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REAL WORLD EVIDENCE : WHAT IS THE BIG DEAL WITH THE FDA'S NEW RWE PROGRAM ?

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609-681-5074 ext 102
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We provide clinical trial biostatistics and programming solutions to the pharmaceutical, biotechnology, life science and research industry. www.princetonpharmatech.com

Background

From start to finish, research, development, and obtaining FDA approval for the use of new medical drugs and devices takes an average of 12 years and 7 years, respectively. This process is often arduous and costly, meanwhile, millions of patients suffer from ailments and conditions that could be eased by the use of these emerging technologies.

Introduction

In an effort to streamline the clinical approval process and accelerate product development to more quickly and efficiently benefit medical patients, lawmakers passed the 21st Century Cures Act (known as the Cures Act) in December 2016. The act authorized $6.3 billion in funding to be allocated for efforts such as improving access to healthcare for small businesses, increasing resources for mental health care and remodeling aspects of medical research and development. As a result of the Cures Act, the FDA has published several new guidelines and protocols regarding changes in research compliance and introducing new techniques. One such change includes the introduction of the Real-World Evidence program, for which the FDA recently published a framework to describe its applications and benefits. This white paper will outline some of the major ideas presented in the framework, and provide a basic understanding of how these concepts can benefit you in your post-market research.

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What is the difference between Real-World Data and Real-World Evidence?

While RWD refers to the raw data collected, RWE refers to the clinical evidence derived from the analysis of RWD.

When it comes to real-world data (RWD) and real-world evidence (RWE), the term "real-world" is in reference to how approved, or post-market, medical drugs, and devices are being used outside of a controlled clinical trial environment. In other words, how they are being used in practice, and how the use of these products affects the health and status of the patients using them each and every day. It is important to note that the use of this information can only be applied to drugs and devices that are post-market, as pre-market products have no real-world experience until they are approved.

The distinction between RWD and RWE is technical but important to understand nonetheless. RWD refers to the data that reflect patients' health status and/or the delivery of healthcare. These data provide opportunities to generate evidence to better understand the clinical outcomes of medical and procedural interventions. RWD can be generated from a variety of sources, including electronic health records (EHR), claims and billing data, product and disease registries, personal devices, and patient-generated health data. The use of RWD can also be implemented in several study designs, such as randomized trials and observational studies.

While RWD refers to the raw data collected, RWE refers to the clinical evidence derived from the analysis of RWD. The evidence generated by RWD typically relates to the usage of a medical product and potential benefits or risks associated with its usage. RWE can be used to inform therapeutic development, outcomes research, patient care, research on healthcare systems, quality improvement, safety surveillance and well-controlled effectiveness studies. It also provides information on how factors such as clinical setting and provider and health-system characteristics influence treatment effects and outcomes. More importantly, RWE may have the potential to allow researchers to answer these questions efficiently, saving time and money while yielding answers relevant to broader populations of patients than would be possible in a specialized research environment.

Why use RWD and RWE?

In taking advantage of the FDA's new RWE program, researchers are able to evaluate the unique aspects of post-market medical products as they are used in the real world. This provides opportunities to use RWE to support the approval of new indications for drugs and biological products already approved or to support and satisfy post-approval study requirements, such as monitoring safety and efficacy. It can also provide evidence for optimal dosages, uses, and applications in real-world settings.

It is widely acknowledged that gaps exist between the scientific evidence collected on medical products during pre-approval clinical trials, and the evidence necessary to inform their optimal use in real-world environments. Effective use of RWD and adequately generated RWE may serve to close this gap. However, there remain issues related to lack of transparent regulatory structures that also accommodated a modern, robust, and diverse evidence base. These issues are addressed through the FDA's RWE framework and will be discussed later, along with methods to alleviate the effects of these issues.

