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The New FDA Real-World Evidence Program to Support Development of Drugs and Biologics

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Abstract

FDA has launched a Real World Evidence (RWE) Program for using real-world evidence (RWE) to help support new indications for already approved drugs or biologics and postapproval studies. The plan also includes stakeholder engagement efforts, demonstration projects, leadership activities, and development of guidance documents to assist developers interested in using real-world data (RWD) to develop RWE to support FDA regulatory decisions. This plan was mandated by the Cures Act passed in 2016. Over the 24-month period from passage of the law until FDA officially announced their program, FDA has gone to considerable efforts to educate the public about the benefits of RWE and encourage researchers to consider situations where RWE trials can generate useful information. Through a variety of stakeholder engagement projects, including publication of articles in medical journals, participation in public meetings, and development of initiatives, FDA has put more effort into preparing the medical community for its new emphasis on RWE than any other new policy that I can recall.

Keywords

FDA, observational, pragmatic, randomized controlled trial, real-world evidence

Introduction to the FDA RWE Program

On December 6, 2018, FDA Commissioner, Scott Gottlieb, announced that FDA is initiating a new strategic program to promote the agency's use of real-world evidence (RWE). This plan was mandated by the Cures Act passed in 2016.[1] The program is called the Real-World Evidence Program.[2] At the same time, FDA released a 37-page document describing its Framework for Real World Evidence Program.[3] The Framework document contains discussions of how to improve the quality of data in RWE trials; the use of RWE in effectiveness trials; the use of RWE in safety studies; the need for a common external real-world data (RWD) control in RWE studies; the need for data standards for submissions; the use of electronic source data for RWE; and stakeholder engagement projects.

Definitions

RWD is information gathered through observations of routine clinical practice from multiple sources that can be linked together to provide meaningful patterns. RWD is based on patients and their clinicians choosing treatments according to the patients' clinical characteristics and preferences[4]—not the needs of a researcher to maintain consistency in recruitment or treatments. RWE is the analysis of RWD from a study designed with a high degree of pragmatism.[4] This new FDA program is intended to leverage information gathered from sources not necessarily established to collect data to use in randomized controlled trials. RWE sources can include electronic health records (EHRs), paper medical records; administrative claims databases, clinical registries, census records, sensors, and even social media.[5,6] Gottlieb also stated that the FDA program is intended to inform and shape the FDA's decisions across its drug and biologic development efforts.[2]

21st Century Cures Act

This was an awaited move by FDA that was triggered by the 21st Century Cures Act (Cures Act) that was signed into law on December 13, 2016.[3] This law was designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.[7] Specifically the law required FDA to develop a framework and guidance for evaluating RWE in the context of regulating drug and biologics (but not devices) to support approvals of new indications for

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previously approved drugs, and to support or fulfill post-approval study requirements.[8] The law extended FDA's ongoing efforts to incorporate the perspectives of patients into the FDA's decision-making process.[9] Cures was intended to allow modernization of clinical trial designs and clinical outcome assessments to speed up development and review of novel medical products.

Observational Studies

The FDA RWE Program will cover observational studies that generate RWE in some capacity from sources other than traditional clinical trials. A clinical trial is a research study in which subjects are prospectively assigned to one or more interventions to evaluate the effects of interventions on health-related outcomes. A traditional clinical trial is usually supported by a research infrastructure that is separate from routine clinical practice and is designed to control variability and maximize data quality. Observational studies are noninterventional study designs in which data is collected on patients within the context of medical care. A retrospective observational study identifies a population and determines the type of treatment from historical data generated prior to the initiation of the study. A prospective observational study identifies a population of interest at the start of the study. Outcomes data are collected from that point forward.[4]

Recent Publications by FDA About RWE

Over the next two years after passage of CURES FDA officials published eight articles in high profile medical journals to explain the benefits of using RWE in regulatory decisions. Two days after the CURES act passed, on December 8, 2016, a team of FDA officials published an article by Sherman et al in the *New England Journal of Medicine*, titled "Real-World Evidence—What Is It and What Can It Tell Us?" The article concluded, "We believe that when the term "real-world evidence" is used, the primary attribute that distinguishes it from other kinds of evidence is related to the context in which the evidence is gathered — in other words, in clinical care and home or community settings as opposed to research-intensive or academic environments. Most important, the distinction should not be based on the presence or absence of a planned intervention or the use of randomization."[6]

