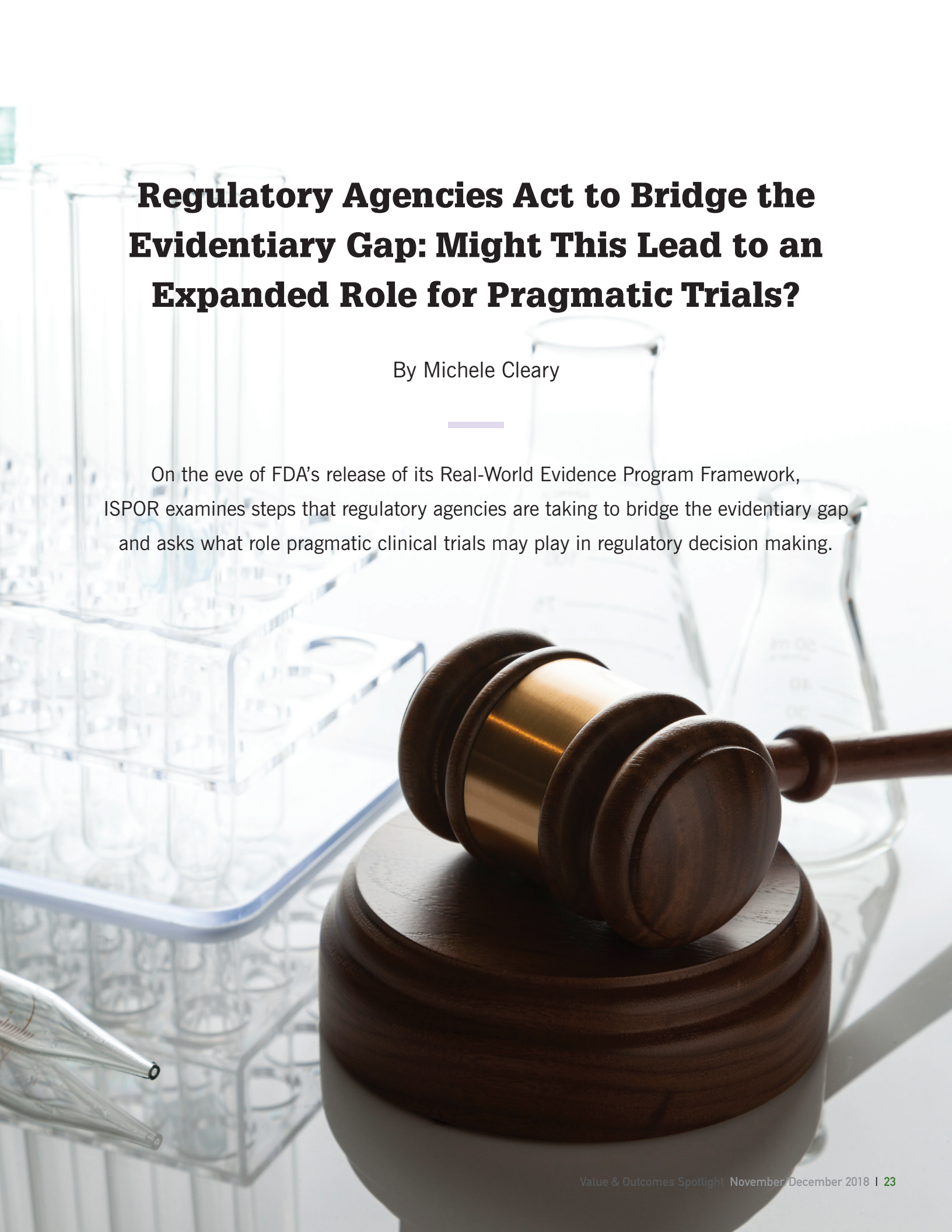
Regulatory Agencies Act to Bridge the Evidentiary Gap: Might This Lead to an Expanded Role for Pragmatic Trials?

By Michele Cleary

On the eve of FDA's release of its Real-World Evidence Program Framework, ISPOR examines steps that regulatory agencies are taking to bridge the evidentiary gap and asks what role pragmatic clinical trials may play in regulatory decision making.



US and EU regulatory bodies have taken steps recently to broaden their use of real-world evidence (RWE) in regulatory decision making. As defined by the US Food and Drug Administration (FDA),[1] RWE is the "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD)." Both the FDA and the European Medicines Agency (EMA) have employed RWE in postapproval safety and efficacy studies. Now, pushed by the explosive rate of biomedical innovation, these agencies are exploring ways to utilize new RWD sources to supplement randomized clinical trial (RCT) data — expanding the "evidence mix," accelerating the approval process, and delivering much-needed therapies to patients in need.

As regulatory agencies expand their interest in RWE beyond postapproval safety and efficacy analyses, the pharmaceutical industry faces uncertainty. Pharmaceutical companies have long used RWE to inform marketing decisions, economic modeling, and pricing — even expanding its use in earlier stages of the clinical drug development pipeline for "go/no-go" decision making. But now with regulatory bodies expanding their acceptance of RWE, companies must ask whether their RWE plans are sufficient to meet both regulatory and payer demands.

