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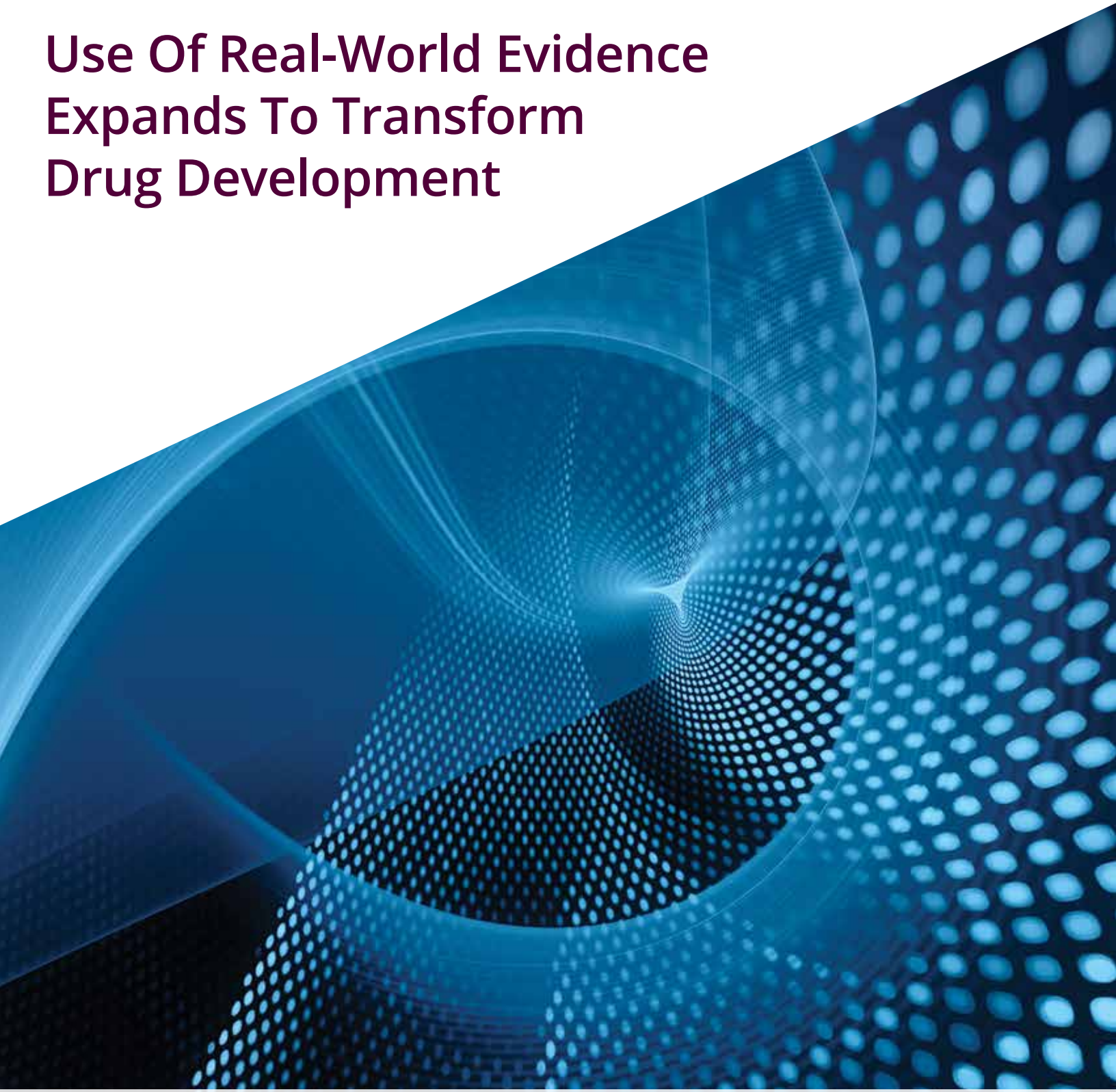
Use Of Real-World Evidence Expands To Transform Drug Development



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Shaping the Future of Drug Development

Real-world evidence (RWE) provides a large and growing source of insights into drug uptake and safety. It is increasingly used in pricing and reimbursement negotiations and to support post-approval label expansions.

