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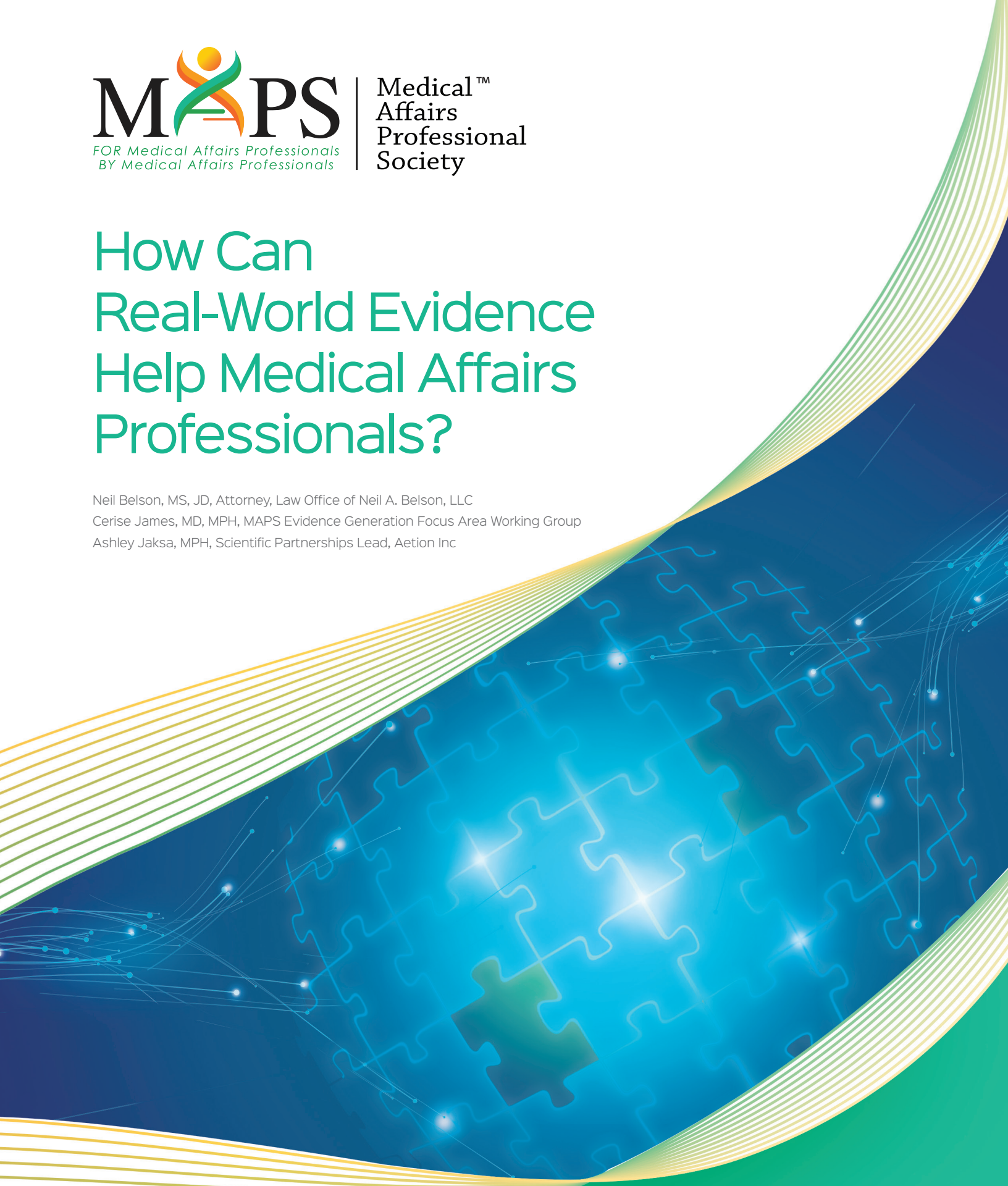
# How Can Real-World Evidence Help Medical Affairs Professionals?

