywords

21st Century Cures Act, medical product evaluation, electronic health records, product registries, disease registries

Introduction

Since the passage of the 21st Century Cures Act in 2016, significant attention has been paid to determining how real-world data (RWD) and the resulting real-world evidence (RWE) may be used to inform regulatory decision making. The Cures Act requires the US Food and Drug Administration (FDA) to develop a program "to evaluate the use of real-world evidence (1) to help support the approval of a new indication for a drug approved under section 505(c); and (2) to help to support or satisfy post-approval study requirements."[1] In December 2018, the FDA published a framework for its program to evaluate the potential use of RWE for these purposes.[2] Many stakeholders are interested in beginning to use RWE in these contexts. This interest is driven in part by the rapidly expanding access to RWD from a variety of sources.

The FDA defines RWD as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices." RWE is defined as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[2]

Many publications have described potential sources of RWD, the strengths and limitations of these sources, analytic approaches and considerations for generating RWE, and the potential uses of RWE in regulatory decision making and decision making by other stakeholders (eg, payers, guideline developers).[3-9] A common theme in these publications is the variable quality of RWD and the lack of widely accepted criteria by which to assess the quality of RWD and the associated RWE. The result is uncertainty about how and when to use RWE in decision making.

The difficulty of assessing quality in RWD and RWE stems from many factors, including the variety of data sources and heterogeneity in study designs and analytic approaches. Quality assessment is further complicated when study designs combine data from multiple sources, such as EHRs and patient registries, or incorporate new tools, such as natural language processing. While many best practices exist for the design, conduct, and analysis of studies using RWD,[10-17] there is not yet a unified set of criteria for evaluating and comparing quality across different data sources and different study designs. To be broadly useful, the unified criteria should synthesize criteria from existing quality assessment tools, while remaining

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flexible to allow for "fit for purpose" evaluations in which the acceptable level of rigor varies depending on the objective. For example, the amount of missing data that is acceptable in a descriptive study of a rare disease is different than the amount of missing data that is acceptable in a study designed to assess the effectiveness of a medical product. This concept of "fit for purpose" is particularly important for RWD, where there are myriad data sources and potential uses.

The purpose of this paper is to describe a unified set of criteria for evaluating the quality and suitability of RWD and RWE across data sources, drawing on the extensive work done in the area of patient registries.

Patient Registries and Real-World Data

A patient registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."[18] The Cures Act and subsequent FDA publications related to RWE specifically identify registries as a source of RWD, and registries have already been used as a source of RWD to support regulatory decision making.[9,19,20]

Unlike many other sources of RWD, registries have benefited from significant investments from the Agency for Healthcare Research and Quality (AHRQ) over the past decade aimed at improving research methods, data quality, and transparency. Of relevance is the AHRQ publication, *Registries for Evaluating Patient Outcomes: A User's Guide.* The User's Guide contains practical information to guide the design, operation, and analysis of patient registries and provides a framework for evaluating the quality of patient registries and evidence derived from patient registries. First published in 2007 and now in its third edition, the User's Guide was identified as a source of information on RWD quality in the FDA's 2017 guidance document on RWE and its recent publication describing the framework for its RWE program.[2,5] The Patient-Centered Outcomes Research Institute (PCORI) references the User's Guide in its standards for patient registries,[21] as do other initiatives focusing on RWD.[10,12]

The quality assessment framework provided in the User's Guide is highly relevant to RWD and RWE. Patient registries fulfill a wide range of purposes across the entire health system landscape, such as generating data for clinical and patient-centered outcomes research, supporting post-marketing surveillance, providing data for quality improvement and value-based care programs, and supporting learning health care systems. To fulfill these purposes, registries draw on multiple data sources and may integrate data collected from EHRs or medical claims, directly from clinicians, and from patients via patient-reported outcome measures or mobile devices. Other efforts, such as distributed data networks (eg, Sentinel), also consider data from multiple sources, but registries are unique in the scale of investment. Thousands of patient registries have been designed to fulfill myriad purposes, as evidenced by the voluntary listing of more than 4600 registries on the Registry of Patient Registries, and many organizations have invested resources in developing and improving patient registry methodology.[22-28]

The quality assessment framework developed for registries reflects this diversity. Criteria are drawn from dozens of existing quality statements related to observational studies, claims data, EHRs, distributed data networks, and other data sources. The criteria have been refined through multiple rounds of peer review and public comment. With some modifications, these criteria could serve as a unified set of criteria to assess quality across RWD sources and study designs and as a foundation for the FDA's further guidance on evaluating RWD and RWE.