In March 2017 a second article about RWE was published by Sherman et al in *Nature Reviews*, titled "Accelerating Development of Scientific Evidence for Medical Products Within the Existing US Regulatory Framework." The article advocated "routinely integrating RCTs and RWE trials into a continuum that progressively demonstrates that a therapy can be used safely and efficaciously, and then quickly pivots to produce evidence to accurately inform clinical use, will yield a comprehensive understanding of how to use medical products in practice."[10]

On August 22/29, 2017, a third article about RWE was published by Jarow et al from FDA in *JAMA*, titled "Multidimensional Evidence Generation and FDA Regulatory Decision Making: Defining and Using 'Real-World' Data." The article concluded, "Many questions about a drug remain unanswered at the time of approval; some of them involve optimal dosing regimen, longer-term outcomes, and outcomes in various subpopulations. It is not feasible to answer all of these questions with a traditional randomized controlled trial (RCT). Using RWE to begin to address these questions is preferable to having no evidence whatsoever."[11]

On September 13, 2017, a fourth article about RWE was published by Khozin et al from FDA in *Journal of the National Cancer Institute*, titled "Real-World Data for Clinical Evidence Generation in Oncology." The article's abstract stated, "Prospective collection of RWD can enable evidence generation based on pragmatic clinical trials (PCTs) that support randomized study designs and expand clinical research to the point of care. PCTs may help address the growing demands for access to experimental therapies while increasing patient participation in cancer clinical trials."[12]

In March 2018, a fifth article about RWE was published by a group of authors, including first author Khozin from FDA again, in *Oncologist*, titled "Characteristics of real-world metastatic non-small cell lung cancer patients treated with nivolumab and pembrolizumab during the year following approval." This article promoted the use of RWE as useful for informing decisions and stated that evidence gathered in conventional clinical trials used to assess safety and efficacy of new therapies is not necessarily generalizable to real-world patients receiving these drugs following regulatory approval. Real-world evidence derived from electronic health record data can yield complementary evidence to enable optimal clinical decisions."[13]

In May 2018 a sixth article about RWE was published by a group of investigators, including Khozin from FDA again, in *Health Affairs*, titled "Real-World Evidence in Support of Precision Medicine: Clinico-Genomic Cancer Data as a Case Study." This article proposed creating a database linking real-world clinical data, genomic data, and mortality data[14] to create a real-world study population that could provide useful generalizable evidence for precision medicine interventions and development of contemporaneous external control arms for RWE studies.

In September 4, 2018, a seventh article was published by Corrigan-Curay et al[15] from FDA in *JAMA* about RWE, titled "Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness." This article discussed potential uses of RWE for regulatory decisions and mentioned two examples of research collaborations between FDA and Flatiron Health, a company developing quality real-world oncology data, as well as FDA and CancerLinQ, the American Society of Clinical Oncology's big data initiative. The article also stated that FDA will be supporting the first randomized clinical trial (IMPACT-Afib) to use Sentinel,

which is its active surveillance system.[16] To date, Sentinel has only been used to assess safety. The IMPACT-Afib trial will test an educational intervention to overcome underuse of oral anticoagulants for reducing the risk of stroke in patients with atrial fibrillation.[17]

On September 11, 2018, an eighth article was published by Irony from FDA in *JAMA* about RWE, titled "Case-Control Studies: Using 'Real-World' Evidence to Assess Association." This article discussed how to supplement RCTs with RWE from case control studies to compare the occurrence of an outcome with and without an exposure.[18]

Meetings and Collaborations

FDA has sponsored several meetings about its RWE initiatives. The first was on September 13, 2017 when, through its cooperative agreement with the Duke Margolis Center for Health Policy, FDA convened a public meeting (titled "Public Workshop: A Framework for Regulatory Use of Real-World Evidence") that informed development of FDA's RWE framework.[19] The FDA provided insights regarding potential uses of RWE for regulatory decisions, but pointed out that are these are just one aspect of a larger challenge, which is to also leverage RWE for other nonregulatory health policy issues, as well.[20]