RWE also has the potential to transform the efficiency and economics of drug development. We are not there yet – this huge, heterogeneous category must first be better defined, understood and trusted, including, crucially, by regulators. But as real-world data (RWD) sources and tools improve, and examples of post-approval use of RWE continue to multiply, confidence is growing. A slow but meaningful shift in the current R&D evidence paradigm has begun.

These were among the conclusions of an expert panel convened on May 2 by Informa Pharma Intelligence and Cytel, a provider of analytical solutions for drug development. Experts from industry and research institutes gathered to outline the forces – such as precision medicine and patient engagement – compelling greater use of RWE in drug development, and some of the efforts underway to address the associated challenges.

The panel also addressed the new kinds of talent and resources – and the mindset – needed to enable optimal use of RWE.

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Use Of Real-World Evidence Expands To Transform Drug Development

REGULATORS ARE WARY OF RWE

RWE emerges from a wide range of data sources and types, and study designs. This huge scope presents exciting new opportunities to better understand the benefits and drawbacks of new and existing medicines, and to identify treatment gaps. But it also presents significant challenges, in particular to regulators seeking to understand and validate such evidence in approval decisions. Regulators' wariness of RWE has been identified in multiple surveys[1] as one of the most significant hurdles facing its wider, more rapid uptake, along with data availability and access cost. The wariness is related to the broad, ill-defined and for now largely uncontrolled nature of real-world data collection and RWE generation, and how such data should be analyzed and interpreted.

"RWE is a rapidly evolving field, where new data or capabilities pop up almost every day." – Charles Makin, Head of Biogen's Real-World Evidence Strategy team

Randomized controlled trials (RCTs) are currently the gold-standard source of efficacy and safety evidence required for new drug approvals. RWE is generated very differently. It may involve evidence generated from data collected in routine clinical practice, including from medical records or claims databases, observational studies, or pragmatic trials. It may emerge from data collected by wearables, social media platforms or any combination of the above. Real-world data must be cleaned, processed, curated, analyzed and interrogated to generate RWE; any one of these manipulations can generate or highlight additional uncertainty, opacity, confounding factors and potential bias.

The rules and standards for doing such RWD analysis, and guidelines around selecting the most appropriate form of data to answer any given question are still in their infancy. Precise definitions of RWE are also lacking. As such, "it's the Wild West," said Cytel CEO Joshua Schultz. "There is a level of suspicion" among many stakeholders, he continued.

Gregory Daniel, Deputy Center Director at the Duke-Margolis Center for Health Policy, which is working with the US Food and Drug Administration (FDA) to better understand RWE, identified the two main questions underlying FDA's concerns around using RWE pre-approval: "Where does the RWE come from?" and "How is it being aggregated and analyzed?" There are no agreed standards on how to reliably classify and combine real-world data from across multiple sources –

health records, patient registries, claims databases, patient-reported outcomes, or epidemiological and population surveys, for instance. The methods used by RWE-generating groups such as Optum, HealthCore, and Kaiser are rarely published, making it hard to assess whether they are appropriate.

Regulators and industry still have much to learn about the limitations and opportunities of using real-world data to support approval, the kinds of data that can be most reliably combined and the most appropriate analytical tools and processes to use. The multiple sources of real-world data mean there will not be a single, short rule-book. Instead, industry and regulators face the challenge of determining which sources of RWD and RWE can most robustly address a given research question, said Francis Kendall, Senior Director in Biostatistics and Programming at Cytel.

Until FDA and other regulators are sufficiently confident to outline what kind of evidence they will accept in support of particular claims, many industry players are reluctant to invest substantially in RWE pre-approval.

