

# GET REAL: Demonstrating Effectiveness with Real World Evidence



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## EXECUTIVE SUMMARY

Although randomized controlled clinical trials (RCTs) remain the gold standard for assessing the efficacy of pharmaceutical medicines, devices and healthcare in general, they are inadequate for addressing questions about the long-term effectiveness and safety of these interventions (Dreyer et al. 2010). Today, as payers and other stakeholders expect such interventions to be safe and effective and provide good value for money, the focus is increasingly on how these interventions perform in the “real world” and whether or not they add value to the healthcare system.

Real world evidence (RWE)-based approaches are increasingly becoming the “new normal”—practical and necessary for bringing a product to the healthcare market, ensuring its relevance in clinical practice and sustaining its value throughout the lifecycle of the product. However, they bring with them their own set of special considerations, including study design, analytical approaches, and sources and quality of data.

**In this white paper, Medpace experts discuss:**

- The value of RWE
- The role of study design in RWE
- Key data sources for RWE-based approaches
- Some unique considerations for RWE studies

## INTRODUCTION

Pharmaceutical and device companies increasingly must demonstrate evidence on real world outcomes in order to differentiate their products in a saturated and competitive environment and prove value to a price-sensitive healthcare marketplace, which includes regulators, insurance companies, healthcare providers and individuals to whom the products will be prescribed. Proving safety and efficacy before product launch alone is not enough to remain profitable while satisfying the additional scrutiny and demands of healthcare stakeholders.

Real world evidence (RWE) involves patient healthcare data, intentionally collected outside of the randomized controlled clinical trial (RCT) environment to provide information on relevant health outcomes, including cost of care. This evidence provides insights into unmet needs, interventional pathways and the clinical and economic impact on patients and the healthcare systems involved.

RWE-based approaches and data sources each have unique benefits and special considerations that must be properly addressed in order to generate trusted, valid and useful data.

## THE VALUE OF REAL WORLD EVIDENCE

RCTs remain the gold standard for assessing the safety and efficacy of pharmaceuticals, biologics and medical devices. However, they are inherently inadequate for addressing questions about the long-term effectiveness and safety of these therapies. In addition, RCTs cannot adequately answer questions about the “value” of these therapies—an increasing focus of regulators, providers, patients and payers.

RWE-based approaches help drug and device companies develop a more complete picture of what happens to patients through their treatment journey. Real world data can provide useful information on comorbidity profiles of the target populations as well as the likely causes of the disease of interest and inform decisions on market access, new indications and related pipeline investments. In addition, they can provide supporting evidence on the economic value of interventions to payers, patients and governmental health agencies.

The value of RWE:

- Provides deeper insight into the patient journey, treatment pathways and effectiveness
- Builds a better understanding of disease patterns
- Provides additional safety data
- Informs launch strategy and market access
- Demonstrates product value
- Maximizes potential return on investment
- Creates sustained value across the product lifecycle and disease portfolios

Traditional RCT Model	RWE Model
<ul style="list-style-type: none"> <li>• Safety, clinical efficacy</li> <li>• Ideal, controlled setting</li> <li>• Several thousand patients over relatively short period of time</li> <li>• Randomization remains most effective tool for reducing bias and confounding</li> <li>• Low recruitment or high dropout can affect sample size/statistical power</li> </ul>	<ul style="list-style-type: none"> <li>• Effectiveness in the real world</li> <li>• Real world setting (busy practices, patients who are not prescreened)</li> <li>• Up to millions of patients over longer durations</li> <li>• Generalizable study findings</li> <li>• Facts about patient journeys and outcomes</li> <li>• Comprehensive clinical effectiveness evidence</li> <li>• Faster patient access to innovation</li> </ul>

## CONSIDERATIONS FOR RWE STUDY

Because there is more room for variability, proper study design is especially important in RWE. The choice of study depends on why the evidence is wanted—for example, to study long-term safety, study effectiveness in multiple care settings or conduct economic analyses. The research question to be answered will dictate the appropriate study type.

Regardless of which study type is chosen, collecting and analyzing data in order to demonstrate real world effectiveness routinely brings up the same questions: How should RWE studies be designed; how should the data be analyzed; and then how will the results be combined with other types of evidence to make healthcare decisions, and how will these decisions be put into routine practice to support a product throughout its lifecycle?