WHEN THE GOLD STANDARD IS NO LONGER SUFFICIENT

With their high degree of internal validity, RCTs are a good fit to demonstrate causality. However, their inherent design — treatment randomization, inclusion/exclusion criteria, standardized follow-up procedures — also limits their external validity, thereby limiting the ability to extrapolate drug efficacy conclusions to drug effectiveness in the practice setting. This difference between clinical research and practice — frequently referred to as the evidentiary gap — is driving regulatory bodies to explore broader use of RWD and RWE.

THE APPEAL OF RWD

RWD can improve our understanding of how safe and effective a drug is in actual clinical practice, uncovering valuable insights regarding both effectiveness and safety that may not be seen within the constraints of clinical trials. Common RWD sources include disease registries, administrative claims data, electronic health records, and a wide range of new biosensor data. The FDA has had significant experience with claims data via Sentinel for safety and effectiveness inquiries. For instance, the FDA recently incorporated effectiveness information derived from a prospective claims data analysis into vaccine labeling. Administrative claims data can help us better understand the natural history of disease, treatment patterns, treatment-specific health services utilization patterns, and health outcomes relative to comparator products. Plus, RWD can generate more cost- and time-efficient evidence than RCT data alone. As the quality and variety of RWD improve, interest in utilizing RWD continues to grow.

While RWD can potentially supplement RCT evidence, RWD present their own methodological challenges stemming from non-random treatment allocation and data quality (incomplete or missing data fields), for example. In addition, study management issues may complicate implementation. For instance, informed consent privacy and data integration also need to be addressed and protocols developed to maintain data integrity. Missing data, accuracy of data; personnel capturing the data may not all be following the same protocols. While statistical methods (eg, propensity scoring, instrumental variables) address many of these concerns, uncertainty surrounding how RWD should be incorporated into RCT data for effectiveness assessments abound, especially as it pertains to regulatory decision making.

WHERE MIGHT RWE FIT IN REGULATORY DECISION MAKING?

RWE has the potential to inform regulators on many fronts, providing critical insight into disease epidemiology, burden of illness, and current treatment standards. It can help refine clinical practice guidelines and illuminate relative value. And such information can help manufacturers prioritize and streamline drug development, accelerating evidence generation to support label expansion for specific products. Coupled with newer RWD sources and next-generation analytics, RWE presents an enormous opportunity to improve and accelerate regulatory decision making. But concerns persist, especially surrounding data accuracy, reproducibility, and incomplete data. Claims data are created to support reimbursement, not research, and hence could introduce unwanted bias into research. EHR data present similar risks. Therefore, in order to maximize the value of RWE into supporting decision-making requires the most appropriate data sources and analytics.

Now regulatory bodies are exploring how best to use RWE to support and/or supplement pre-market decisions, asking when or whether RWE should be used to evaluate new therapies or new indications for existing products. There had been a lack of guidance on systematic approaches for the inclusion, analysis, and interpretation of RWD for regulatory decision making. These new regulatory initiatives explore appropriate study designs for generating RWD and developing further analytic methods for synthesis of RWD from different sources through initiatives.

A NEW FUTURE FOR RWE UNDER THE 21ST CENTURY CURES ACT

Signed into law in late 2016, the 21st Century Cures Act aimed to modernize research, accelerate treatment discoveries, and expedite access to new medicines.[2] The Act included initiatives

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to incorporate patient perspectives into drug development (Section 3002) and rules clarifying how pharmaceutical companies may share healthcare economic information with payers and formulary decision makers (Section 3037).

The Cures Act also mandated the FDA to establish a protocol for integrating RWE into regulatory decision making (Section 3022) — expanding its current use in postmarketing surveillance capacities to perhaps becoming integral to all phases of medical product development. The law directs the FDA to develop guidelines that define appropriate uses of RWD, that evaluate how RWE may be used to support approval of new indications for approved drugs, and to support or satisfy postapproval study requirements.

By the end of 2018, the FDA is required to draft a framework for the implementation of the RWE program that describes sources of RWE (eg, ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities); the gaps in data collection activities; the standards and methodologies for collection and analysis; and the priority areas, remaining challenges, and potential pilot opportunities. Draft guidance on circumstances where RWE can be used and standards for use is slated for October 2021.

EMA EXPLORES RWE INITIATIVES

Like the FDA, the EMA has a long history of using RWE in postauthorization drug safety surveillance studies.[3-5] Recently, the EMA has introduced 2 initiatives that utilize RWE to accelerate the authorization of new treatments.

• The Adaptive Pathways (AP) approval path helps accelerate access to products serving areas of unmet need — rare conditions where sufficient RCT data may be difficult to generate.[6,7] The AP approval path permits limited approval for these targeted populations through iterative evidence generation — pragmatic and real-world studies designed to complement RCTs.

