Paper RW01

Utilizing RWD and RWE: An Introduction to Core Concepts and Requirements

Chris Hurley, MMS Holdings Inc., Canton, MI, USA
Aditya Gadiko, MMS Holdings Inc., Canton, MI, USA

ABSTRACT

This paper is intended to help guide the reader toward a better understanding of core concepts and requirements for using real-world data (RWD) to derive and utilize real-world evidence (RWE) in drug development. Explanation and examples of RWD lay a foundation to explore its potential applications within the clinical paradigm. Knowledge shared in this high-level overview reflects regulatory framework guiding strategy for use of RWE, identification of necessary standards and definitions of RWD and RWE, learning from demonstration projects, and first-hand experience with technical tools researched while developing this paper. Putting it all together introduces the reader to current-practices in the application of RWE and RWD in the drug development process.

INTRODUCTION

In the last twenty-five years we have seen a dramatic shift in the way the pharmaceutical, healthcare, and insurance industries collect, analyze and report data. The rapid adoption and advancement of technology, not just in health sciences but in all aspects of our lives, has brought an explosion of data that may be purposefully curated, combined, and analyzed to provide very useful and timely information. Core concepts regarding this data will be discussed, including explanations and examples of RWD and generating RWE within drug development. Potential applications of RWE will be discussed all within the bounds of the regulatory framework for RWE. As the industry is starting to more rapidly adapt to the strategies and use of RWE, we will take a high-level look at select use cases, demonstration projects, and provide a first-hand account of helpful tools that may be used to identify and explore the use of RWE with clinical trial data.

REGULATORY FRAMEWORK

The 21st Century Cures Act was passed in 2016 with the remit to accelerate the discovery, development, and delivery of 21st century cures, and for other purposes. Subtitle C – Modern Trial Design and Evidence Development[1] contains a section describing the potential use of real-world evidence to help support approvals for new indications and support or satisfy post approval study requirements. This act also laid the Framework for FDA's Real-World Evidence Program[2]. Many of the concepts described in this paper are consistent with this framework describing the use of RWE for answering the regulatory question.

Additionally, international clinical research networks and agencies are key players in determining the place of RWE in regulatory decisions. Current programs and frameworks can help provide support for harmonizing the rules and guidance for RWE generation. In Table 1, recommended links to helpful documents published by regulatory and other organizations within each respective region are provided.

Table 1. Helpful RWE Documents

Europe	Innovative Medicines Initiative (IMI) IMI GetReal project European Medical Information Framework (EMIF) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
USA	FDA's RWE Framework Duke-Margolis RWE Collaborative Bipartisan Policy Center
Canada	Canadian Agency for Drugs and Technologies in Health

DEFINITIONS

Real-World Data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from several sources, for example:

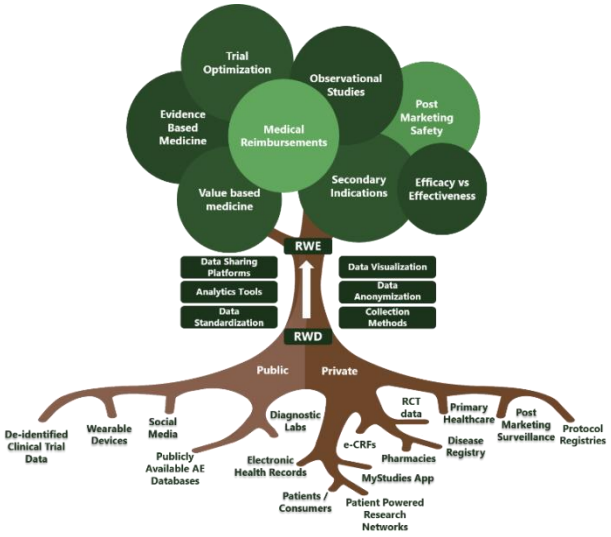
- Electronic Health Records (EHRs)
- Claims and billing activities
- Product and disease registries
- Data gathered from other sources that can inform on health status, such as mobile devices

Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including, but not limited to, randomized clinical trials like large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

