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Issue Brief

Expanding the Use of Real-World Evidence Can Make FDA Regulatory Decisions Faster, Cheaper, and Just as Safe

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Introduction

New information technology gives the U.S. an opportunity to accelerate the development, review, and approval of new medicines. This can be done through greater use of real-world data (RWD) and real-world evidence (RWE) rather than through the results of expensive clinical trials alone.

Recent nominees for senior Department of Health and Human Services (HHS) leadership roles, such as Jim O'Neill, have proposed previously that the U.S. Food and Drug Administration (FDA) require only that new medicines are safe before they are sold, not that they are also effective.[1] In fact, O'Neill's suggestion was the approach that FDA followed until 1962. Under this policy,[2] greater use of RWD and RWE could help facilitate researchers' evaluation of a medicine's efficacy after it is marketed to the public.

FDA reviews applications to market new pharmaceuticals and oversees clinical trials designed and sponsored by new drug developers. In these clinical settings, researchers conduct randomized controlled trials (RCTs) in which participants receive either an experimental drug or the standard of care. Then the researchers assess which group fares better. This rigorous process generates valuable information about a drug's benefits and risks in an idealized setting, but it can be time-consuming and expensive. For treatments for rare diseases, this is especially challenging. The process for drug development and approval can benefit greatly by leveraging RWD, including routinely collected health information such as medical and insurance records. While not appropriate for all contexts, these data can supplement the information gleaned from traditional trials.

The high cost of the clinical trials required by FDA deters drug development and approval, hindering patients' access to new therapies. Greater use of RWD, which is collected outside of conventional idealized trials, and RWE about the benefits and risks based on such data can dramatically lower the cost of assessing new drugs. Trials that use this information from routine clinical conditions, rather than relying on the controlled experimental environment alone, are called pragmatic clinical trials.

The 2016 21st Century Cures Act[3] directed FDA to facilitate the use of RWD and RWE in the review of drug marketing applications and labeling changes—yet progress has been glacial, despite the potentially dramatic cost reductions. While FDA has issued numerous industry-facing guidance documents on RWD and RWE, the agency has not reported the challenges to increasing the use of these data and evidence and has not adopted quantitative goals for such use.

FDA should increase the use of RWE in drug regulation by increasing transparency into its use of RWE, supporting more research into the reliability of RWE, and committing to specific quantitative goals. Specifically, one-half of all supplemental applications for new uses of drugs should incorporate RWE by 2030. Also, there should be increased use of RWE in novel rare disease treatments. If FDA fails to adopt these goals, Congress should require them. In addition, an independent organization such as the National Academies of Sciences, Engineering, and Medicine (NASEM) should evaluate what regulatory obstacles in the U.S. hinder the use of pragmatic trials and should make recommendations for legislative or regulatory actions that might help overcome such obstacles.

A Different Type of Drug Trial

Concerns about the high and rising costs[4] of conventional drug trials have long fueled proposals for reform.[5] Some insightful suggestions for reform come from medical experts familiar with approaches used outside the United States. The U.S. Institute of Medicine[6] in 2012 published "Novel Ways to Get Good Trial Data: The UK Experience," a discussion paper by three British authors.[7] The paper explored the advantages of a community-based, cradle-to-grave universal health-care system for quick and low-cost pragmatic randomized trials. An advantage of these trials is that they generate assessments with external validity—meaning the results can be generalized beyond the experimental context of conventional trials—about the safety and effectiveness of competing medical products.

The recent "Randomised Evaluation of COVID-19 Therapy" (RECOVERY) trial used RWD from the U.K. and demonstrates several key advantages of this method in cost and speed, relative to conventional trials. RECOVERY illustrates how pragmatic randomized trials can quickly and cheaply feed into regulatory decisions and improve public health. Unlike conventional drug trials, pragmatic randomized trials do not address the benefits and risks of experimental drugs in idealized settings. Instead, such innovative trials provide information on the benefits and risks of new drugs in typical clinical environments.