FDA has also sponsored a three-meeting series convened by the National Academies of Sciences, Engineering, and Medicine (National Academies) over the past 1.5 years to support medical product development and evaluation, as well as foster development and implementation of the science and technology of RWE generation and utilization. Workshop 1 ("Incentives" on September 19–20, 2017) focused on how to align incentives to support collection and use of RWE in health product review, payment, and delivery, as well as incentives needed to address barriers impeding the uptake of RWE, including barriers to transparency. Workshop 2 ("Practical Approaches" on March 6–7, 2018) illuminated what types of data are appropriate for what specific purposes and suggested practical approaches for data collection and evidence use by developing and working through example use cases. Workshop 3 ("Application" on July 17–18, 2018) examined and suggested approaches for operationalizing the collection and use of RWE.[21,22]

FDA has announced that they are engaged in a project managed by the Clinical Trial Transformation Initiative (CTTI) to evaluate the use of RWD in randomized trials to generate RWE about medical products.[3] On June 12-13, 2018, CTTI convened an expert meeting with key stakeholders, including FDA, to explore the appropriate use of electronic health records and payment claims (RWD) in randomized controlled trials (RCTs) to generate RWE in support of regulatory decision-making.[23] FDA has also created a RWE program based on its Sentinel Initiative that that contains curated electronic health data from more than 100 million people from 31 health plans and academic organizations. The program, called, FDA-Catalyst, enables researchers to conduct PCTs embedded in their real-world delivery systems.[24]

Where Do We Go From Here?

It is clear that FDA is heavily supporting the adoption of RWE trials as important sources of evidence to be used for regulation of drugs and biologics. RWE studies have much to offer as a complement to RCTs. Some disadvantages to pharmaceutical companies who fund RCTs for approvals or expansions for indications are that RCTs are expensive, they require a long time to complete, and recruitment can be difficult if the eligibility requirements are strict.[25] Clinicians often question the generalizability of RCTs in the real world because their subjects might be a subset of patients who are most likely to benefit, but the product is approved for a larger group than was part of the registration study. Therefore, the postapproval results on a wide population might turn out to be disappointing. Furthermore, in an RCT there can be a study effect that tends to make many interventions appear particularly appealing during the trial.

FDA is encouraging investigators to step forward with RWE to support expanded indications for already-approved drugs and biologics in the course of applications for new indications or new intended use populations. At the same time FDA is facilitating collection and analysis of RWE with many initiatives, including new guidances related to RWE, which will help establish this type of evidence as a valuable robust complement to RWE.[3] As datasets expand, evidence collection processes become more rigorous, and reporting processes become more standardized, it is likely that FDA as well as clinicians, public health leaders, and payers will all become increasingly interested in how products perform in the real world and not just the somewhat sterile setting of a RCT. These stakeholders will seek out and collect new sources of RWE.

However, RWE studies have their own risks of bias, which can be controlled for in a RCT. RWE trial biases include nonrandomized risk factor distribution (confounding bias), intervention allocation by degree of illness (treatment selection bias), and nonrandom engagement with therapy (adherence bias). Patients who are most likely to have a favorable outcome, if systematically assigned to a particular intervention, will do better irrespective of the intervention, and the RWE study will be biased in favor of their intervention. Missing or inaccurate data can also bias a RWE study.[26,27] These risks must be carefully eliminated as much as possible in a RWE study. There is a growing literature and set of methodologic and procedural recommendations of how to address confounding and bias in observational RWE studies. Much progress has been made in dealing with these issues in observational studies and a number of recommendations have been made by many experts working on task forces and expert panels.[28-33]

Nonregulatory RWE Studies

Even as use of RWE for regulatory purposes is being facilitated by FDA, many trials are also currently being conducted on interventions that do not require FDA approval. These include lifestyle activities, optimal drug dosing, and selection of best practices. Such nonregulatory studies can all be performed with RWE much easier than with RCTs, providing that the potential flaws of the RWE paradigm can be overcome by emerging standards and policies for collection, analysis, and reporting of real-world data.[34] RWE trials are becoming more widespread, and the ongoing support of FDA will accelerate their growing importance.

Abbreviations

CTTI, Clinical Trial Transformation Initiative; EHRs, electronic health record systems; PCTs, pragmatic clinical trials; RCTs, randomized controlled trials; RWD, real-world data; RWE, real-world evidence.

Declaration of Conflicting Interests

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