By using data that already exists in various databases, research teams can limit the resources and time needed to gather this information otherwise. Most sources of RWD are built through the collection of data routinely gathered for purposes unrelated to their use as RWE, such as medical records and disease registries. Repurposing this information can provide important evidence that may otherwise be unattainable in research settings.

How can RWD and RWE be used in practice?

RWD in Practice

The FDA may use RWD to monitor post-market safety, identify adverse events and to make regulatory decisions. On the other hand, medical product developers generally use RWD and RWE to support clinical trial designs and observational studies to generate innovative, new treatment approaches. RWD may potentially be used as some or all of the evidence necessary for understanding medical device performance at different points in the total product life cycle (TPLC). Other purposes for which RWD may be used include generating hypotheses for future studies, serving as control data, providing evidence to expand product use, and generating post-market safety data. A longer list of more specific RWD applications can be found in Box 1.

RWD sources can be used as data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials; pragmatic clinical trials; and observational studies (prospective and/or retrospective). Furthermore, the FDA has been implementing the National Evaluation System for health Technology (NEST) to leverage RWD in order to more quickly identify safety problems and to better understand the benefit-risk profile of devices used in clinical care. Whether RWE provides acceptable valid scientific evidence or not depends on whether RWD are of sufficient quality, that is, whether RWD were accurately and reliably captured at clinically relevant time intervals throughout the device lifecycle. Under the right conditions, RWE may be suitable to support the clearance or approval of a new device, or the expansion of the indications for use of devices that are already on the market.

RWE in Practice

The generation of RWE is only as accurate and reliable as the data source from which it is extrapolated. Data sources can vary greatly in quantity and quality of available data, and the FDA lays out methods to identify reliability and reconcile issues that may arise due to the data variability. Consequently, the FDA has recommended limited circumstances in which to utilize RWE, to ensure research quality. RWE may be used to supplement the total evidence required for post-market clearances or approvals. Other applications of RWE in pre-market decision-making may also be possible, particularly as RWD systems and analysis methodologies advance.

When developing a new RWD source, consultation with FDA and other stakeholders is recommended to ensure that relevance and reliability are addressed in the initial design. A study protocol and analysis plan should be created prior to accessing, retrieving, and analyzing RWD, regardless of whether the RWD are already collected (retrospective) or if they are to be

collected in the future (prospective design). The FDA recommends the use of the pre-submission process when considering the development of a study using RWD in a regulatory submission.