Specifically, the RECOVERY trial was a pragmatic trial that randomized about 49,000 patients to a variety of different Covid-19 treatments, at a cost of about $500 per patient. This is highly cost-effective; on a per-patient basis, this is roughly 1.6% of what it traditionally costs to conduct a Phase 3 trial for an anti-infective drug.[8] Moreover, RECOVERY delivered answers quickly, opening in March 2020[9] and delivering its first results on June 16, 2020.[10] The trial found that steroids reduced death by one-third in hospitalized patients with severe Covid-19. Later, RECOVERY showed that patients with severe Covid-19 benefited from another drug, tocilizumab.[11] FDA used this evidence

in granting emergency-use authorization for tocilizumab and later approved expanding its on-label use for this purpose.[12] Finally, RECOVERY included participants who might have been excluded from a traditional trial, such as pregnant women and immunocompromised people.

The U.S., by comparison, did not carry out a pragmatic trial of Covid-19 therapies akin to RECOVERY, with high-level regulators like former FDA Principal Deputy Commissioner Janet Woodcock criticizing the use of "small crappy trials" and calling for more work to make clinical trials more affordable.[13] Before considering why trials like RECOVERY are so rare in the U.S. and what might be done to facilitate them, this brief reviews the recent history of congressional and administrative efforts to increase the use of RWE in drug trials considered by FDA.

Congressional and Administrative Actions

21st Century Cures Act

The 2016 21st Century Cures Act states that the secretary of HHS "shall establish a program to evaluate the potential use of real world evidence to help to support the approval of a new indication" for an already approved drug and "to help to support or satisfy postapproval study requirements."[14] FDA regulations use "indication" to describe the approved conditions of use that must be noted on the label of an approved drug product.[15] The act defines RWE as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials."[16] FDA is directed to issue guidance to the industry on the circumstances in which the industry and HHS secretary may rely on RWE and approve new uses of already approved drugs as appropriate. FDA guidance can also set the standards and methodologies for the collection and analysis of RWE. The 21st Century Cures Act allows the secretary to use RWE for other purposes, provided a sufficient basis exists for such use. Importantly, the act notes that the potential use of RWE does not alter the standard of evidence for approval of new pharmaceuticals.

FDA's 2018 framework for its RWE program provides these definitions:[17] [18]

- "Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources."
- "Real-World Evidence (RWE) is the *clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."

In this context, "routinely collected" means data collected outside of investigations intended to comply fully with FDA's lengthy regulations for new drug applications,[19] which target activities to test the safety and effectiveness of experimental pharmaceuticals. FDA's definitions of RWD and RWE include both randomized trials in real-world settings and studies or investigations using RWD without random assignment (i.e., observational or noninterventional studies).

A 2020 commentary[20] by officials from FDA's Center for Drug Evaluation and Research (CDER) suggests that there is no simple solution to the problem of when RWE and RWD are appropriate substitutes for traditional clinical trials in regulatory decisions. For example, pragmatic trials are probably inappropriate for an investigational drug (a drug that is not FDA-approved for marketing and is still being evaluated for new and potential uses) with a poorly understood safety profile, especially one that requires special protocols to administer.

Sponsors may also rationally wish to extract as much data from a trial as possible and prefer to conduct trials in settings where highly specialized (and expensive) laboratory testing is available. In some settings, randomization itself may be inappropriate. For rare diseases with a poor and well-understood prognosis and no approved treatment, for example, the use of a control group is ethically challenging. Thus, determining whether the use of RWE and RWD in a given regulatory decision is appropriate may best be determined on a case-by-case basis.

Prescription Drug User Fee Act

FDA has committed to advancing the RWE program as part of the agency's prescription drug user fee program. User fees, collected from drug industry applicants who want to have their product approved by FDA, are a major source of revenue for the agency. The user fees allow for an increase in FDA resources dedicated to drug application review. In 2022, President Joseph Biden signed into law the FDA User Fee Reauthorization Act, the seventh version of the Prescription Drug User Fee Act (PDUFA), first enacted in 1992. PDUFA is responsible for a sizable portion of the budgets of the Center for Biologics Evaluation and Research (CBER), which regulates traditional biologics such as vaccines, and CDER, which regulates prescription brand-name and generic drugs, over-the-counter drugs, and most therapeutic biologics.[21]

FDA typically secures increases in industry user fee funding by agreeing to make commitments that should improve the performance of its review of new drugs and biologics.[22] One of FDA's commitments associated with the 2022 reauthorization, "Advancing Real-World Evidence for Use in Regulatory Decision-Making," states:[23]

> [T]he Advancing RWE Program seeks to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements.