PROVENANCE

Prior to the definitions of RWD[3] and RWE published within the FDA Framework in December 2018, there was no real consensus on the exact definition of each. As we consider the provenance and flow of data in real-world applications, as demonstrated in Figure 1, one observes that RWD flow from many public and private sources at the root of a fertile data landscape. RWD are processed through data sharing platforms using appropriate collection, standardization and anonymization methods and form a solid trunk from which analysis algorithms and visualization tools are applied to create the RWE that branches out across many use cases and applications. In 2017, a study conducted on behalf of GetReal[4] Work Package 1 identified thirty-eight definitions from assessing just fifty-three documents and twenty interviews. In this study, RWD and RWE were often defined in high-level terms for health intervention data that was not typically collected in conventional randomized controlled trials (RCTs).

Figure 1. RWE Tree



EMERGING REGULATORY USE CASES FOR REAL-WORLD EVIDENCE

The real beauty and utility in the tree are the various applications of RWE across the entire drug development life cycle. For instance, RWE can be used to shorten drug development timelines, shorten patient recruitment times, conduct observational studies, reduce the costs of clinical trials, increase safety by using synthetic or external comparator arms for high risk trials, improve the probability of technical and regulatory success, observe post marketing safety, analyze market access and medical re-imbursement, and study and/or apply for secondary indications.

RWE is beginning to be accepted by regulators, physicians, and patients in a small subset of disease areas, such as oncology, rare or orphan diseases, and other similar therapeutic areas. These are typically characterized by a lack of other therapeutic options, where the disease is considered life-threatening, where it affects a small population size, and/or the effect is easily measured. As RWE becomes increasingly accepted, we can look forward and see that there are at least five major use cases emerging for using real-world evidence in the benefit assessment by regulators. Companies are just starting to include RWE in regulatory submission packages that meet the criteria below.

- <u>RWE used to establish historical controls</u>:
  For ethical or other reasons, patients cannot be randomized to placebo. Instances include life-threatening orphan diseases, having no adequate therapeutic options. For cases like this, historical controls are needed. Before the adoption of EMR, physicians would physically scour old patient paper records to build historical controls for regulatory submissions. Now, with collection of electronic medical records as the norm, this patient-level data can be assessed on a larger number of patients more easily and effectively.

- <u>Early approval then RWE post-market monitoring</u>:
  Drugs for life-threatening diseases without adequate treatment options might be approved based on strong early clinical evidence. In these instances, approval may be based on only Phase II or III randomized clinical trials with the requirement to complete post-market monitoring via RWE only. Some companies have struggled with patient recruitment and have been unable to get enough patients within a reasonable

timeframe to meet regulatory requirements for post-market randomized controlled trials. Post-market RWE analytics may be a better approach in these cases.

- On-label RWE from another country submitted:
  These are cases where a drug has already been approved outside of the United States. For instance, after an initial rejection for an expanded indication, NovoSeven[5] was approved for those indications based on RWE collected through registries located primarily in Europe and Canada.

- Medically accepted alternative-use RWE submitted for new indications:
  EMRs may contain rich data on drugs being used off-label. Documentation for medically accepted alternative uses, such as recommendations in clinical guidelines developed by physicians, is fertile ground for analysis and application for new indications. There have already been a small number of successful regulatory submissions using this off-label data, including the expanded indication for Ibrance[6] for the treatment of men with HR+ HER2- metastatic breast cancer, so this practice is expected to grow.

- Medically-accepted alternative-use RWE submitted for expanded populations:
  Like RWE supporting use for new indications, EMRs contain rich data on drugs being used off-label for new populations, including those not included in initial approval such as children, pregnant women, and disease sub-populations that include patients with less severe disease. RWE was the sole data source evaluated by the FDA[7] for the approval of the Sapiens transcatheter heart valve for an expanded patient population.