Neil Belson, MS, JD, Attorney, Law Office of Neil A. Belson, LLC
Cerise James, MD, MPH, MAPS Evidence Generation Focus Area Working Group
Ashley Jaksa, MPH, Scientific Partnerships Lead, Aetion Inc



A MAPS EVIDENCE GENERATION FAWG WHITEPAPER



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# ABSTRACT

The use and acceptance of real-world evidence (RWE) in the pharmaceutical and biotechnology industries has increased dramatically in the last 5 years. Approximately 70% of new drug and biologic regulatory submissions to the U.S Food and Drug Administration (FDA) now include RWE.[1] Nearly 95% of pharmaceutical industry respondents, in a recent survey by Deloitte, expect RWE to play an important role in their companies by 2022.[2] Medical Affairs (MA) professionals are in a unique position to champion the use of RWE internally and communicate its value both internally and externally. This white paper focuses on providing MA professionals with the background and history of RWE, and its potential applications in the biopharma industry, so that they may incorporate this knowledge into their areas of functional expertise, and ultimately, benefit patients and consumers in their healthcare decision-making.

# INTRODUCTION

Medical Affairs is an essential (non-revenue) business function within the pharmaceutical and biotech industry consisting of a combination of key activities including Field Medical, Health Economics and Outcomes Research (HEOR), Evidence Generation, Publications, Stakeholder Management, Medical Education, Medical Information, etc. – all of which can impact decision-making and ultimately patient experience and outcomes. Today's MA professionals need a deep understanding of the science, data capabilities, and an ability to dialogue with the Triple Aim stakeholders including providers, patients, and payers. In their work, MA professionals utilize information collected throughout a product life cycle (e.g., utilization patterns, economic and clinical outcomes). MA can elevate the performance across medical activities, ultimately resulting in better experiences and outcomes for patients and physicians.[3] MA leverages innovations in evidence generation to help accelerate patient access to treatments. In addition, MA plays a pivotal role of informing internal business processes and strategies for RWE. With RWE becoming a larger focus of drug development efforts and an additional tool for communicating a product's clinical value, MA professionals need to understand the strengths and weaknesses of RWE, how to effectively use RWE and how to communicate its value to internal and external stakeholders.

# WHAT IS REAL-WORLD DATA AND REAL-WORLD EVIDENCE?

Real-world Data (RWD) is data relating to "patient health status or the delivery of health care routinely collected from a variety of sources."[4] Examples of RWD include data derived from electronic health records (EHRs), medical claims data, data from product and disease registries, patient-generated data including from in-home use, and data gathered from sources that can monitor and measure a patient's health status, such as digital health technologies. RWE is not simply anecdotal data. Rather, RWE is clinical evidence derived from RWD (Figure 1). RWE uses data generated from day-to-day medical practice to evaluate the benefits or risks of a medical product. RWE studies can be prospective, retrospective or both – that is, they can utilize pre-existing data, future data, or a combination of both.

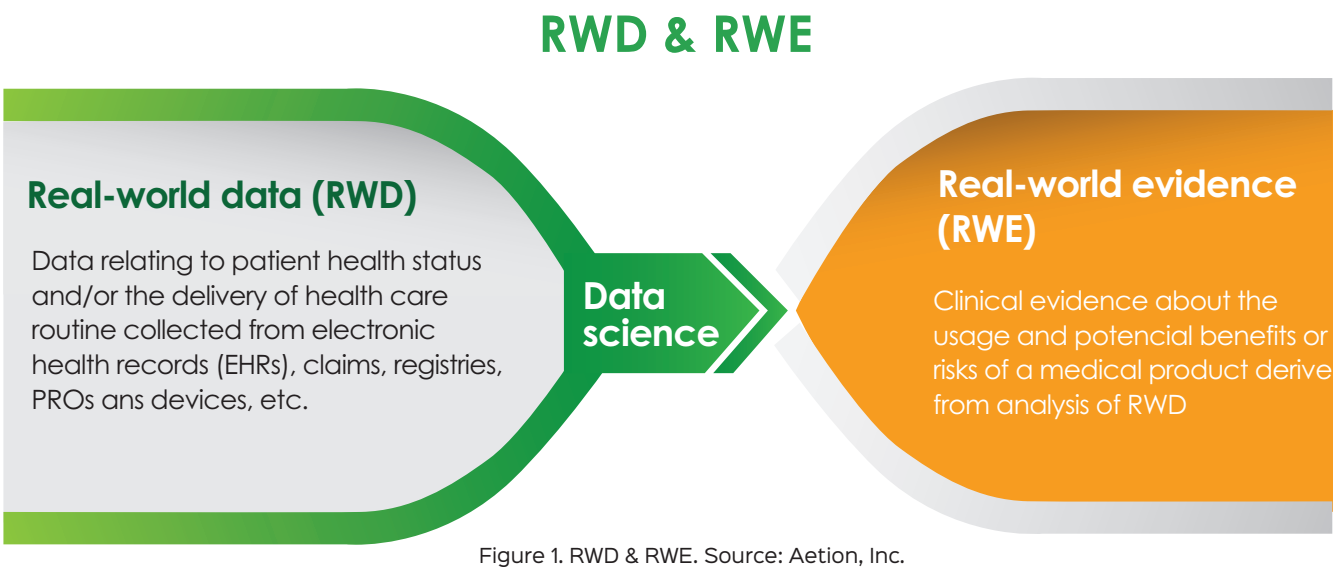



Figure 1. RWD & RWE. Source: Aetion, Inc.