The commitment document describes in detail a process for FDA's pilot Advancing RWE Program, including a review of plans for RWE studies and submission of one or two "eligible and appropriate" proposals to use RWE and RWD twice annually in fiscal years 2023 and 2024 and one to four such proposals twice annually in fiscal years 2025 to 2027.[24]

Assessing FDA's use of such proposed studies is quite difficult because the PDUFA commitment letter sets limits on the public disclosure of information about such studies. The sponsor of the RWE/RWD proposal and FDA must "agree on the information that FDA may share publicly" to participate in the Advancing RWE Program.[25] If they are unable to come to an agreement, "that proposal will no longer be part of the Advancing RWE Program and the Agency will proceed with an alternate submission." These provisions mean that the agency's public reporting on its use of RWE is constrained by the need to get the sponsor's agreement for each such disclosure.

The PDUFA commitment letter also states[26] that "FDA will report aggregate and anonymized information, on at least an annual basis … describing RWE submissions to CDER and CBER."[27]

The reports by CDER[28] and CBER[29] about their use of RWD and RWE in regulatory decisions in fiscal year 2023 indicate that only tocilizumab and lacosamide, an antiseizure medication, have been approved using RWE. These reports provide no clear insights into what aspect of the data and evidence available for tocilizumab and lacosamide persuaded FDA in making regulatory decisions for these products. To put these two cases in perspective, in 2023 alone, FDA approved[30] more than 100 applications for new indications to repurpose existing drugs, suggesting that many more of those repurposing applications could be supported in part by RWD and RWE. Furthermore, the reports do not mention the use of RWD and RWE for treatments for rare diseases,

although some observers note that such use "would be of particular value to the development of drugs for rare diseases where it is incredibly valuable to triangulate safety and efficacy data from multiple sources to gain confidence in the findings."[31]

Publicly available information on FDA's use of RWE is inadequate to identify obstacles to greater use of RWE in FDA's regulatory decisions. It is also inadequate to identify the roles of mere bureaucratic reluctance at FDA or risk aversion on the part of sponsors considering using such data and evidence in their drug approval applications.

RWE and RWD Can Expand Approved Uses

Both the 21st Century Cures Act[32] and the 2020 commentary by FDA officials[33] on uses of RWD and RWE in regulatory decisions recognize that drugs may have additional uses beyond those listed on approved labels. RWE can be used to justify new indications for already approved drugs.

A recent report by NASEM explains that RWD and RWE may be especially important for new treatments of rare diseases.[34] Approximately 7,000 to 10,000 life-threatening rare chronic diseases afflict some 30 million Americans and around 300 million people globally, according to the report. A large majority of such diseases have no approved treatment, partly because they are so rare that recruiting patients for a standard placebo-controlled trial is difficult if not impossible. The report states:[35]

> The low prevalence of rare diseases and conditions, incomplete understanding of their underlying biology, ethical challenges in giving placebo to patients with rare diseases in double-blind clinical trials, and limitations in the ability to conduct randomized clinical trials (RCTs) for new therapies for them, have necessitated the collection and use of data from sources other than traditional RCTs for marketing authorization applications for rare disease drug products.

The NASEM report mentions several examples of the use of RWD and RWE for rare disease therapies, often called orphan drugs. To take one example, in 2023 FDA approved SKYCLARYS (omaveloxolone), the first approved treatment for "Friedreich's ataxia, a rare, inherited, neurodegenerative disease that typically affects children and teens and gradually worsens over time."[36] The sponsor submitted supplemental data with its new drug application, including data from "a cohort of natural history participants."[37] In other words, the drug sponsor submitted RWE along with its application, and the rarity of the disease combined with the positive results from clinical RWE led FDA to expand the use of omaveloxolone.[38]

FDA should do more to encourage RWE and RWD including nonrandomized studies for rare diseases, especially those with a poor prognosis and well-understood disease progression.