EXAMPLES OF RWD IN PRACTICE

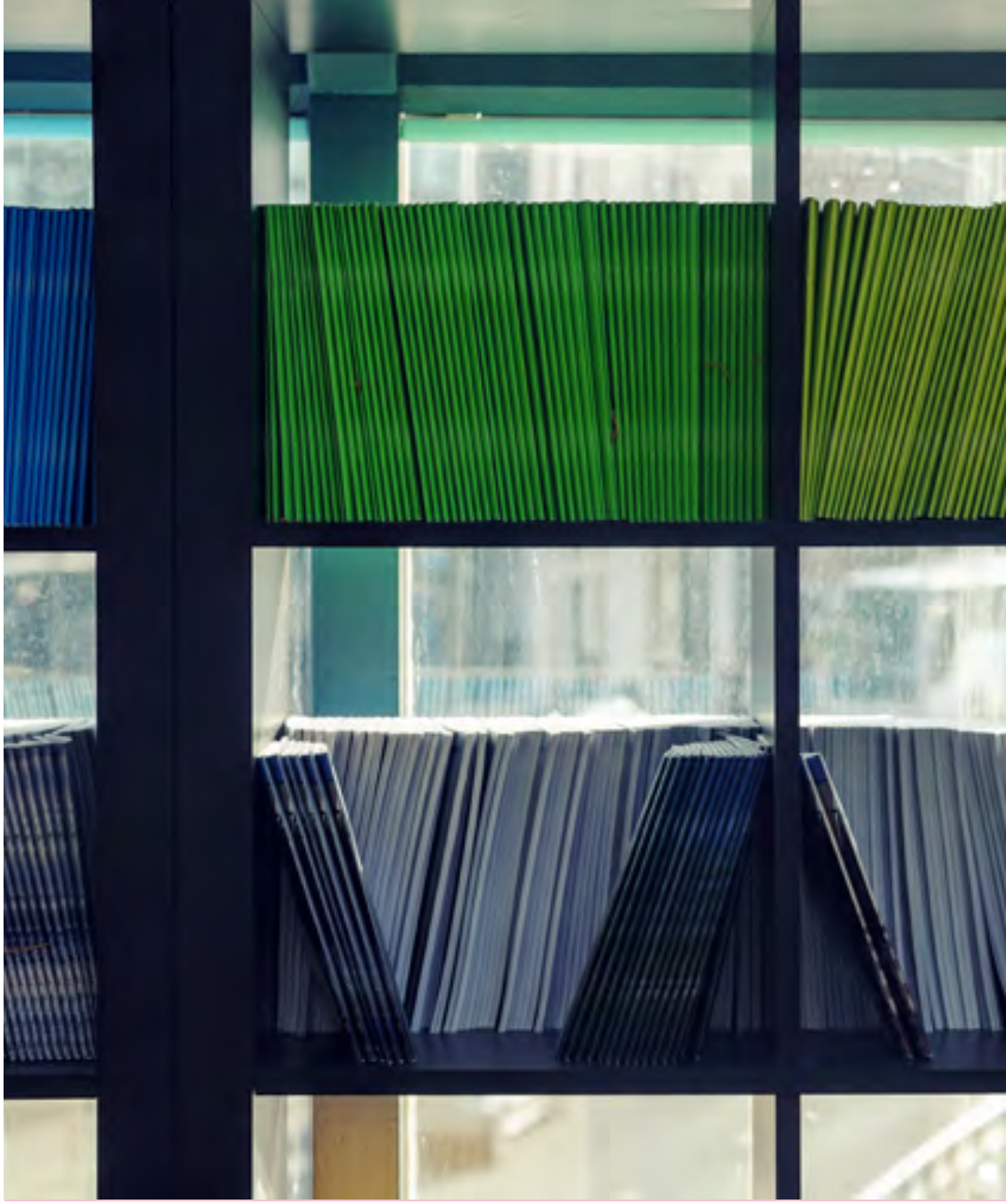
- for generating hypotheses to be tested in a prospective clinical study;
- as a historical control, a prior in a Bayesian trial or as one source of data in a hierarchical model or a hybrid data synthesis;
- as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance in a setting where a registry or some other systematic data collection mechanism exists;
- as evidence to identify, demonstrate, or support the clinical validity of a biomarker;
- as evidence to support approval or granting of an Humanitarian Device Exemption, Premarket Approval Application (PMA), or De Novo request;
- as support for a petition for reclassification of a medical device under section 513(e) or (f)(3) of the FD&C Act;
- as evidence for expanding the labelling of a device to include additional indications for use or to update the labelling to include new information on safety and effectiveness
- for public health surveillance efforts. Through ongoing surveillance, signals are at times identified that suggest there may be a safety issue with a medical device. RWE may be used to refine these signals for purposes of informing appropriate corrective actions and communication;
- to conduct post-approval studies that are imposed as a condition of device approval or to potentially preclude the need for post-market surveillance studies ordered under section 522 of the FD&C Act;
- in certain circumstances, for use in generating summary reports of Medical Device Reports (MDRs); and
- to provide post-market data in lieu of some pre-market data

Sources of RWD and Applications of RWE

Accuracy is essential when compared to verifiable source documentation for RWD elements, regardless of whether RWD is collected by administrative databases; or abstracted, aggregated and stored in disease- or treatment-specific databases (i.e., registries); or collected and aggregated through other means.

