A Collaborative Approach to the Intersection of the Real World With the Highest Quality Standards

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The 21st Century Cures Act calls for real-world evidence to help support regulatory decision making. A collaborative community model can help this cause by bringing together multiple stakeholders, including academic thought leaders, regulatory bodies, pharmaceutical industry partners, and patient advocacy groups around a real-world, shared, deeply detailed, high-quality data set.

Immediately following the initial approval of medications, there is frequently a gap between the information generated from phase 3 clinical trials and their optimal use in usual clinical practice. The 21st Century Cures Act was adopted in 2016 with the goal of encouraging innovation in clinical trials and accelerating drug development. One important aspect of the 21st Century Cures Act required the US Food and Drug Administration (FDA) "to evaluate the potential use of real-world evidence to help to support the approval of a new indication for a drug… [and] to help support or satisfy post-approval study requirements."[1] Thus, the FDA has organized efforts to understand and develop guidance on the use of real-world evidence (RWE) to enhance the understanding of marketed drugs. RWE has been defined as healthcare data from a variety of sources outside of clinical research. In this list of sources, FDA includes "electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications."[2] When the quality of RWE is high, multiple stakeholders can benefit.

Although clinical trial data are perceived as the gold standard, the intersection between data from clinical research and usual clinical practice that maintains the highest level of quality has tremendous promise for complementing standard clinical trials, advancing the regulatory process, and improving patient care.

These stakeholders can interpret and collaborate on collections of RWE and bring important perspectives to the dataset. This group may include academic thought leaders, regulatory bodies, pharmaceutical industry partners, patient advocacy groups, and payers. As the utility and use of high-quality RWE continues to evolve, a multistakeholder approach to research holds great promise.

To illustrate this collaborative approach, this manuscript will walk through an example within a turnkey primary biliary cholangitis (PBC) real-world evidence community, a study of participants with PBC. PBC is a rare, chronic, cholestatic liver disease that may progress to cirrhosis if left untreated. These patients are at risk for developing clinical events, including complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and death. First-line therapy for PBC is ursodeoxycholic acid (UDCA). Unfortunately, approximately 1 out of 4 patients do not have sufficient response to UDCA. Obeticholic acid (OCA), the first new agent approved in decades for the treatment of PBC, provides an additional option for those with an inadequate response to UDCA alone. The PBC collaborative community mentioned above has over 500 participants in the United States and captures real-world insights on OCA use, effectiveness, and adverse events in a wide variety of patients taking OCA. The top academic thought leaders in PBC designed the protocol and continue to direct study decisions with regulatory input. Partners include those from industry and from the PBCers, a patient advocacy group.

In light of recent reports of improper prescribing practices, patients with moderate-to-severe liver disease enrolled in this study have been of particular interest. The FDA-approved label recommends an OCA starting dose of 5 mg daily with titration to a maximum dose of 10 mg daily for noncirrhotic and early stage cirrhotic patients. However, the label specifies that clinicians should limit the starting dose to 5 mg weekly in patients with moderate-to-severe liver impairment with titration to a maximum of 10 mg twice per week.

In a news release prompted by reports of serious adverse events connected to OCA through the FDA Adverse Events Reporting System (FAERS), the FDA announced that some clinicians were prescribing the standard dose to patients with moderate-to-severe liver impairment, rather than the adjusted dose. In several of the reported cases, patients with moderate-to-severe liver impairment incorrectly received daily dosing of OCA. Ultimately, the FDA added a boxed warning and dosing table to the OCA package insert and an informational medication guide for patients. Longitudinal follow-up of patients in this PBC cohort has and will continue to provide long-term safety and effectiveness data in a diverse population of patients with mild and advanced liver disease being treated with OCA. The concerns, input, and actions of multiple stakeholders have already helped to shape its ideal use.

As RWE gains traction in the regulatory realm, high-quality, academically backed sources will become increasingly important. By definition, patients in the real world include those of all backgrounds and with the entire spectrum of disease severity; there is "renewed interest in the use of real-world data [RWD] to... bridge the evidentiary gap between clinical research and practice."[3] Although clinical trial data are perceived as the gold standard, the intersection between data from clinical research and usual clinical practice that maintains the highest level of quality has tremendous promise for complementing standard clinical trials, advancing the regulatory process, and improving patient care. It takes the convergence of a collaborative group of stakeholders around these data to truly illuminate their potential.

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REFERENCES

1. 21st Century Cures Act (Public Law 114-255); Sec. 505F December 13, 2016.

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3. Corrigan-Curay J, Sacks L, Woodcock J. Real-world evidence and real-world data for evaluating drug safety and effectiveness. *JAMA*. 2018;320(9):867-868.

ADDITIONAL INFORMATION

For further articles on the 21st Century Cures Act, you may refer to the November/December 2018 issue of Value & Outcomes Spotlight, available at https://www.ispor.org/publications/journals/value-outcomes-spotlight.