Extending the Quality Criteria for Patient Registries to RWD and RWE

We propose the following unified set of criteria to evaluate RWD and RWE. These criteria are adapted from the User's Guide[18] to apply to RWD and RWE more generally. In some areas, these criteria were supplemented with more recent quality assessment criteria, such as those contained in the 2017 FDA guidance document on RWE,[5] the 2018 FDA document describing the RWE program,[2] the National Medical Device Registry Task Force report,[29] the Regulators Forum Registry Working Group report,[30] the Clinical Trials Transformation Initiative (CTTI) recommendations[31] for registry trials, and other published literature.[3,4,13,32]

Data Quality

Data quality refers to the characteristics of RWD that influence its reliability and relevance for regulatory decision making. At a minimum, RWD intended to support regulatory decision making should meet the following criteria:

- Data are captured consistently using clear, operational definitions and predefined rules for abstraction of structured and unstructured data. A data dictionary is available.
- Standardized definitions of key outcomes measures and standardized data dictionaries are used whenever feasible.
- Data checks for range and consistency are used to improve accuracy of the data.
- Sufficient and reliable information on the outcomes of interest and necessary confounding variables are available.
- The product of interest is sufficiently identified in the data source.

Research Quality

Research quality refers to the scientific process, meaning in this context the design, operation, and analysis of a study intended to develop RWE suitable for regulatory decision making. At a

minimum, studies intended to develop RWE should meet the following criteria:

- Develop a formal study protocol and statistical analysis plan a priori. Clearly define specific aims, population inclusion/exclusion criteria, exposure and outcome variables, and analytic plans. Follow existing good practices for clinical research protocols and include the same elements that are included in a traditional clinical trial protocol and statistical analysis plan.
- Identify likely sources of bias and document plans to address them.
- Use formal statistical calculations to specify the sample size necessary to measure an effect with sufficient statistical power.
- Ensure that planned follow-up is sufficient to address the primary objective.
- Document a plan for handling missing data.
- Devote sufficient efforts to minimizing loss to follow-up and missing data.
- Ensure that appropriate protections for human subjects are in place.
- Develop and document data management and data quality assurance plans, including plans for site and data monitoring and for source data verification.
- Provide standard instructions for data collection/abstractors and training for study personnel.
- For studies using existing data sources, use uniform and systematic methods for collecting and cleaning data and document these methods.
- Maintain adequate documentation (eg, audit trail) to verify proper handling of data.
- Collect sufficient information to link data with other databases, such as the National Death Index, electronic health records, or other registries, for validation purposes.
- Post the study on a public registry, such as the Registry of Patient Registries or ClinicalTrials.gov, to support transparency and reproducibility.

Evidence Quality

Evidence quality refers to the relevance and reliability of the resulting evidence for use in regulatory decision making, including assessments of external validity and internal validity. At a minimum, studies intended to provide RWE should meet the following criteria:

- Sufficient information is available for exposures, characteristics, risk factors, potential confounding factors, and outcomes. Exposure data used to support the main research questions were as specific as possible and permit identification of the product of interest.
- Selection bias was evaluated by describing the representativeness of the analysis population in terms of how closely it reflects the characteristics of the target population.
- The potential impact of systematic errors, missing data, and confounding factors were considered.
- Sufficient longitudinal data are available to capture the main outcomes of interest. The potential for differential loss to follow-up was evaluated, and the impact of loss to follow up on the conclusions drawn by the study was considered.
- A sample of data was validated against source documents.
- Validated and accepted analytic techniques and tools were used, and appropriate methods were used to address potential confounding. All analytic methods were described with enough detail to allow replication of the methods in another study. The data elements used in any models are identified.
- Sensitivity analyses were used to examine and quantify the effect on the association between the exposure of interest and the main outcome of interest.

Next Steps

Tools to assess the quality of RWD and the associated RWE will be a critical component of the FDA's RWE program. The criteria described here add to the existing literature by synthesizing quality criteria related to specific data sources or study designs into a unified set of criteria that are broadly applicable to RWD and RWE. In particular, these criteria build on the tools developed for patient registries, which have evolved over the past decade, are widely used, and are supported by the practical information on designing and operating studies to meet these criteria provided in the User's Guide.

Given the immense interest in this area, it is likely that stakeholders will continue to explore strategies for generating RWE while the FDA develops further guidance to support its RWE program. The good practices for designing, operating, and analyzing studies of RWD described in the User's Guide offer a foundation that can be adapted to fit specific purposes and data sources. The unified quality criteria described here are a useful tool for evaluating quality of RWD sources and the resulting RWE. These criteria also may be relevant for evaluating the quality of RWE for use in other contexts, such as coverage decisions.

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