Verifiable source documentation for RWD elements includes, but is not limited to: paper or electronic inpatient and outpatient medical records and case histories, diagnostic laboratory and imaging data, patient preference information, patient-reported outcome measures, UDI and other device identifiers, and performance data that exist within the device such as self-diagnostics, error codes, and patient diagnoses/treatments delivered.

The generation of RWE is only as accurate and reliable as the data source from which it is extrapolated.



When is it appropriate to use RWD/ RWE to support decision making?

Primarily, RWE has been used to evaluate the post-market safety of approved medical technologies. Currently, the agency carries out post-market safety monitoring of the approved indications via the Sentinel system, which has data on more than 100 million individuals within the network of 18 data partners and collaborating institutions.

With the recent implementation of the RWE program, the FDA is exploring how RWD/RWE can be used to support regulatory decisions regarding product effectiveness. Under the scope of the RWE program, the FDA will not consider evidence from conventional randomized trials as RWE. Instead, RWE must be generated through trial designs that have the potential to generate RWE. These trial designs are discussed further in Box 2.

Although data generated via conventional randomized controlled trials are not considered RWD by FDA standards, clinical trials that incorporate healthcare system data may generate RWE and may be used to assess potential benefits or risks of a drug. Here are two studies that demonstrated successful integration of RWD into conventional clinical trials in synthesizing RWE to support benefit/ risk assessment of the interventions:

ADAPTABLE

Aspirin Dosing: A Patient Centric Trial Assessing Benefits and Long-Term Effectiveness) trial

VALIDATE-SWEDEHEART

(The Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry) trial

Observational studies have been the source of RWD to support regulatory safety decisions; however, due to non-random assignment of treatment, it is challenging to establish a causal inference that must be addressed to support effectiveness decisions. The FDA is aware of the rigorous development of study designs and statistical methods to replicate randomized trials in the settings of observational studies; therefore, as part of its RWE program, the agency will consider the potential role of observational studies as RWD in its contribution to support evidence in drug effectiveness.

EXAMPLES OF RWD IN PRACTICE

HYBRID DESIGN CLINICAL TRIALS:

In a hybrid design trial, certain elements of the study could rely on the collection and analyses through RWD extracted from medical claims, EHRs, or laboratory and pharmacy databases. Hybrid trials could use RWD for one clinical outcome (e.g., hospitalization, death) in combination with other traits that were harvested via conventional randomized trials (e.g., specified entry criteria, monitoring and collection of additional study endpoints by dedicated study personnel).

OBSERVATIONAL STUDIES:

Any non-interventional clinical study design, whether prospective or retrospective, can be considered for generation of RWE. In a retrospective study, the population of interest is identified and exposure/treatment are determined the from historical data (i.e., data generated prior to the initiation of the study). The variables and outcomes of interest are determined at the time the study is designed. In a prospective observational study, the population of interest is identified at the start of the study, and exposure/treatment and outcome data are collected from that point forward. Observational clinical studies may also be used to generate RWE that is relevant to determine effectiveness of a treatment, therefore the FDA will consider the evaluation of observational clinical studies using RWD to support product effectiveness determinations.

PRAGMATIC CLINICAL TRIALS:

The pragmatic clinical trials can include some elements that more closely resemble routine clinical practice. Pragmatic trials often rely on RWD and have the potential to generate RWE.

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Relevance and Reliability of RWD

The quality and significance of RWE are only as robust and reliable as the data from which it is generated. In order to determine the suitability of RWD for regulatory decision-making, the FDA assesses the relevance and reliability of the source and its specific elements.