## TYPES OF RWE STUDIES

- Phase IV trials
- Pragmatic trials
- Registries
- Post-authorization safety/efficacy studies
- Observational studies (prospective and retrospective)
- Pharmacoeconomics studies
- Expanded access/compassionate use programs

Absence of randomization creates methodological challenges and invites the possibility of systematic errors (bias) and the mixing of effects (confounding) (ISPE 2008; Berger 2009; Cox et al. 2009; Gliklich et al. 2014; ENCePP 2010; FDA 2013). The impact of these challenges depends on the type of study design involved—cohort, case-control, case-crossover, case-cohort or cross-sectional. A number of these study designs involve techniques which, when appropriately applied, can minimize the effects of bias and confounding and produce valid study findings.

Currently, there are no universally accepted standards for RWE research. Instead, there are different sets of guidelines offered by regulatory agencies and associations involved in these studies (STROBE 2007; Eudralex 2008; ISPE 2008; ISPOR 2009; ENCePP 2010; Dreyer et al. 2010; FDA 2013). Despite their differences, all stress the decisive roles of data quality, study design and analytical methodology.

Among the various study designs for gathering RWE, the cohort study is considered to provide the strongest evidence. This design involves assigning each member of the study population to a group on the basis of his or her exposure status, observing them over a specified period of time and comparing the groups to an outcome of interest. This means the exposure status of each patient is determined at baseline or at a specified formal start of follow-up. However, the problems associated with simplistic assumptions about exposure classification in RWE studies have been described elsewhere (Kiri and Gilbert 2009; Kiri 2012; Stampfer 1995; Miettinen and Caro 1989; Guess 1989). This is a problem that is often ignored when designing a simple registry using the cohort approach to assess the safety or effectiveness of an intervention. To identify and reduce this form of bias (i.e. exposure misclassification), assumptions should be tested as part of study development and alternatives to the cohort design should be explored. There are analytical options for addressing time-varying or intermittent exposure, although the appropriateness of each option may depend largely on its own set of assumptions, notably the methodologies involved in nested case-control, case-time-control, case-crossover and case-cohort designs.

Among industry-sponsored RWE studies, cohort studies based on patient registries and pragmatic trials pose the greatest sets of challenges primarily because they can also involve prospective collection of data. Although patient registries are increasingly becoming the design of choice for post-authorization safety studies (PASS), the most common sources of RWE remain observational studies based on routinely collected data: primary care datasets (such as the Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN) in the UK and the Disease Analyzer in both the UK and Germany), electronic medical records (EMRs) and medical claims databases.

Each type of study has unique requirements, benefits and challenges; therefore, specialized experience with scientific design and analysis is required. Some key points to consider:

- Design appropriate research questions for the product
- Align robust study approaches/methodology to those key questions
- Anticipate which stakeholders will need what type of information

## RETROSPECTIVE VS. PROSPECTIVE DATA SOURCES FOR RWE RESEARCH

Real world data are generally grouped into retrospectively and prospectively collected data. There is also a set of studies—cross-sectional surveys—that does not fall neatly into either category.

A common feature of studies which are based on retrospectively collected data is independence between the data collection processes and the study objectives. Generally, prospective studies require patient recruitment; therefore they typically have a study protocol and require informed consent.

Key Sources	Characteristics
<b>Retrospective Data</b> <ul style="list-style-type: none"> <li>Primary and secondary care</li> <li>Retrospective chart reviews</li> <li>Medical claims</li> <li>EMRs</li> </ul>	<ul style="list-style-type: none"> <li>Assess extremely large populations</li> <li>Good for assessing rare outcomes and long latencies</li> <li>Database studies can be quick and relatively inexpensive</li> <li>Involve fewer resources and less study time than prospective studies</li> <li>More susceptible to bias in both data collection and analysis and the influence of unidentified confounders</li> <li>Wider availability of claims data, growing availability of EMRs</li> </ul>
<b>Prospective Data</b> <ul style="list-style-type: none"> <li>Registries</li> <li>Observational studies</li> <li>Prospective chart reviews</li> <li>Large pragmatic trials</li> </ul>	<ul style="list-style-type: none"> <li>Assess extremely large populations</li> <li>Generally requires patient recruitment</li> <li>More robust than retrospective studies</li> <li>More expensive than retrospective studies, less expensive than clinical trials</li> <li>Can answer certain questions that clinical trials cannot</li> </ul>
<b>Other Data</b> <ul style="list-style-type: none"> <li>Cross-sectional surveys</li> </ul>	<ul style="list-style-type: none"> <li>Good for determining the level or frequency of a particular attribute or set of related attributes</li> </ul>

