AV POLICY FOCUS: REAL WORLD EVIDENCE

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Real World Evidence – Why It Cannot Replace Clinical Trials

WHAT IS REAL WORLD EVIDENCE?

The FDA defines real world evidence (RWE) as "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD)."[1]

RWD are "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." RWD sources include:

- Electronic health records (EHRs);
- Claims and billing activities; and
- Product and disease registries

RWD do not tell us how to compare new medical products against either existing alternatives or no specific treatment. For example, electronic health data are often incomplete and sometimes inaccurate especially as these data systems have enormous variability and often lack interoperability across health systems.

WHY ARE REAL WORLD DATA IMPORTANT?

Monitor drug safety. Data gathered *after* a drug's approval can be used to monitor side effects or long-term toxicity of a given drug. Often, the studies used by FDA confirming safety and efficacy to approve a drug (pre-approval studies) are too small and short to evaluate all possible harms.[2] Collecting RWD can allow researchers to observe and describe the impact of medical products on a wider population[3], and further evaluate safety signals generated from pre-approval studies. Randomized clinical trials often have multiple exclusions (for age and comorbidities) and in turn may not be reflective of the average population of patients who will likely use a given drug.

Inform approvals for new uses of drugs already on the market. For instance, FDA approved additional indications for transcatheter heart valves with evidentiary support form data collected in a post-market valve registry that was created as a result of a Medicare coverage decision.[4]

CAN RWE REPLACE CLINICAL TRIALS IN EXAMINING THE EFFICACY OF DRUGS?

No. Evidence gathered from RWD is a biased look backwards without scientific or statistical controls. Researchers since the 1940s have been aware of these biases and the potential erroneous presumptions inherent in analyses of RWD because clinicians do not prescribe therapies randomly. In contrast, information gathered in clinical trials is based on a participant's unbiased random assignment to one or more potential treatments (including standard treatment). This cancels out potential biased differences between patients other than the intervention received.

Drugs that receive FDA approval through the accelerated approval program are required to conduct trials that confirm the drug's benefits after it has been approved and marketed. A recent study examined whether it would be feasible to use RWD sources to emulate these confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.[5] Of the 50 confirmatory trials required by the FDA, none could be emulated using RWD. These findings suggest that currently available RWD sources and observational methods are unlikely to replace post-approval confirmatory trial requirements.

Although RWE has demonstrated promise in complementing clinical trial data for medical products, there has not been demonstrated evidence to suggest that RWE can be used to replace clinical trials and that it may be premature to pursue this goal legislatively or administratively.

HOW CAN RWE SUPPORT EVIDENCE GATHERED IN CLINICAL TRIALS?

RWE cannot and should never be the sole basis for drug approvals. It represents data that often are neither validated nor verified. With this in mind, policymakers should strengthen the evaluation and use of data gathered from observational sources by:

- Clarifying the definitions of "real world data" and "real world evidence" to appropriately classify research stemming from those definitions and to ensure that data gathered from observational sources not be conflated with confirmatory evidence determined from randomized control trials and that the latter not be supplanted by the former in the determination of safety and efficacy of human drug products.
- Encouraging the FDA to focus on true measures of diversity in clinical trials, rather than using RWD/RWE as a proxy for making clinical trials more representative.
- Ensuring that FDA requires observational studies conducted with real world data align with long-established FDA substantial evidence requirements. Such studies must produce scientifically valid data and those producing the data shall affirmatively confirm that the data meets the FDA's evidentiary requirements.
- Ensuring patient privacy protections are in place and aligned with informed consent documents to safeguard against health data being sold for regulatory decision-making around medical products.
- Clarifying product labels of FDA- approved drugs and biologics to include the limitations of RWE study findings.
- Using RWE strictly to augment but not replace randomized control trials that confirm direct patient benefit for accelerated approvals.

Endnotes

1 *Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence — What Is It and What Can It Tell Us? New England Journal of Medicine. 2016;375(23):2293-2297. doi:10.1056/NEJMsb1609216*

2 *Commissioner O of the. FDA's Sentinel Initiative - Background. FDA. Published online February 4, 2022. Accessed April 20, 2022. https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background*

3 *Hartz A, He T, Wallace R, Powers J. Comparing hormone therapy effects in two RCTs and two large observational studies that used similar methods for comprehensive data collection and outcome assessment. BMJ Open. 2013.*

4 *Dhruva SS, Ross JS, Desai NR. Real-World Evidence: Promise and Peril For Medical Product Evaluation. P T. 2018;43(8):464-472.*

5 *Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. JAMA Network Open. 2021;4(11):e2133667. doi:10.1001/jamanetworkopen.2021.33667*