Pushing the Frontiers of Regulatory Science

Today, broadening the use of pragmatic randomized trials and increasing selective use of nonrandomized observational trials for rare diseases are possible. However, substantially greater uses of RWE and RWD likely require advances in regulatory science. Inferring causation with non-observational studies is challenging, but this caution should not preclude FDA support for research to advance uses of RWE and RWD. FDA has already funded some research into these questions.

For example, one might ask whether investigations of the health effects of drug products conducted without randomization yield estimates close to those from conventional RCTs. Fortunately, FDA oversees and supports numerous research projects on this question.[39] An FDA database[40] last updated in November 2023 lists two completed RWE projects using observational RWD.

One recent report[41] "aimed to emulate RCT designs" with "observational analogues" and determine whether pragmatic, nonrandomized studies can produce similar findings to the RCT designs. The report found "a Pearson correlation of 0.82" between the two types of studies and that RWE "studies can reach similar conclusions as RCTs when design and measurements can be closely emulated, but this may be difficult to achieve." An important strength of this study is that after developing the study design, "all attributes of the database studies were predefined and protocols were registered at ClinicalTrials.gov"[42] before the analysis began. Such preregistration helps to limit intentional or inadvertent tailoring of the study execution to support any particular finding.

A more recent study, published in 2024, conducted a meta-analysis of differences in effect sizes between the results from RCTs and RWE studies.[43] Most of the differences could be attributed to whether the treatment started in the hospital, the discontinuation of some baseline treatments when an RCT began, and delayed onset of drug effects. Taking into account these three factors, the scholars found that heterogeneity between results of RCTs and RWE was almost nil.

These results suggest that, in some contexts, nonrandomized data can achieve results similar to RCTs, but more research should be conducted. Continued funding for research exploring these types of questions is essential for pushing regulatory science forward.

Conclusion and Recommendations

I recommend the following steps to facilitate reforms that would lower the cost of assessing which new drugs and new uses of drugs have benefits that outweigh their risks.

1. An independent organization such as NASEM should evaluate what legal and regulatory obstacles in the U.S. hinder the use of RWD in a randomized trial such as RECOVERY and should make recommendations for legislative or regulatory actions that might help overcome such obstacles.

2. Incoming leadership at FDA should expand the agency's annual reporting about its use of RWD and RWE in regulatory decisions. This would provide information about when RWD and RWE are acceptable to the agency and when they are not. Concerns over inappropriate disclosure of confidential commercial information should not impede such efforts, provided that

additional descriptions of the use of RWD and RWE in marketing applications do not allow identification of specific companies or products. This increase in reporting should distinguish between labeling changes that include new indications and confirmatory evidence in instances where conventional RCTs are especially challenging, such as treatments for rare diseases.

The NASEM report concludes[44] that FDA should collect and disseminate information on how state-of-the-art regulatory science informs regulatory decision-making for rare disease drug products. This new reporting would clearly distinguish pragmatic randomized trials from nonrandomized observational investigations, though both use RWD to generate RWE.

3. FDA should fund more projects to see how RWE and RWD can work in various settings. RWD and RWE have the potential to save time and money, but multiple empirical questions about their proper application remain and merit additional research.

4. FDA should set a strategic goal for the use of RWD and RWE in regulatory decisions. An ambitious but achievable goal would be to have half of supplemental new drug applications and biologic applications approved using pragmatic randomized trial data by 2030. Additionally, RWD and RWE should be used in 10 applications for novel rare disease treatments approved in 2030, including nonrandomized trials. FDA approves about 20 new molecular entities for rare diseases annually.[45]

   Currently, FDA does not appear to have such goals, even though the promise of RWD and RWE has been known for years. Adopting a quantitative strategic goal for the use of RWD and RWE in regulatory decision-making would signal that FDA is serious about increasing their use. Congress should direct FDA to set such a goal if the agency does not set one on its own.

Greater use of RWD and RWE could dramatically lower the time and expense of preparing marketing applications for medical products and conducting post-marketing studies of the drugs' safety and efficacy.

With fewer barriers to complete drug applications, product developers will invest in increased innovation and competition among new products. The promise of pragmatic trials, RWD, and RWE in regulatory decisions demands that FDA do more to promote their use.

Endnotes

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