## SPECIAL CONSIDERATIONS FOR RWE STUDIES

Each RWE-based data collection approach presents its own challenges and considerations – whether it is based on routinely collected data that are readily available or requires processes for data extraction or prospective data collection. For prospective and retrospective studies, the main data collection issues include:

- Motivating sites to participate in these studies
- Maintaining good relationships with sites
- Obtaining patient consent if required
- Selecting appropriate data extraction tools
- Access to clinical records by external abstractors if site staff unavailable

Challenges to the validity of RWE (both internal and external) extend beyond the quality of data collection and can include confounding by indication, channeling of treatment and contra-indication. The usefulness of RWE studies can be further enhanced by the use of propensity scores, instrumental variables or other appropriately derived indicator variables (Grootendorst et al. 2010).

### Study Protocol

The protocol development process is vital in a RWE study. The key challenges of the study should be fully described and the methods for the resolution of each of these justified as feasible and appropriate, bearing in mind the following properties (Giezen et al. 2009; Kiri 2012):

- **Ecological validity:** dual challenges of recruiting the right population to ensure real-life setting is adequately captured and reflected and fulfilling vital risk management plan (RMP) obligations
- **Achievable study objectives:** challenge of ensuring the best possible study design and analysis for each critical objective
- **Tailored operational processes:** challenge of ensuring effective conversion of each study design into the best possible operational model and adequate collection of follow-up data

## ACCESSING MULTIPLE DATA SOURCES

Although evidence from RWE studies is now considered vital—especially for the evaluation of drug safety issues, disease epidemiology and health services research—these studies are often conducted in singular databases isolated from other data sources. This common practice continues despite the growing awareness of the potential advantages offered by large heterogeneous representative populations which can be obtained by pooling data from diverse sources.

Today, a number of regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recognize the value of data from multiple sources for surveillance activities. Several projects involving the development and assessment of processes for the linkage of data from diverse sources for the indicated activities have been conducted. These include the FDA Sentinel Initiative and Observational Medical Outcomes Partnership (OMOP) programs as well as Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge (EU-ADR) and PROTECT programs (Platt, et al. 2009, 2012; Stang et al. 2010; Coloma et al. 2011; Abbing et al. 2013).

One benefit of combining multiple data sources is the ability to pool larger, more representative populations of the full spectrum of users of pharmaceutical products, especially new drugs which may have low uptake or slower market penetration and drugs used for rare diseases (Hammond et al. 2007; McClellan 2007). In general, larger databases created from pooled data (total population, total follow-up time or total exposure time to drugs) are likely to command more power to detect signals with lower strength of association than may be possible in an individual database. In addition, combined datasets facilitate the analysis of more representative populations that reflect variations in predisposition to and manifestation of diseases in specific categories or subgroups such as race/ethnicity or exposure strata. This allows for the possibility of different patients reacting differently to medicines, which, in turn, enables better characterization of drug utilization within a wider spectrum of the population as well as the assessment of a larger variety of drugs (Dieleman et al. 2009; Coloma et al. 2011).

## ACCESSING MULTIPLE DATA SOURCES

Data from multiple sources are particularly useful for:

- Safety surveillance
- Assessment of rare events (conditions, outcomes and treatments)
- Comparative effectiveness research
- Evaluating sub-groups and monitoring health status across the population spectrum
- Benchmarking treatment patterns and care provision across the different levels of clinical services and regions

There are, however, some challenges involved with accessing multiple data sources. First, different databases often involve different coding schemes for medical events and drugs as well as differences in information sources (e.g. general practitioners' records, hospital discharge diagnoses, death registries and laboratory values). It may not be possible to construct a single, completely reusable data extraction algorithm for the medical event search in all the databases (Trifirò et al. 2014). Second are the complications involved in creating a suitable remote environment for storage and safe access to the standardized data from the different databases.

