Lessons from China and the United States on the Use of RWE in Regulatory Submissions

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As the world raced to develop vaccines and therapeutics to combat the global coronavirus pandemic in 2020, the use of real-world evidence (RWE) accelerated because it offers an opportunity to support faster, more cost-effective drug and vaccine development. It also benefits clinical trial patients with rare and life-threatening diseases. For example, RWE-based external control arms could ensure patients receive an active treatment in a clinical trial, rather than be allocated to a placebo control regimen.

The United States and China are at the forefront of exploring how RWE could support regulatory decision-making. At Parexel, we've learned how companies can be more effective at collecting real-world data (RWD) and generating RWE.

China	United States
April 2021: Guiding Principles for Real-World Data Used to Generate Real-World Evidence	2021: Guidance on RWE to be released
November 2020: Technical Guidelines for Clinical Evaluation of Medical Devices Using Real-World Data (for Trial Implementation) and Interpretation of the Technical Guidelines	May 2019 Guidance: Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
August 2020: Technical Guidelines for Real-World Research Supporting Child Drug Development and Evaluation (Trial)	December 2018: Framework for FDA's Real-World Evidence Program
January 2020: Announcement of the State Food and Drug Administration on the Guiding Principles (Trial Implementation) for Publishing Real-World Evidence to Support Drug Development and Evaluation	August 2017 Guidance: Use of Real-World Evidence to Support Decision-Making for Medical Devices
	December 2016: Public Law 114-255 21st Century Cures Act (Section 3022. Real-world evidence.)

Table 1. Recent releases of key FDA and CDE guidance documents on RWD and RWE

What we've learned in China

The government's commitment to RWE is real. In 2020, the Chinese National Medical Products Administration's (NMPA) Center for Drug Evaluation (CDE) issued several guidance documents on RWE and RWD (Table 1). In addition, the agency formalized draft guidance on using RWD to generate RWE in April 2021. Companies interested in using RWE can benefit from a close reading of the agency's activities in this area.

Since December 2018, China's Bo Ao Lecheng International Medical Tourism Pilot Zone has provided an alternative pathway for foreign medical devices and drugs to enter the country. The pilot zone is a collaboration between the CDE and the government of Hainan, an island province at China's southernmost point, and its RWE program is a testing ground for how a larger rollout may work.

For example, in March 2020, the NMPA approved Allergan plc's XEN Gel Stent for glaucoma, making it the first imported medical device utilizing RWE for registration in China. Allergan obtained permission to collect RWD through the Hainan pilot zone's RWE program. Overseas companies currently apply to collect RWD in the pilot zone to supplement foreign clinical trial data, and applications increased sharply after the Allergan approval.

In December 2020, Hainan province established the Hainan Real-World Data Research Institute, an institute to develop standards for the use of RWE and RWD to replace bridging studies and as key evidence.

Early entry to this fast-evolving field means there will be challenges to address. However, companies that engage now can foster relationships with Chinese investigators and institutions that could speed up RWE research studies.

RWE questions may be constrained by available data. Before designing an RWE study in China, companies must consider what type of RWD is available. The process of asking and answering research questions in China is shaped by limitations in the existing RWD.

For example, in the United States, researchers pose a hypothesis first and then look for data to test it against—there is a high likelihood that relevant data are available somewhere, and data can be collected prospectively if needed. In China, the data market is less mature. Researchers still start with a valid research question, but they may have to work harder to find the data in existing sources. Thus, there is a higher likelihood they will need to collect RWD from site-based or hybrid studies. But even if no historical data are available, RWD prospectively collected from the Chinese population may answer research questions more easily than conducting a randomized trial.

The concept of RWE is widely accepted in China. There is a strong cultural acceptance of the concept of real-world research in China. Traditional Chinese medicine's legacy makes RWE intuitive and common sense to many investigators and practitioners. This environment is different from the United States, where many researchers are familiar with RWE but may take a more conservative approach, especially if they question the methodology. Companies collecting RWD and generating RWE will generally get a positive reception in China, but they still must have a rigorous methodology.