"From a regulatory/acceptability perspective, the pivotal question we grapple with is what kind of evidence will matter to FDA?" – Charles Makin, Biogen

REGULATORS ARE GETTING ON BOARD

FDA is taking on the challenge of integrating RWE into approval decisions. The 21st Century Cures Act demands as much. The agency in December 2018 issued the first of several anticipated guidelines around RWE.[2] The guidance does not provide clear answers as to where RWE can be used in product submissions, but it does signal the agency's commitment. "FDA is doing a lot. It is a slow process, requiring lots of experts to weigh in," said Daniel. The Duke-Margolis Center is also involved in other RWE-focused collaborations.

FDA already uses RWD routinely in the post-approval setting, for instance in its nationwide Sentinel

drug safety monitoring program.[3] In that context it is appropriate to mine data, in a hypothesis-free fashion, in search of any safety signals. Yet in the pre-approval setting, when determining effectiveness, effect sizes may be much smaller. Causality and biological plausibility of any effect needs to be established and understood.

RCT Duplicate is among the projects FDA has commissioned to build an empirical evidence base to support use of RWD in some circumstances.[4] Run at Harvard Medical School's Brigham and Women's Hospital in Boston, in collaboration with healthcare technology company Aetion Inc., RCT Duplicate aims to replicate the results of published RCTs using RWD sets, to find out whether the use of RWE rather than clinical trial evidence would have led to the same regulatory decision and, ultimately, the same impact on patient health.

RCT Duplicate may address some of FDA's concerns over data quality, accuracy, study transparency, confounding measures and bias. It may help outline the types of clinical questions that RWE may be able to answer, and under what circumstances. It may also elucidate the RWE trial designs and settings that provide the most robust conclusions.

RWE DEMANDS A NEW EVIDENCE FRAMEWORK

FDA is, understandably, working from its current, RCT-dominated evidence paradigm. The validity of RWE is being defined in large part by the extent to which it mirrors RCT evidence. Yet as Cytel's Schultz pointed out, the evidence landscape has evolved. There is no longer a simplistic, binary distinction between high-quality pre-approval data and grittier post-approval data collected in real-world settings. Today, the situation is more nuanced, with "a spectrum" of evidence types and strengths. "It has got harder to easily define [data and evidence types]," he said, going on to suggest new categories of evidence such as "research-grade."

Similarly, the appropriate tools and statistical thresholds for RWD analysis are different from those used in RCTs. There are different skills involved. Data scientists don't follow the same approach as most of the life science statisticians analyzing global RCTs. Data scientists – a broad, imprecisely defined category of experts in aggregating and analyzing large data sets, typically with a mathematics or computer science background – will tend to look for correlations within and between large data sets and may be less concerned about understanding the reason for those correlations, including any causal relationship. They will be bolder in using predictive analytics, rather than confirmatory analytics. "There is a tension between data scientists and statisticians," said Schultz.

In the real-world evidence sphere, the traditional research method can be turned on its head. A clinical question and trial design can be retrofitted to the best real-world data available (e.g., oncology medical and claims data). This is one of the reasons regulators wary of RWE for approval decisions: it allows developers to cherry-pick data to confirm a hypothesis, post hoc. For regulators, the clinical question should come before the data.

Pilot projects are underway, among research and policy institutes like Duke-Margolis and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) to work out how to improve the transparency and rigor of real-world trials. Efforts include publishing real-world trial protocols on clinicaltrials.gov prior to study commencement.[5]

TRICKLE DOWN EFFECT: FROM POST- TO PRE-APPROVAL

Despite the challenges, RWE is gaining traction in the development setting, both at FDA and within biopharma. FDA has already used RWE – for instance, natural history studies – to support the approval of drugs used to treat very rare diseases, where treatment effects can be dramatic, and disease course relatively predictable.[6]