# HISTORY OF RWE

Before examining the future potential of RWE, it is helpful to understand how RWE developed. The organization and management of RWE can be traced back to several federally funded health programs.

# FDA SENTINEL INITIATIVE IN THE UNITED STATES

The FDA is one of the first U.S. governmental organizations to adopt a focused program on the collection and use of RWD. Both during and after the clinical development process for pharmaceuticals, the FDA requires manufacturers to monitor safety and adverse events based on real-world use of drugs.

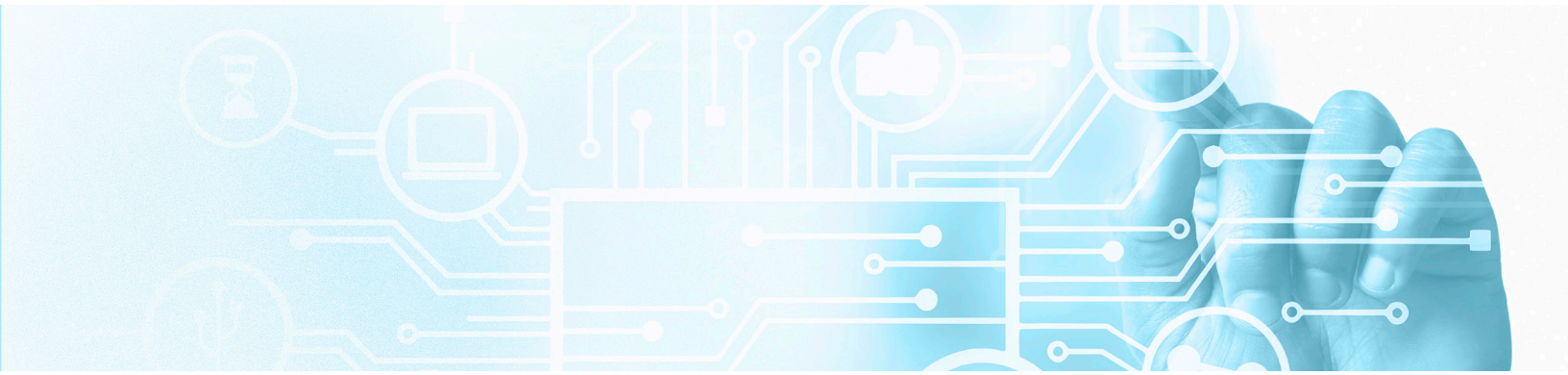
FDA's Sentinel Initiative was perhaps the first systemic use of RWE in a regulatory context. The Sentinel Initiative uses RWD to monitor the safety of medical products following their approval by FDA. The Sentinel Initiative originated in the FDA Amendments Act (FDAAA) of 2007 and launched in May 2008.[5] The program uses a national electronic reporting system to monitor the safety of drugs, medical devices and other medical products in real-world practice. The Sentinel Initiative receives de-identified RWD from a group of health organizations located across the country. By systematically collecting and evaluating data from regular patient use, the Sentinel Initiative transformed the way researchers monitor the post-approval safety of medical products.

# 21ST CENTURY CURES ACT IN THE UNITED STATES

The 21st Century Cures Act (the Act), enacted in December 2016, was a turning point in the development of RWE in the United States. Prior to the Act, FDA's primary use of RWE had been in the post-approval safety surveillance of products that were already on the market. The Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355g), requiring the FDA to create a framework to evaluate the potential use of RWE in two contexts related to product approvals: To help support the approval of a new indication for a drug or biologic already approved under section 505(c) of the FD&C Act, and to help to support or satisfy post-approval study requirements.[6]