RWE can be an integral component of the data package across the lifecycle from proof of concept through loss of exclusivity. Including RWE at all points along the entire spectrum would increase the knowledge of all stakeholders regarding potential benefits and side effects. With more robust data, improved methodologies, and greater clarity about regulatory frameworks, RWE analytics in the short term could support:

- Increasing therapeutic effectiveness:
  Suggesting new and effective benefits for new products or for additional indications and assessing the optimal doses of approved products

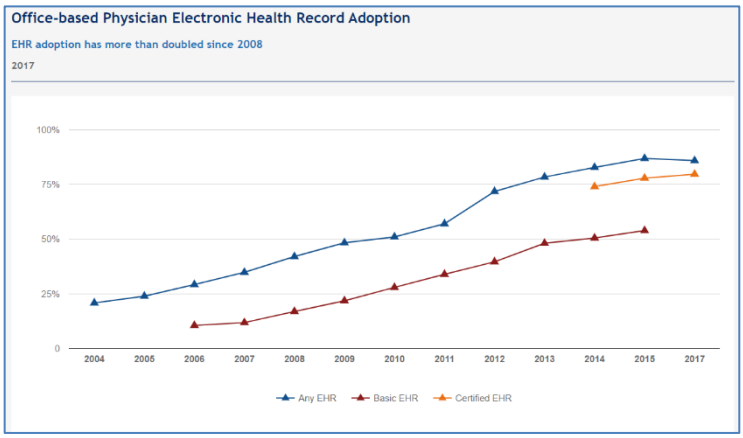
- Understanding special populations that could benefit from a product:
  This includes protected populations such as the elderly, pregnant, or pediatric patients, while also enabling better understanding of effectiveness in patient sub-populations

- Fulfilling post-marketing requirements:
  Committing to RWE analytics after approval to further understand product benefit

- Enhancing the label:
  This will better inform patients and healthcare practitioners of important information not included in approved indication, such as adding benefit/risk information from observational studies

Typical RWD sources include – patient registries, healthcare databases, pharmacy and health insurance databases, patient powered research networks, and social media. One of the major reasons for the burgeoning amount of Electronic Health Records (EHRs) is that insurers are requiring this electronic data from physicians and hospitals before they are reimbursed. Figure 2 demonstrates just how prevalent EHR adoption has become, more than doubling since 2008. Of course, one does not need to think hard about the growth of RWD on social media as people generally love to share personal stories online.

Figure 2. EHR Adoption



RWD EXAMPLES – TRY SOME TODAY!

Have some fun with Twitter RWD:

- Go to www.twitter.com
- Type "Humira" in the search bar
- Count the number of tweets that you think are Adverse Events

Follow this link to see the same RWD in action: https://bitly.com/TwitterRWD. In this case, the link is performing a very simple sentiment analysis by searching Twitter for "Humira". According to Wikipedia[8], "Sentiment Analysis is the use of natural language processing, text analysis, computational linguistics, and biometrics to systematically identify, extract, quantify, and study affective states and subjective information." This link is simply performing a pre-defined search on Twitter for "Humira," but the results are real-time Tweets. See how many seem to be mentioning adverse reactions to Humira.

Try opening some additional data sources with these other links we defined in bitly:

- Wearables like Apple Watches, Fitbits etc. → http://www.bitly.com/JJWatchAFib
- FDA's MyStudies App → http://bitly.com/FDAMyStudiesApp
- National Healthcare Databases and Accessibility → http://bitly.com/RWDSources

The third link will open a screenshot showing a list of national databases, what they are, how many lives are involved in each, and the type of industry access that is available. This is a great place to start your search for high-value real-world data pools.

During the writing of this paper, PHUSE and FDA announced the Data Science Innovation Challenge. Prototypes will be presented at the US Connect in Orlando in March 2020. These demonstrations will show excellent examples of utilizing RWE for the following challenges, 1) Opioid/substance use disorder; 2) Drug safety surveillance using social media; 3) Approach for predicting drug interactions.

POTENTIAL DATA MODELS

In August 2019, to address the unprecedented growth of EHRs, the Bipartisan Policy Center released a report - Expanding the Use of Real-World Evidence in Regulatory and Value-Based Payment Decision-Making for Drugs and Biologics[9]. Several references and recommendations were made to adopt Application Programming Interface (API) provisions that would require health IT developers to support API enabled services using the HL7 FHIR® standard and related implementation specifications.

