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Best Practices in the Curation and Use of Real-world Data in the Regulatory Pathway

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Abstract

The fit-for-use of RWD including data quality and provenance are critical components that will aid the Federal Drug Administration (FDA) to assess the adequacy of RWE (Real World Evidence) to support it on the regulatory pathway. We review the best practice in the curation and use of Real World data in support of RWE submissions to the FDA.

Introduction

The use of real-world data (RWD) and its synthesis (real-world evidence (RWE)) has historically been important in assessing the safety of medical treatments in the general population. The passage of the 21st Century Cures Act in 2016, and in particular the inclusion of section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) which required the FDA to create a framework for the evaluation "of the potential use of real-world evidence (RWE) to help support the approval of a new indication already approved….or to help support or satisfy drug post-approval study requirements," will make the use of RWE more prevalent in assessing the effectiveness of new therapeutics within the regulatory pathway [1].

To-date, there has been limited use of RWE as a part of the regulatory pathway in the United States. A recent study showed that there were 34 studies that used RWE in the regulatory pathway between 1954 and 2020. A majority (44%) of these studies were in oncology and hematology, and 12% were in neurology. More than 50% of the products were indicated for use in rare diseases or pediatric patients. Over 80% of these treatments received orphan designation and little less than 60% included RWE in the product label [2]. Additionally, Xcenda (2021) showed that only 20% of 267 regulatory submissions in 2019 contained some component of RWE [3].

A natural question is: why has there been such a low uptake of RWE within the regulatory process? Afterall, the use of RWE may overcome issues related to cost, time and patient burden associated with traditional randomized controlled trials and is generally easier to implement.

Potential reasons contributing to the low rate of RWE use in the regulatory process include a lack of a pre-specified study design, small sample sizes, data relevancy, quality and reliability, and methodological concerns. Indeed, FDA's RWE guidance documents address these challenges and limitations [4].

In these draft guidance documents, FDA maintains that RWD used in the regulatory process must be fit-for-purpose, and fundamental to its appraisal are the strength of the clinical study methodology and the data reliability (i.e., accrual, quality control) and relevance. Among FDA's considerations are also issues related to bias and data missingness that may be inherent in RWD. Due considerations given to these issues will allow for a higher uptake of RWE in the regulatory process, not only in oncology and neurology

but in other therapeutic areas as well.