By establishing a legislative mandate for FDA to evaluate RWE for regulatory approvals, the Act represented Congressional recognition of RWE's potential. This mandate to evaluate RWE in drug approvals also created new incentives for industry to invest in RWE. In response to the Act, the FDA published the "Framework for FDA's Real World Evidence Program," in December 2018, which outlines its plans to develop guidance for industry on how RWE can and will be used in regulatory approvals.[4] It is important to note the differences of trial designs and studies that will be covered

by the RWE Program. "Under FDA's RWE Program, evidence from traditional clinical trials will not be considered RWE. However, various hybrid or pragmatic trial designs and observational studies could generate RWE. FDA's RWE Program will cover clinical trials that generate RWE in some capacity (i.e., sources other than traditional clinical trials) and observational studies."[2] Recently, the FDA released new Draft Guidance documentation on potential use of EHRs and medical claims in clinical studies to support regulatory decisions.[6] This new guidance was released to satisfy, in part, the mandate under section 505F of the FD&C Act to issue guidance about the use of RWE in regulatory decision-making, and provides recommendations on selecting data sources to maximize the completeness and accuracy of the data derived from EHRs and medical claims for clinical studies.



# GLOBAL USE OF RWE

Like the United States, global regulatory and health technology assessment (HTA) agencies recognize the potential of RWE. In the European Union, the EU Commission created the adaptive pathways approach in 2014 to support regulatory submissions of RWE.[7] Similar to the FDA's RWE Program, global regulators and HTA agencies are in the process of developing an understanding and industry guidance on where and when RWE can be used in decision-making. For example, the Big Data Task Force by the European Medicines Agency (EMA) and the Heads of Medicines Agencies focuses on describing the RWD landscape to identify steps where these data can be used to support innovation and public health in the EU.[8] This group has recently released guidance of the use of registry studies in regulatory approval.[9] Japan's Pharmaceutical and Medical Devices Agency (PMDA) has issued numerous guidance documents on the use of RWE in post-marketing surveillance and is working on expanding guidance to use of RWE in regulatory approvals.[10] HTAs like the National Institute of Health and Care Excellence (NICE) are also actively working on incorporating RWE into decision-making processes.[11]

# WHY THE TIME IS RIGHT FOR RWE

FDA's Acting Commissioner, Dr. Janet Woodcock, has repeatedly referred to FDA's traditional system for approving new drugs or biologics, using randomized controlled trials (RCTs), as "broken" and not serving the interests of patients.[12] RWE can address some of the significant limitations of RCTs. For example, RCT results may have limited generalizability beyond the actual test population because RCTs generally have strict inclusion and exclusion criteria, which may not accurately reflect the clinical patient population.

Dr. Woodcock and other FDA officials have written that we must consider two key dimensions of RWE to realize RWE's full promise.[13] The first is the setting in which evidence is collected or generated, including the data source(s) as well as the specific methods used to collect and curate the data. The second is the methodological approach used to conduct the research. Understanding these dimensions and the inherent limitations of RCTs is a substantial opportunity for RWE to supplement (and potentially accelerate) the clinical trial evidence base and contribute to regulatory decision-making.

> *In my organization, HEOR/RWE is external to Medical Affairs. RWE is important because it fills the gaps CT's does not fill. In addition, it will provide answers in real time on drug comparisons, hospital utilization, economic burden and clinical impacts.*
>
> ***Associate Director Medical Affairs Oncology, Spevak***

While regulatory accelerated approval programs may speed up access to innovative lifesaving therapies, these programs can also result in less clinical comparative evidence at the time of launch and increased uncertainty in the clinical evidence base for decision-makers. Researchers have observed a decrease in drugs approved with at least 2 pivotal studies,[14] and an increased use in surrogate end points and single-arm studies.[15] At the same time, computing power and data collection, including RWD, have increased. For example, hospitals produce 50 petabytes of clinical data per year. However, 97% of this data goes unused.[16] A substantial opportunity exists to capitalize on this large volume of collected but unused RWD to reduce uncertainties across the drug development lifecycle and increase the focus on what treatments work and for whom in real clinical practice.

# USES OF RWE ACROSS THE DRUG LIFECYCLE

While the development process is an obvious area for RWE benefits to be realized in the pharmaceutical industry, there are many other ways in which MA professionals can use RWE across the product lifecycle to support their companies (Figure 2). For example, RWE can support product differentiation and demonstrate the product's value proposition to payers and patients. Rare disease and oncology drug developers are increasingly using RWE in submissions to support single-arm studies with external control arms. In addition, there is expanding opportunity to use RWE in medical communications. The FDA allows a variety of studies and analyses, including RWE, to be used in medical communications that are consistent with labeling.[17] This is a major opportunity for MA professionals to communicate the therapeutic value of their products to outside stakeholders.