### ***Possible Approaches***

Data from multiple sources (within and across countries) can be made suitable for conducting RWE studies of multiple types. Suggested approaches to enhance the quality and usability of combined databases include:

- Harmonize protocols by standardizing medical events coding as well as definitions of the outcomes, exposures and covariates of interest. This will enable separate analyses of each database as well as subsequent common assessment which will reduce the heterogeneity between the individual studies and facilitate the interpretation of combined results. This is in contrast to the common practice of meta-analysis based on diverse and independent studies. The wide-ranging designs and conduct of these studies generally lead to loss of information (Abbing et al. 2010; Blake et al. 2012; Andrews et al. 2012).
- Standardize relevant features of the individual databases by using a common data model that involves common programming decisions based on suitable software. This means that locally standardized input files (of patients, drugs and events) can be created from each database and then linked via a unique patient identifier and managed locally (Coloma et al. 2011).
- Develop a storage system that makes the individual databases accessible from a common platform as anonymized data at an appropriate level. This storage system should be based on a common data model that complies with any governance and/or ethical guidelines relevant for the individual databases. Ideally, the development process should involve the active participation or consultation of the stakeholders with the individual databases, beginning at conception and continuing through to completion and implementation (Trifirò et al. 2014).

#### **Standardized Features Enhance Usability of Individual Databases**

A good example of using a common data model to standardize relevant features of individual databases is the Canadian Network for Observational Drug Effect Studies (CNODES). It is a network of investigators and linked databases in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec and Nova Scotia that includes a mechanism for accessing data from the United Kingdom Clinical Practice Research Datalink (CPRD) (Suissa et al. 2012)

## CONCLUSION

There is universal agreement among the various stakeholders in pharmaceutical, biologic and device development that evidence from research into such products should be based on causal inference. However, not everyone is familiar with the benefits and limitations associated with the different approaches to establishing causality. Both RCTs and RWE studies are susceptible to different forms of bias which can undermine the validity of causal inference (Rubin 2010; Schulz 1995). Although randomization remains the most effective tool for reducing bias, this may not be feasible in certain settings. Even RCTs can be susceptible to bias when a substantial number of study subjects either discontinue or change treatment in contravention of the study protocol (Hernán and Hernández-Díaz 2012). While there are good reasons why RCTs are regarded as the best method for assessing the effectiveness of health care interventions, the associated problems of low recruitment and high dropout can result in sample size or statistical power issues and limit the generalizability of study findings. Of course, in some situations a trial may be inappropriate, inadequate or even impossible to conduct.

Although RWE studies are rated lower than RCTs in the hierarchy of evidence because of the absence of randomization, they are increasingly viewed as viable alternatives and complements to RCTs, mainly because they reflect real-life utility of drugs, devices and other products (Concato et al. 2000; Papanikolaou et al. 2006 Kiri 2012). When properly conducted, RWE studies are capable of providing compelling information which, in certain circumstances, may be as valid as evidence from RCTs (Benson and Hartz 2000; Vandenbroucke 2004; Loke et al. 2004). The collection and evaluation of RWE can serve as a complement to RCTs by providing a more complete picture of what is happening to patients, building a better understanding of disease patterns, providing additional safety data, offering additional data for economic analyses and helping to better inform healthcare decision makers and policy leaders.

## ABOUT THE AUTHOR

*Matthew J. Page, Ph.D., M.P.P., Epidemiologist at Medpace, has a diverse background in academia and research including previous experience at UBC where he employed numerous methodologies including cost-effectiveness analysis, cost-utility analysis, and budget impact modeling. Most recently, he was an Assistant Professor of Public Health at The College of Charleston, where he taught courses in epidemiology and biostatistics. Matt earned his Ph.D. in Epidemiology from Emory University, his M.P.P. in Public Policy from The College of William and Mary, and his B.A. in History from The University of Michigan.*