The quality and use of RWE in the post-approval setting is growing. Vertex and Biogen are both using real-world evidence to support optimal use of their drugs, post-approval. Biogen undertook real-world studies to assess the long-term effectiveness of its multiple sclerosis drugs Tecfidera (dimethyl fumarate) and Tysabri (natalizumab), and to support the use of biomarkers to monitor disease progression and inform treatment decisions.[7] Vertex's five-year real-world trial of cystic fibrosis drug Kalydeco (ivacaftor) suggested such long-term use could lower the risks of transplantation, hospitalization and death.[8]

As proof-of-concept and confidence is established in the less risky post-approval environment, RWE should find its way into pre-approval in a more systematic fashion rather than only in exceptional circumstances.

And it has to, argued Schultz: "Our industry's business model will not work in the future without RWE." The emergence of precision medicine is forcing greater use of RWE in development. As diseases narrow, including in oncology where conditions are increasingly defined by genotype rather than tumor location, it will become both impractical and unaffordable to run RCTs across all tumor-types and treatment combinations. The result will be "more flexible alternatives to such trials, providing the opportunity for RWE to inform approvals," said Alex Mutebi, Director, Global Real-World Evidence at Vertex Pharmaceuticals.

"What we're missing is the value that RWE brings to patients, in their own setting, whatever that is."
– Francis Kendall, Senior Director, Biostatistics and Programming, Cytel

The growing prominence of patient-reported outcomes and quality-of-life metrics among regulators and health technology assessment (HTA) organizations is likely to provide another tailwind to the greater use and acceptance of RWE pre-approval.

An impact report published in late 2017 by the Tufts Center for the Study of Drug Development found that although commercial activities still account for the majority of drug developers' use of RWE, nearly 40% of organizations surveyed also use it in development.[9]

ACTIONS – ACROSS MINDS, AND ORGANIZATIONS

For real-world evidence to transform drug development, more education is required around RWD and RWE. So is a shift in mindset, away from full reliance on traditional RCT-centric evidence frameworks.

All data have their limitations; RWD is no exception. The key is to understand those limitations and take a reasonable, pragmatic approach to minimizing them. "We can't spend $100 billion on research, and use [a traditional RCT approach] to answer every single question," argued Biogen's Makin. Real-world data will be in many ways "imperfect" as they are, by definition, generated in the real world not in the highly controlled setting of an RCT. "You have to be comfortable with that," Makin added, and use data science and good study design to reduce ambiguity as far as possible.

"As we get better at recognizing data shortcomings, we will collect better data." – Alex Mutebi, Vertex

Organizations are re-tooling in anticipation of the far larger future role for RWE. Those surveyed in the Tufts impact report predicted a 25% increase by 2020 in the number of their staff involved in collecting and analysing RWD.[9] Mary Jo Lamberti, Associate Director, Sponsored Research and Assistant Professor at Tufts, called for greater cross-industry collaboration to help accelerate the use of RWE: "Companies are so siloed, both from other sectors, and within themselves. Greater collaboration would be helpful."

An informal 2018 survey by Cytel indicated that most biopharma and CRO organizations have a data science department (though there was some selection bias, as the survey was carried out among statistical programmers at the Pharmaceutical Users Software Exchange (PhUSE) Annual Conference), and are using its data analysis function primarily on clinical trials databases and in-house data assets.[10]

A dearth of data scientists remains a challenge to wider RWE acceptance and uptake, along with issues of trust and cost. Yet the panelists were optimistic about the wider use of RWE, despite expressing frustration at the slow pace of change. There are several collaborative, multi-stakeholder efforts and pilot studies underway, seeking to set precedents for the safe and effective use of RWE in development, and

to help understand the strengths and weaknesses of different data types.[11]

Such collaborations must expand and multiply. As RWE analytics grow more sophisticated, more widespread and better-understood across the industry, RWE's potential across drug development, approval and beyond is becoming much clearer. The panelists anticipate a future where regulators routinely accept RWE, including pre-approval.

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