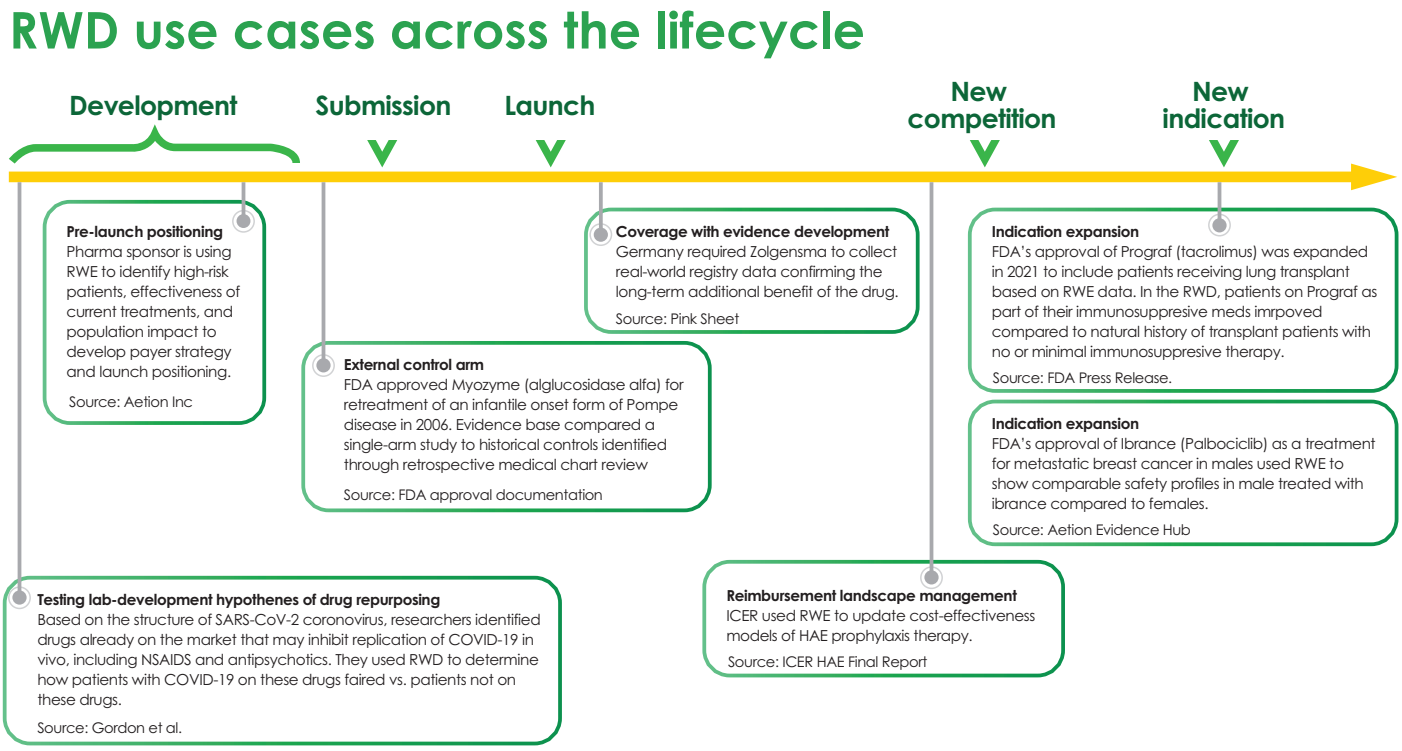



Figure 2. RWE Use Cases

# CHALLENGES IN RWE AND HOW RESEARCHERS ARE ADDRESSING THEM

There is often a misconception that RWE is in opposition to RCTs, but this creates a false dichotomy. A full picture of drug efficacy, safety, and effectiveness should include both high-quality RCTs and RWE. RWE studies may offer advantages in some situations. For example, an RWE study may be the most appropriate study design choice when randomization is not feasible or ethical, a fit-for-purpose data set exists, outcomes are measurable in RWD, and key confounders can be captured.[18, 19]

Even when RWE is relevant to the research question, researchers must use proper study designs and principled methods to address bias and confounding concerns, and must transparently report study design and implementation. To ensure the RWE is high-quality, researchers should follow existing recommendations from key decision-makers and stakeholders.[20] While these recommendations are not yet comprehensive, best practices do exist to help researchers manage study design, RWE study implementation, and reporting.