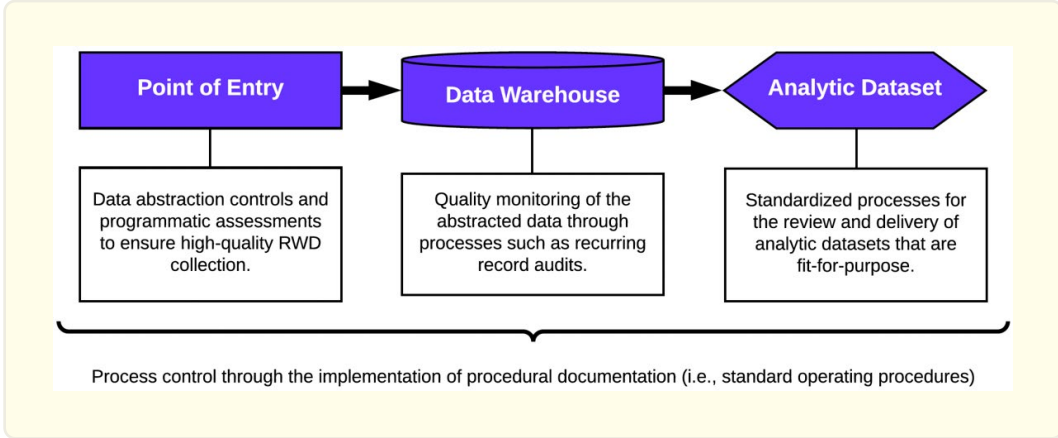
Data Curation

As an illustration, COTA, Inc. has developed a quality management system which adheres to FDA's guidance on RWD/RWE. The COTA database consists of longitudinal, de-identified clinical data pertaining to the diagnosis, treatment, and outcomes of patients with cancer who are cared for at COTA-partnered healthcare providers. COTA's network of healthcare providers is a mix of academic and tertiary cancer care centers in the United States (US) distributed over a diverse geography. COTA's agreements and partnerships with provider organizations allow complete access to the patient's electronic health record (EHR), including historical information provided by referring institutions. COTA collects patient data from the time of the initial cancer diagnosis through the most recent documentation in the EHR.

All data outlined in COTA's disease-specific data dictionaries are collected from the EHR at the time of data abstraction. Where patients do not receive all their care at a singular primary site, COTA reviews and collects data from all available outside records that are scanned into the EHR and/or detailed by the treating physician. Patients who do not have sufficient documentation or have significant gaps in their patient journey within the EHR are excluded from COTA datasets.

COTA leverages both human and technologic methods to transform structured and unstructured data into a standard data format. Patient data is abstracted from the EHR by abstractors with oncology expertise. Each patient record within the COTA RWE database is stored in a common data format, which enables patient tumor site-specific standardized comparisons across a variety of treatment venues. COTA's data is fully source attributable, site and EHR agnostic and employs standard coding systems and ontologies. A primary focus is data flexibility which lends itself to data integration and facilitates deep scientific discovery through comparison to other data sources that utilize the same ontologies. Patient-level attributes are consistent across all tumors. The end-result is a comprehensive, longitudinal, high-fidelity real-world database able to generate actionable insights that fill in knowledge gaps within clinical oncology and answer critical clinical questions.

More importantly, COTA has developed an end-to-end quality management system (QMS) that conforms to the FDA's draft guidance and ensures the collection of high-quality RWD that can be transformed into fit-for-purpose datasets. The development and evolution of COTA's QMS has been informed by expert guidance and incorporate industry best practices learned through continued industry partnerships and collaborations. COTA's QA approach monitors data quality across key milestones in the data pipeline: at the point of data entry, in production-level data tables, and within each analytic dataset.



COTA is active in a number of key partnerships that have helped to shape the landscape and evolution of the RWE industry. For example, COTA has been a part of the Friends of Cancer Research collaboration in oncology since the first pilot project in 2018 [5, 6]. This collaboration brings together various RWD vendors to contribute data and analyze outcomes following a common protocol to understand areas for standardization and correlations across datasets. Additionally, through its Research Collaboration Agreement with the FDA, COTA and the FDA have jointly explored various clinical questions using RWD. COTA is also an active member of the Clinical Research Data Sharing Alliance (CRDSA) and Aetion CARE Initiative, both of which are working to advance the industry's understanding and use of RWD/RWE in the regulatory space.

There are previously demonstrated statistical methods for addressing potential biases that may occur when using RWD, particularly within the use case of external comparator cohorts. These methods include exact matching, propensity score matching, and other related weighting techniques (e.g., inverse probability of treatment weights). Additional research has examined the combination of multiple data sources to improve the comparability of RWD to RCT. Less is understood about how to overcome inherent differences between RWD and clinical trial data, such as the inability to calculate response to treatment uniformly across the two data sources and how to create surrogate endpoints. However, critical work is being conducted across the RWD industry through the aforementioned alliances and initiatives to address gaps between the evidence generated using real-world and RCT data.

Conclusions

The passage of the 21st Century Cures Act in 2016 ushered in a new era for the use of RWD/RWE in the regulatory space. Successful use of RWD/RWE in this space depends on the clinical trial methodology and the fit-for-use nature of the RWD, including data quality and provenance. In alignment with finalized FDA guidance documents, adherence to best practices including rigorous quality standards is critical to the future utilization and success of RWE in the regulatory pathway.

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