The Centers for Medicare and Medicaid Services (CMS) also released a proposed rule requiring Medicaid, the Children's Health Insurance Program (CHIP), Medicare Advantage plans, and Qualified Health Plans in the Federally-facilitated Exchanges to provide enrollees with electronic access to medical claims and other health information electronically through open APIs using the same standards proposed by The Office of the National Coordinator for Health Information Technology (ONC)—the HL7 FHIR® standard.

PHUSE has dedicated a working group toward Investigating the use of FHIR in Clinical Research[10]. As there has been a substantial increase in the amount of EHR data, it is logical to see an increase in the need for standards to be able to link this with clinical trial data for research purposes. A visit to the wiki page will reveal the current issues, actions, deliverables and a couple of very informative webinars on the use of FHIR in Clinical Research.

As industry utilizes an increasing scope of RWE, the needs for standards and common data models will also increase. Standards Development Organizations will be pushed to develop semantic relations to facilitate neuro-networks and end-to-end automation. The CDISC 360 Project is a good example of this attempt to facilitate automation with linked data.

The PHUSE working group Going Translational with Linked Data, led by Tim Williams and Armando Oliva, met at the CSS 2019 conference where the team shifted strategy to smaller, modular projects. In the future, these may provide the ability to automate some of the ingestion of RWE through the capabilities of linked data and the RDF. The proposed new focus increases cooperation with the Food and Drug Administration and the Maintenance and Support

Services Organization (MSSO, for MedDRA). As the capabilities of this team increase with experience from the collaboration with the FDA and MSSO, they may increase the ability to reach out and build semantic relations with other data models and sources of RWD.

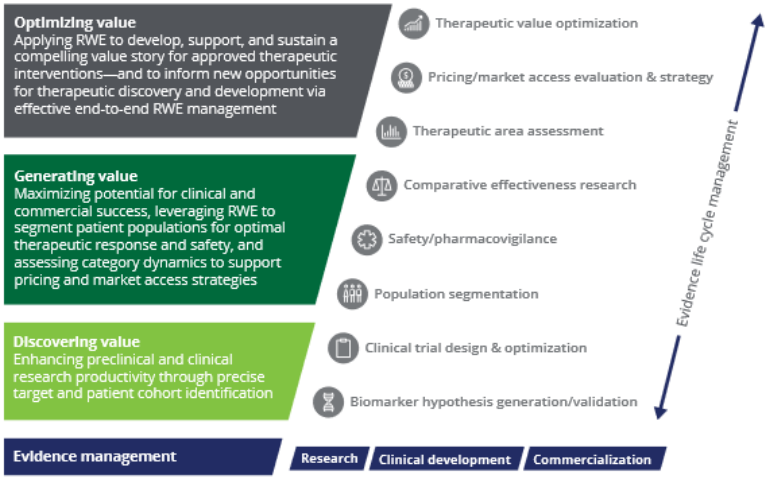
POTENTIAL APPLICATIONS OF RWE

Each year, the ConvergeHealth unit of Deloitte[11] sends out surveys to pharmaceutical executives and the theme in July 2018 was about how "End to end evidence management" will affect both clinical and commercial activities. Over 90% of global pharma companies are utilizing RWE to derive value in some form or another, including using it for decision making at an enterprise level.

Executive responders revealed the current thinking from this benchmarking survey. In Figure 3, Evidence life cycle management shows the value drivers within four phases starting with the base of Evidence management then moving up through the life cycle of discovering, generating and optimizing value. While Figure 4 shows the current and expected future areas where RWE is having the most impact within their organizations.