Assuring adequate transparency is an important requirement for RWE development. Some regulators and payers are concerned that product sponsors could replicate studies with slightly altered parameters and then "cherry-pick" the studies that produce the desired results. To address this concern, the ISPOR-ISPE RWE Transparency Initiative[21] is focused on setting guidelines around transparency including pre-registering RWE study protocols (similar to what is done with RCTs on clinicaltrials.gov) and setting standards for how RWE studies should be reported (e.g., STaRT RWE template[22]).

Challenges also exist in the collection of RWD. There are numerous national initiatives focused on these RWD challenges, from groups detailing what data elements and outcomes are most relevant for decision-making[23] to initiatives focused on democratizing data and interoperability.[24]

# FUTURE OF RWE AND THE ROLE OF MEDICAL AFFAIRS PROFESSIONALS

ISPOR ranked RWE as its #1 top global trend in HEOR for 2022-2023.[25] With developing RWE guidance from regulators and HTAs and robust demonstration projects highlighting the value of

RWE, the future for RWE studies for healthcare decision-making seems bright. As RWE becomes part of the health care mainstream, Medical Affairs professionals have an opportunity to guide their internal and external stakeholders in adopting RWE. MA professionals can take advantage of this opportunity by championing the use of RWE where applicable, working with stakeholders to ensure RWE studies meet high-quality methodological standards, collaborating with internal and external stakeholders on projects that fill known gaps in RWE methodology to push standards forward and making sure that their companies and organizations are aware of the benefits RWE can offer.

# MEDICAL AFFAIRS PROFESSIONALS - CALL TO ACTION

Medical Affairs professionals throughout the industry are becoming more knowledgeable about RWE and partnering within their own organizations to ensure RWE is integrated into Medical Affairs plans and value discussions globally. This change is based on converging factors such as: Acceptance and use of RWD and RWE in regulatory decision-making; provider and payer use of RWE to establish effectiveness in both clinical and cost comparisons; and the evolving role of informing healthcare policy decisions globally.[26] This trend hallmarks a call to action for the MA community to further leverage the vast clinical acumen to support RWE opportunities within their respective medical organizations. The future for MA is very promising thanks to the RWE opportunities that have become a core component of Medical Affairs strategy. With the acceptance and guidance of RWE as a source of scientific evidence, MA professionals now have a primary role and responsibility of incorporating and communicating the value of RWE to stakeholders, ensuring use of high-quality RWE, and utilizing demonstration projects to further promote RWE adoption. We summarize below three areas where MA professionals can most effectively incorporate RWE into their organization:

## Communicate the value of RWE to internal and external stakeholders

Both HEOR and MA functions have an influential opportunity to further increase the importance of RWE and its role in informing healthcare decisions. HEOR and Publications teams can identify gaps in the literature and opportunity to publish more value-driven studies, including RWE, to align with the strategic plan of the scientific platform. Furthermore, HEOR is strategically positioned to advise and inform on the best digital technologies in healthcare that will improve healthcare delivery assessments and outcomes in effective ways.[26]

## Establish high-quality RWE metrics

MA professionals along with their HEOR/RWE colleagues should utilize their role of linking meaningful RWE metrics to the strategic planning process by defining the goal of product adoption and access, the education and awareness strategy, and the core activities to promote the adoption goal. Establishing these metrics will connect the value proposition of RWE to Medical Affairs.

## Utilize demonstration projects to push RWE adoption forward

Regulators and industry are learning by doing and demonstration projects are a key tool to understanding where RWE can be used and what methodological choices result in high-quality studies.[27] With MA professionals' depth of stakeholder connectivity both internally and externally, they can play a key role in shepherding the development research questions on RWE use cases and connect groups across the field to answer these questions. A joint decision-maker and industry understanding of key challenges in RWE can go a long way in determining RWE's appropriate use and progressing the field.

> *Today's cutting-edge concepts historically were generated from Medical Affairs and are used by Commercial and Market Access teams for post marketing efforts. As a cost saving measure, RWE upstream planning efforts in CT's (controlled trials), can mitigate fewer protocol amendments (very costly per change), lower cost, faster recruiting, and expanding entry criteria resulting in a cost savings to the organization simply by thinking ahead and incorporating RWE into the CT plan.*
>
> *Senior Director Oncology HEOR/RWE, Nelson*

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