Wednesday 24 July 2024

14:00-15:30 Invited Session 7 (Main Room)

Regulators' view of randomized and non-randomized evidence in drug development (Chairs: Adbel Babiker, Giota Touloumi)

FDA and Real-World Evidence

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A "randomized trials vs. observational studies" dichotomy oversimplifies what is more appropriately described as a spectrum of study designs ranging from randomized controlled trials (RCTs) to externally controlled trials to observational (non-interventional) studies. At the same time—and despite referring to traditional sources of data and types of study design—the terms real-world data (RWD) and real-world evidence (RWE) have become popular. In this context, the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) uses its existing evidentiary standard when evaluating randomized or non-randomized studies of drug-outcome associations.

As historical background, FDA has for decades encountered what we now call RWD/RWE (such as data from single-arm trials compared to historical controls). Increased interest in "RWE" is attributable to multiple factors, including improved access to detailed clinical information in the era of big data as well as research showing that non-interventional studies—despite various threats to validity—can generate results that emulate randomized trials. An FDA RWE Program, launched in 2018, has formally integrated assessments of RWD/RWE into day-to-day operations. Corresponding efforts reflect an understanding that evidence from non-randomized studies can serve as an addition to—not a replacement of—RCTs.

Numerous challenges exist when assessing drug-outcome associations using non-randomized comparisons and/or routinely collected clinical data. Nonetheless, trustworthy evidence can be generated when reliable and relevant data are analyzed using a rigorous study design. For example, a Cochrane report (https://doi.org/10.1002/14651858.MR000034.pub2) stated "on average, there is little evidence for significant effect estimate differences between observational studies and RCTs" and "factors other than study design per se need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies." An emulation of 32 RCTs using claims data and observational cohort designs (https://jamanetwork.com/journals/jama/fullarticle/2804067) found that although often not achievable, such studies "can reach similar conclusions as RCTs when design and measurements can be closely emulated."

As a notable regulatory example of RWE—based on a non-interventional study comparing data from a well-established registry with data from historical controls—CDER approved tacrolimus (Prograf®) in combination with other immunosuppressants for prevention of organ rejection in patients receiving lung transplants. Three additional issues are relevant: point-of-care RCTs

generate RWE when outcomes are identified using RWD; FDA is actively supporting efforts to update clinical trial regulations and promote clinical trial innovation; RCTs will continue to be the main approach to generating evidence for drug approvals.