Figure 3. End-to-end evidence management approach

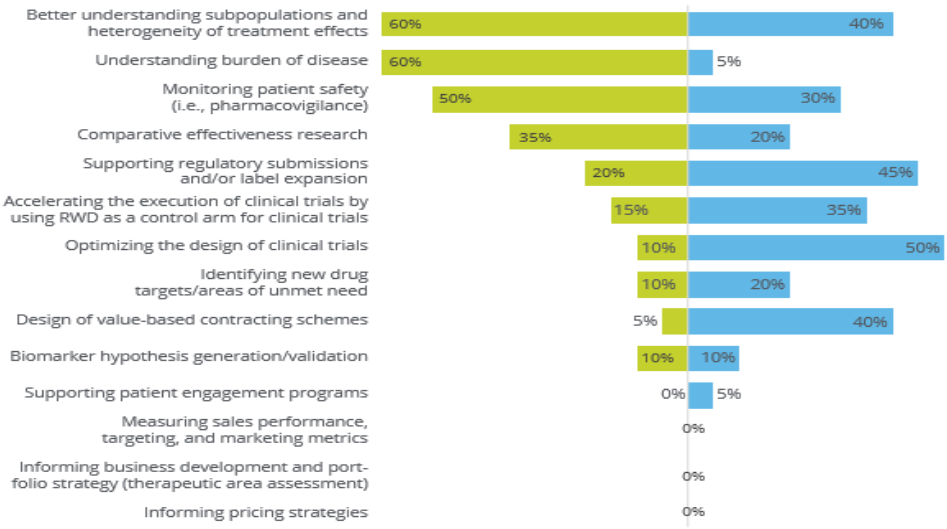
Pharma companies can maximize the value of their data by using it for decision-making at an enterprise level (vs. traditional siloed approaches)



Source: Deloitte analysis.

Deloitte Insights | deloitte.com/insights

Figure 4. Please rank the three most impactful areas of current and future RWE application within your organization



Note: The figure denotes current and future application areas ranked amongst the top three by respondents and expressed as a percentage.

Source: Deloitte's 2018 RWE Benchmarking Survey.

Deloitte Insights | deloitte.com/insights

CREATIVE USE OF RWE

It is not always straightforward to determine what data can be used to support a regulatory decision. Sometimes a little out of the box thinking is necessary. The challenge was that support for an orphan drug response required

identification of prevalence for a disease subset population that was not obtainable through scientific literature. The orphan drug application had been held in abeyance on two previous occasions due to concerns from the Office of Orphan Products Development (OOPD) regarding prevalence. The solution employed creativity and flexibility to identify real-world data routinely collected from the delivery of health care. Using actual sales data from the US and shipment data from Europe for a marketed competitor would best support a prevalence estimate in the subset disease population. The analyzed data effectively demonstrated that the population subset was less than the threshold of 200,000 patients required for orphan products. In the right circumstances, there is limitless potential for the creative use of non-traditional data and RWE in drug development and global regulatory submissions.

TOOLS TO UTILIZE RWD

Typically, RWD is not going to be structured in the same way as the static SAS datasets found in clinical trials. Because of the potential of very large datasets, streaming data, unstructured and unformatted data, cloud-based systems will be deployed for the data collection, storage and engineering tasks. Similarly, the needs for programming tools are different as well and require a set of skills pertaining to the Julia, Python and R programming languages in addition to SAS, including Viya, and others that can handle big data. Meshing the domain knowledge of the clinical programmers and statisticians with the skilled data scientists using the scripting languages may require a learning curve for everyone.

CHALLENGES

It is clear from the current use of RWE in the US and elsewhere that many stakeholders see great value in RWE and are exploring ways to make use of these data sources. However, several challenges have been identified that have meant utilization of RWE is far from universal. A common reservation is around the 'quality' of RWE. In practice this comprises a variety of factors, which are discussed below.

REGULATORY AND PRIVACY HURDLES

To date, RWD and RWE in the current drug development paradigm have largely been applied in early discovery, the post market phase of safety surveillance, and for comparative effectiveness evaluation. Health authorities are moving in the right direction but still must provide greater clarity on the acceptability of RWE in decision making and provide guidance on standards and best practices of both methodology and analysis when integrating RWE for regulatory submissions.

There are an increasing number of companies like app developers, companies, manufacturers of wearables, and social media sites that hold a wealth of health information. These sources can be leveraged for real-world evidence but are not subject to existing privacy protections under HIPAA. Privacy and consent issues are likely to be very important as data gathering can only occur with the permission of individuals and populations. This strongly implies that public information is vital for this area of medicine to develop. This is a complex problem and beyond the scope of this paper.