## ABOUT MEDPACE

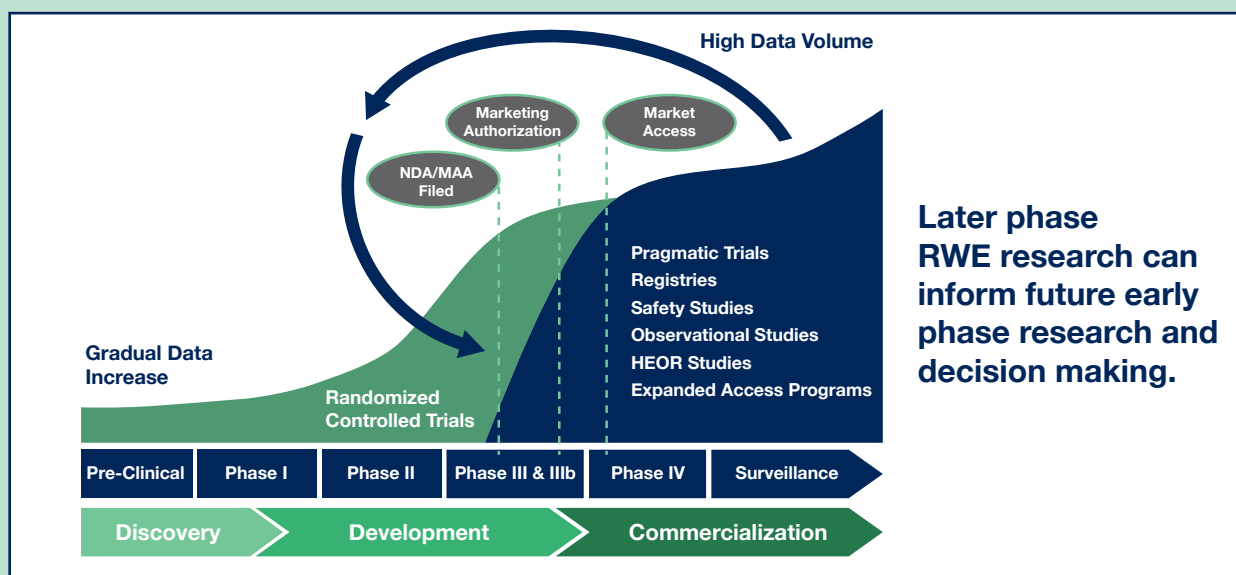
Medpace is a scientifically-driven, global full-service clinical research organization (CRO) providing Phase I-IV clinical development services for drug, biologic, and device programs. Medpace's physician-led, high-science, and disciplined operating approach leverages regulatory and therapeutic expertise to accelerate the global development of safe and effective medical therapeutics across all major areas including oncology, cardiovascular, metabolic/diabetes, infectious disease, and neuroscience. Learn more at [Medpace.com](http://Medpace.com).



## MEDPACE RWE CAPABILITIES

### Understanding the value story

Medpace engages with Sponsors from early development through approval and post-marketing safety requirements to tell the “value story” of your product. Medpace designs and conducts RWE-based approaches to complement data collected from RCTs to provide an accountable, seamless, integrated, and efficient approach to drug and device development. This includes an understanding and appreciation that later phase, RWE research can inform future early phase research.



### eXperts

Our team of real world and late phase strategists and researchers can help you demonstrate the safety, effectiveness and quality of your drug, combination product or medical device to key stakeholders. With a 20+ year history in designing and conducting clinical research across all phases of development, Medpace experts bring keen insights to RWE research and understand how to integrate the data throughout the development cycle.

### eXperience

Medpace’s relevant experience includes more than 130 interventional and observational RWE studies involving over 40,000 patients at more than 2,000 sites. These RWE studies complement the existing Medpace full-service model.

Drawing upon our extensive experience, we can help Sponsors determine the best timing for initiating RWE analyses, whether it be earlier or later in the drug development cycle. We have experience with various sources of claims data and EMRs, including United States (US) Centers for Medicare & Medicaid Services, US Veterans Affairs, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), and several payer claims and hospital billing databases.

### eXecution

Medpace has the capability to conduct standalone or piggyback economic analyses, including cost-minimization analysis, cost-effectiveness/cost-utility analysis, cost-benefit analysis, and budget impact modeling. In addition, Medpace can generate RWE through the design and execution of prospective and retrospective observational studies, registries, and other safety studies.

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