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What we've learned in the United States

RWE-based external control arms (ECAs) are gaining momentum. The FDA has allowed the use of RWE to support revisions of approved indications or drug-combination labels, in post-marketing studies, and for guiding clinical trial design. However, the agency has not accepted RWE-based external control arms (ECAs) as a replacement for randomized controlled trials. But it is actively exploring potential uses, particularly whether and how ECAs could serve as comparators for single-arm trials, particularly in rare and life-threatening diseases.

For example, we recently worked with a client to construct an ECA that provided essential context for a Phase II single-arm trial's efficacy results. We began identifying RWD sources after intense, detailed, early interactions with the FDA on ECA study design, endpoints, and analytic plan. We performed a full-scale feasibility analysis of 13 different secondary datasets in the United States and Europe, including electronic medical records (EMRs). Secondary data are data gathered outside of the context of an RCT and include EMRs, insurance-claims databases, patient and disease registries, and population health surveys, among other sources. We narrowed the choices down to three viable U.S.-based data sources and direct on-site retrospective chart reviews from Europe. Due to privacy regulations and incomplete data, we did not utilize any secondary datasets from the EU.

We assessed different technologies and vendors to aggregate and de-duplicate the data, given the complex mapping process. We successfully matched patients 1:1 with the Phase II study population against nine covariates. While it took the sponsor over 24 months to enroll the trial's treatment arm, we developed, analyzed, and submitted the ECA to the FDA in only 16 months. The product was approved about eight months later, well ahead of schedule. In April 2021, at an RWD/RWE conference in Hainan, the CDE used this study as an example to explain the design of an external control arm.

Data quality is key to an ECA's validity. The methodology used for data collection and assessments in an ECA determines the quality of data available for accurate population matching to the active treatment arm. One way to ensure quality is to apply epidemiologic principles of observational research to the ECA study design, methods, and operations and then systematically evaluate and resolve potential biases.

Data quality may differ between the clinical study cohort and the ECA, so sponsors must prove that data collection is adequate, accurate, and non-differential. Sponsors also need to be aware of discrepancies in the type of data collected, duration of follow-up, and completeness of data between the active arm and the ECA. Importantly, RWD should match clinical trial data on as many covariates as possible.

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There are no guarantees. Rigorous planning and implementation are required to construct an ECA, with interaction and buy-in from regulatory agencies throughout the process

Despite following best practices and understanding regulatory expectations precisely, sponsors cannot assume that regulators will use their ECA to support approval. Therefore, companies need to actively collaborate with the FDA and NMPA to define better requirements for the acceptability of RWE in the approval process. It will take time and effort to forge a reliable regulatory pathway for ECAs, but, given the pressing need for better treatments to address life-threatening diseases, it's imperative to include RWE as one of the options for regulatory approval.

Ask the right questions. Before considering an ECA, companies need to start by framing a research question and evidence objectives and then answering five key questions:

1. Does the disease have a well-documented, highly predictable course?
2. Are covariates that influence the outcomes of the disease well-characterized?
3. Are real-world variables comparable to clinical trial variables?
4. Is the primary endpoint objective?
5. Does the investigational agent show evidence of marked efficacy?

If the answers to these questions are yes, a company should perform an iterative feasibility evaluation, including scientific and regulatory landscape assessments, site feasibility (if applicable), data and medical informatics assessments, and payer expectations. It's best to have a structured approach with a gated go/no-go decision step to maximize efficiency.

Tailor your RWE strategy for best results

There are important opportunities for utilizing RWE in the United States and China today, and companies need to tailor their approach by locality. If applied correctly, RWD can create valid RWE, which can be used in the approval process by regulatory agencies, offering an additional pathway to demonstrate the effectiveness of drugs for unmet medical needs.

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