• The EMA's Clinical Trial Regulation (536/2014) expands the definition of "clinical trial" to 3 categories: clinical trials, noninterventional studies, and low-interventional clinical trials.[8] The low-interventional clinical trial begins with a noninterventional study of an authorized drug and incorporates some form of additional diagnostic or monitoring procedures (procedures that expose patients to minimal risk or impact). These low-intervention clinical trials are used to investigate safety and efficacy questions that have arisen since authorization — often through a pragmatic clinical trial design.[9]

ASIAN REGULATORY AGENCIES EXPLORING RWE

In Asia, many countries are exploring the use of RWE in regulatory decisions, with great variability by country stemming largely to differences in RWD sources. Japan appears to be most proactive in the region with its Medical Information Database Network, a repository of clinical data that is expected to be used in regulatory decision making. Singapore's drug regulatory agency, the Health Sciences Authority (HSA), is exploring an Adaptive Licensing pathway similar to the one recently piloted by the EMA. In the Philippines, companies are required to conduct postmarketing studies on all marketed drugs to assess safety, tolerability, and effectiveness across more diverse populations. Finally, both China and India have demonstrated growing interest in the implications and applications for RWE in product development.[10]

CAN PRAGMATIC CLINICAL TRIALS HELP FILL THE EVIDENTIARY GAP?

As regulatory agencies explore new uses and standards for RWE, the acceptance of pragmatic clinical trials (PCTs) remains unclear. PCTs present a unique balance between RCTs and observational trials common with other types of RWD. Embedded within a more realistic clinical practice environment, PCTs offer a broader patient mix and outcome measures, as well as more streamlined data collection (possibly with linkages to EHRs), than what are often captured with most RCTs. Hybrid trials — combining elements from both clinical and pragmatic clinical trials — could provide further insight into real-world treatment effectiveness.

Yet challenges persist. PCTs are often plagued with incomplete or inaccurate data — both issues that may greatly limit their use in regulatory settings. Many pragmatic trials rely on RWD sources, such as registries or EHRs, that allow easier subject recruitment and study implementation, thus keeping research costs low and time-to-completion short. Clear identification of product effects is critical to regulatory decision making. PCTs may be too simplified for regulatory needs.

AWAITING REGULATORY GUIDANCE

The FDA will be sharing its framework for RWE (Section 3022) any day. Meanwhile, the EMA has just begun to evaluate the use of RWE under 536/2014. And finally, regulatory agencies across Asia are debating their RWE strategies.

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Uncertainties abound. How do these bodies differ in their acceptance/view of RWD? Will all bodies take a similar view of retrospective data? Will there be a place for PCTs in these new RWE regulatory initiatives? Or will regulatory bodies look strictly to observational studies, free from research intervention, treatment assignment, inclusion/exclusion criteria, or monitoring protocols? And finally, how should pharmaceutical companies prepare for these changes? How should they refine their RWE research agendas to meet the needs of all regulatory bodies?

To help clarify their response, the FDA is currently funding a study to determine whether observational methods can be used to replicate drug-effectiveness findings from roughly 30 RCTs. The FDA believes this research will better inform their understanding of observational study methods and whether these methods should be applied to drug effectiveness evaluations.[11] The Agency notes: "Further research is needed to determine when large data sets and statistical methods are sufficient to correct for systematic bias in sampling, ascertainment, or missing data that may arise in observational studies—a particular problem with retrospective studies in which less well-characterized patients limit adjustments for confounders."

The FDA has reinforced its view regarding the importance of patient perspectives when discussing RWE:

"…if research is to fulfill its goal of being patient centric, it will be necessary to leverage technological advances, such as mobile health, to capture the patient experience beyond the clinical delivery system and establish a more comprehensive picture of how medical products function beyond the controlled confines of traditional randomized clinical trials."

In recent communication with ISPOR, the FDA has stated an interest in "exploring pragmatic approaches to each stage of a >

clinical trial."[12] However, they stated that while they were open to a variety of potential sources for RWD, they articulated 3 key considerations as they implement their RWE Program:

1. Whether the RWD are fit for use;

2. Whether the trial or study design used to generate RWE can provide the necessary scientific evidence to answer or help answer the regulatory question; and

3. Whether the study conduct meets FDA regulatory requirements.

The ISPOR/ISPE Task Force released their good practice guidelines for RWD studies of treatment and comparative effectiveness.[13] These recommendations coupled with the new regulatory guidance will be critical in supporting manufacturers meet regulatory expectations for RWE use in healthcare decision-making.

While there appears to be growing consensus across regulatory agencies regarding the benefit of increased real-world observations across all phases of drug development, questions remain. Clearly, RWE represent a cost-effective way to include unique groups (eg, rare diseases) into trials with iterative evidence generation. PCTs allow for longer follow-up periods and can incorporate patient-reported outcomes – attributes often missing from traditional RCTs. RWE can help manage trial expenses, thereby allowing for more affordable treatments to market faster.

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Much rides on the current FDA study of effectiveness studies mentioned above. Will results drive the FDA, EMA, and other regulatory bodies to accept RWE, and specifically PCTs, to expand real-world evidence of treatment effectiveness in real-world practice environments with novel patient populations? Or will the bias inherent in PCTs limit their use?

For now, waiting continues.

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