Factors associated with the relevance of RWD primarily are:

SUFFICIENT DETAILS

The RWD contain sufficient details to capture the use of the device, exposures, and the outcomes of interest in the appropriate population (i.e. the data apply to the question at hand)

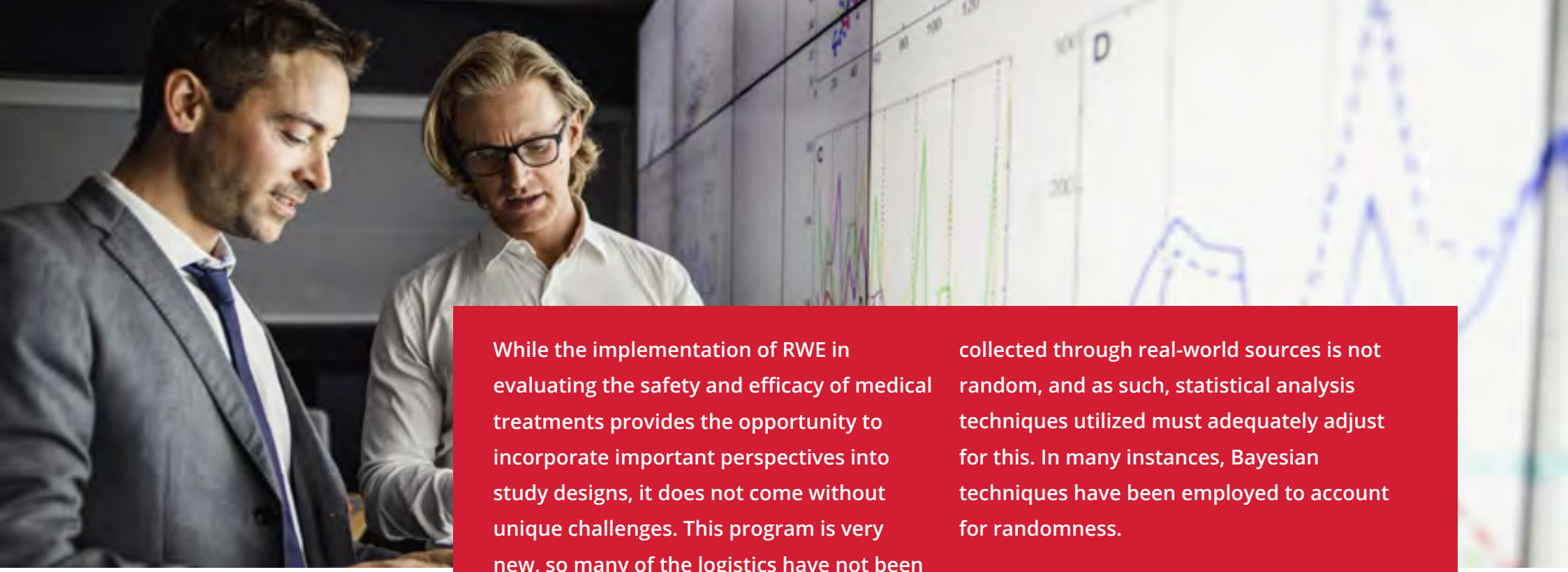
CAPABILITY TO ADDRESS SPECIFIC QUESTIONS

The data elements available for analysis are capable of addressing the specified question when valid and appropriate analytical methods are applied (i.e. the data are amenable to sound clinical and statistical analysis)

INTERPRETABLE

The RWD and RWE they provide are interpretable using informed clinical/ scientific judgment.

Reliability of RWD is also associated with several factors. The primary factors the FDA considers for assessing the reliability of RWD include how the data were collected (data accrual), and whether the people and processes in place during data collection and analysis provide adequate assurance that errors are minimized and that data quality and integrity are sufficient (data assurance). Data assurance consists of the quality of data element, population, adherence, completeness and consistency across sites and over time, and so forth. In addition, the RWD analysis protocol should be prospectively defined.



ASK OUR EXPERTS

What will the future of using RWD/RWE look like?