This challenge is exacerbated by legal frameworks that restrict data sharing and access to patient identifiable information. This in turn can reduce the ability of health care organizations to share data so that it can be linked across different datasets. Even if researchers are aware that relevant data exists, data governance may mean they are not able to access it, face delays in access, or can only access a subset of the data. A balance needs to be struck between protection of private information and informing real-world research. The PHUSE Deidentification working group has done a wonderful job developing deidentification standards for clinical trial data. But there is a wide world of data outside of clinical trials that would be useful as RWE if we can overcome the privacy issues. Take a look at the PHUSE Connect Software Demonstration Streams for privacy solutions demonstrated by providers.

DATA MINING / DATA ACCESS

Data mining occurs when analysts re-examine existing datasets to generate new information. Data mining is not inherently bad and can be very useful for generating new information from existing data. However, a concern in the context of RWE is that commercial organizations can cook the data. That is, they continue to reanalyze datasets using different modelling approaches until preferential outcomes are delivered. The vulnerability of RWE to manipulation via repeat analyses with non-disclosure of unhelpful results underlines the need for strict protocols, analysis plans and well-defined research questions.

STANDARDS

For a set of standards to be useful, all stakeholder groups are required to buy into them and agree that they offer the most suitable guidance for the development, conduct, analysis and/or reporting of RWE. A couple of themes seem to resonate with considerable constraint to the adoption of RWE standards. “The RWE area is evolving so rapidly that standards can’t keep up with what we are able to do with the data.” “Lack of consensus has meant that RWE is often not considered to be high quality compared to trials and is not considered high quality for evidence-based medicine”. Ideally, organizations like PHUSE will work with Standards Development Organizations so that all studies can be conceptualized, designed, conducted, analyzed and reported according to a common set of standards. This will increase transparency, reliability, and trust in the results of RWE.

CONCLUSION

This high-level look at the core concepts and use of RWE shows that insightful analysis of RWE may be very beneficial for drug development. Creativity is necessary as the early adopters of RWE continue to move this industry forward, but that creativity is constrained within the bounds of the RWE framework and in keeping with the tenants of privacy practices. Finding, accessing, integrating, and using RWE is challenging. Until the adoption of RWE is a mature practice, it will require increasing collaboration between and within industries, not just for standardization and sharing of data, but for better understanding of the use cases and analyses of the underlying RWD. Organizations such as PHUSE promote this collaboration and provide a forum where these challenges may be examined, discussed, and ultimately overcome, thereby increasing the prospects for faster adoption of RWE resulting in the faster development of new therapies or expanding the use of current therapies for deserving patients.

REFERENCES

1 https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf
2 https://www.fda.gov/media/120060/download
3 The definition of RWE provided by section 3022 of the Cures Act was subsequently revised by a technical amendment in Section 901 of the FDA Reauthorization Act of 2017 (Public law 115-52).
4 https://www.valueinhealthjournal.com/article/S1098-3015(17)30171-7/abstract
5 https://laegemiddelstyrelsen.dk/da/nyheder/2018/temaarrangement-om-big-data-og-medicin/~/media/2C04BFEB74AB46AD81A5B329EC9AFA39.ashx
6 https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/6/fda-used-real-world-evidence-in-heart-valve-approval
7 https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer
8 Sentiment Analysis in Wikipedia, retrieved 03OCT2019 from https://en.wikipedia.org/wiki/Sentiment_analysis
9 https://bipartisanpolicy.org/report/expanding-the-use-of-realworld-evidence-in-regulatory-and-value-based-payment-decision-making-for-drugs-and-biologics/
10 https://www.phusewiki.org/wiki/index.php?title=Investigating_the_use_of_FHIR_in_Clinical_Research
11 https://www2.deloitte.com/us/en/insights/industry/life-sciences/2018-real-world-evidence-benchmarking.html?icid=dcom_promo_featured%7Cglobal;en

ACKNOWLEDGMENTS

We’d like to thank Susheel Arkala, Narasimha Ayyalas, Olivia Teague, and Ravi Yandamuri from MMS Holdings Inc. for their contributions to this paper.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Christopher Hurley
MMS Holding Inc.
6880 Commerce Blvd
Canton, MI 48187
Work Phone: +1-734-245-0469
Email: churley@mmsholdings.com
Web: www.mmsholdings.com