While the implementation of RWE in evaluating the safety and efficacy of medical treatments provides the opportunity to incorporate important perspectives into study designs, it does not come without unique challenges. This program is very new, so many of the logistics have not been entirely worked through, and the long-term impacts are largely unknown. Researchers looking to utilize RWE must find vendors that are able to obtain the data from medical facilities or database administrators. Additionally, this data must meet current FDA evidentiary standards, meaning it must appear as though it was collected through controlled, randomized clinical trials. Data collected through real-world sources is not random, and as such, statistical analysis techniques utilized must adequately adjust for this. In many instances, Bayesian techniques have been employed to account for randomness.

Moving forward with RWE studies will require carefully selected data sources, adequate statistical analysis methods, and in-depth understanding of FDA standards and compliance. Choosing an experienced CRO that understands these obstacles can alleviate the headache that these challenges create, and improve the likelihood of FDA approval.

How does RWD/RWE support decision making?

The aggregation of RWD (e.g., in medical device registries) and RWE can be especially useful for post-market monitoring of the safety of products during their use in real-world settings and additional evidence for effectiveness.

When generating RWE, attention should be paid to evaluating RWE in the context of regulatory decision-making depends not only on the evaluation of the methodologies used to generate the evidence but also on the reliability and relevance of the underlying RWD

- **Whether the RWD is fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory questions**
- **Whether the study conduct meets FDA regulatory requirements (e.g. for study monitoring and data**

In general, the FDA does not endorse one type of RWD over another, so long as the data is of sufficient quality, in reliable format (e.g ICD-10-CM codes or LOINC system), and that it is of relevance (i.e. the variables collected capture relevant exposure, outcomes, and other covariates).

When it has been determined considering RWE in supporting a drug's effectiveness can be suitably generated from the RWD, the FDA evaluates the study designs involving RWD. The agency generally sees promise in the opportunities created by pragmatic clinical trials. However, under appropriate circumstances, hybrid trial designs that include both traditional and pragmatic trial elements may also be considered. Additionally, RWD can serve as the basis for the external control group in non-randomized, single arm trials.

Who is using or has used RWD/ RWE?

With the introduction of the RWE program, the FDA has been looking for opportunities to employ the use of integrative, real-world information. Here are a couple of situations in which they have considered research including RWD:

In the October 2018 ,18 meeting for Prucalopride (Motegrity), the FDA agreed to use the data from two non-interventional studies for long term safety submission. One was a non-interventional pharmacoepidemiology study that used national claims data from four European countries. The other one was a non-interventional epidemiologic study conducted to estimate the adjusted incidence ratio for a major adverse cardiovascular event (MACE). In the same application, the FDA agreed to use the data from a phase 3 trial conducted in 1999 to support the generalizability of results from non-US pivotal studies to the US patients' population.

In the NDA meeting held on February ,26 2019, for Selinexor tablets, the application also included a retrospective observational study through the use of electronic health records (RWD) characterizing the survival distribution of patients similar to that of the STORM trial. The purpose of the retrospective study was to form an indirect comparator for the trial; however, without having reviewed and consented the protocol and statistical analysis plan (SAP), the FDA could not be certain that the protocol and SAP were prespecified and unchanged during the data selection and analyses. Also, because there were major differences between the STORM trial and RWD, the agency determined RWD are not compatible with those obtained during STORM. Therefore, after reviewing the submitted evidence, the agency concluded that the study is inadequately designed and conducted to serve as the comparison group to STORM due to lack of pre-specified analyses and various methodological issues such as selection bias, misclassification and immortal time bias.

Although these cases represent different outcomes with regard to the use of RWD, we expect more and more new applications for drugs and medical devices using RWD and RWE. As the application of the RWE program increases, it is expected there will be reductions in the cost of drug development and shorten the time of new drug and device approvals, especially in terms of safety and efficacy.

Where can more information on RWD and RWE be found?

You can read more on the FDA's RWE program, other FDA compliance issues, and biostatistical research approaches in drug development, by checking out our blog at www.princetonpharmatech.com/blog/. You can also follow us on Twitter and LinkedIn, where we will announce upcoming publications, and relevant news in the FDA approval process.

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