Review Article
Challenges and Risks regarding the use of Real World Data – a visualization

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Short Title: Real World Data Challenges Radar

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Number of Tables: 1

Number of Figures: 2

Word count: 3366 (incl. abstract and body text, excl. title page, reference list or figure legends)

Keywords: Real World Data, Real World Evidence, Data Quality, Risk, Compliance

Abstract

Background: The life science industry has a strong interest in Real-World Data (RWD), a term that is currently being used in many ways and with varying definitions depending on the source. In this review article, we aim to provide a summary overview of the challenges and risks regarding the use of RWD and its translation into real-world evidence and further classify and visualize RWD into the research landscape in the form of the RWD Challenges Radar.

Summary: The study identified three types of challenges -organizational, technological, and people-based- that must be addressed when deriving evidence from RWD to be used in drug approval and other applications. It further demonstrates that numerous different aspects, such as the context of the application field and the associated industry, must be considered. A key finding in our review is that the regulatory landscape must be carefully assessed before utilizing RWD.

Key Messages: Establishing awareness and insight on the challenges and risks regarding the use of RWD will be key to taking the full advantage of the RWD potential. As presented in this review, the RWD Challenges Radar will support the establishment of awareness by providing a comprehensive overview of relevant aspects to be considered when employing RWD.

Introduction

The digital world allows unprecedented access to vast amounts of data on real-world conditions that were beyond imagination just a few years ago (for example, sensor data from fitness devices available for analysis by insurance providers). The life science industry is interested in using this type of data, named 'Real World Data' (RWD) and is currently pioneering the integration of this data into their experiment and regulatory pipelines. The development and approval of drugs, treatments, and therapies are driven by various regulatory requirements; therefore, it is risk-rich and costly. RWD opens new possibilities for providing clinical evidence regarding the use and potential benefits or risks of new drugs, treatments, and therapies outside the context of prescriptive randomized clinical trials (RCTs). The use of RWD to inform on health-related decisions is defined as 'Real World Evidence' (RWE). An essential question related to RWE remains unanswered: What challenges are faced when deriving evidence from RWD?

The risks associated with the use of RWD can be aggregated in three areas along the dimensions of 'Time' and 'Business Exposure' as shown in Figure 1 [1]. As perceived over time and ranging from short to long term, these aggregated risks relate to 'Compliance Controversies', 'Registration Failure,' and 'Business Model Disruption' respectively. In this study, we primarily focus on the short- and medium-term risks of using RWD in the life science industry.

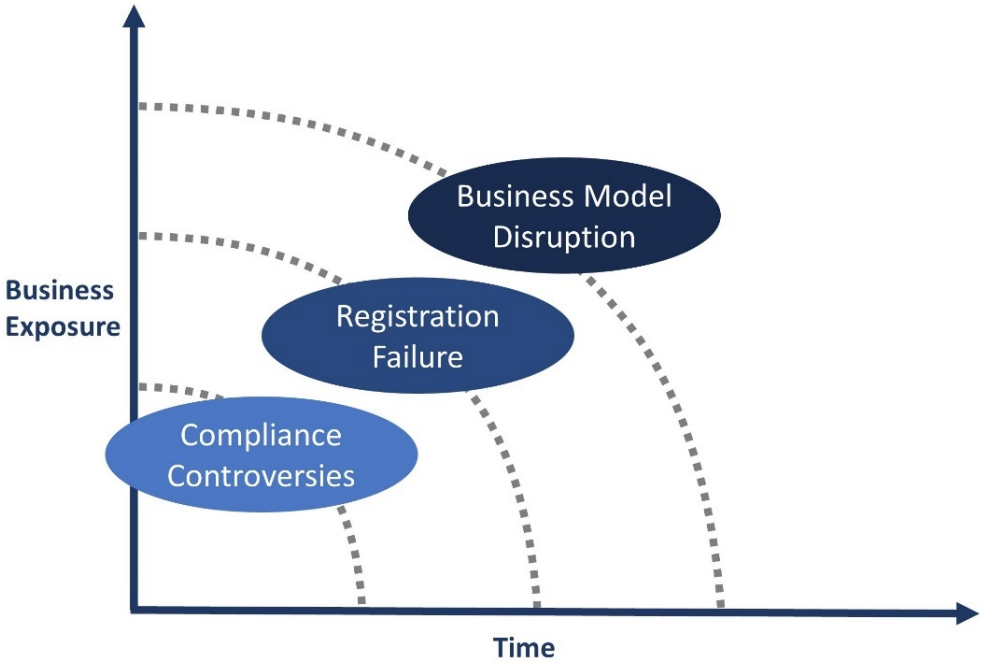

Figure 1 Risk fields in the Context of RWD [1]

Definitions and Concepts

The following section provides an overview of relevant definitions and concepts in relation to RWD.

Real-World Data (RWD)

RWD is a term that has varying definitions depending on the source. The Association of the British Pharmaceutical Industry (ABPI), an influential British organization representing British biopharmaceutical research companies, defines RWD as 'data obtained by any non-interventional methodology that describes what is happening in normal clinical practice' [2]. This definition refers to medical research; the term 'non-interventional' can be explained as procedures 'without any intervention during the course'. In contrast, RAND Europe, a reputable nonprofit institution that helps improving policy and decision making through research and analysis refers to RWD as an 'umbrella' term, which stands for different types of data related to healthcare that is not collected in context of conventional RCTs [3]. The International Society for Pharmacoeconomics and Outcome Research (ISPOR), a relevant player that promotes health economics and outcomes research to improve health decision making, defined RWD as simple as 'Data used for decision making that are not collected in conventional RCTs.' [4].

Real-World Evidence (RWE)

RWE is generated through the use of RWD to make meaningful health-related conclusions. The surge of electronic health records (EHRs), as well as other technologies, enables researchers to understand the real-world patient's experience better. For example, the use of a smart phone to measure the distance traveled by the patient to measure fitness activity. In contrast, the New England Journal of Medicine asserted to exclude data from clinical research settings such as in EHRs from their definition of RWE [5]. Similarly, researchers from the United States Food and Drug Administration (FDA) defined RWE as 'information on health care that is derived from multiple sources outside typical clinical research settings, including EHRs, claims and billing data, product and disease registries, and data gathered through personal devices and health applications' [6].

Efficacy Effectiveness Gap

The 'Efficacy Effectiveness Gap' (EEG) is the discrepancy between the real-life efficacy of a drug once it is available in the market and the outcome of the same drug in a standardized environment under ideal conditions in the context of RCTs [7]. The EEG poses a challenge on the decision making process of drug licensing when it is based solely on the efficacy analyses of RCTs [8]. The EEG can be related to 'lower than anticipated efficacy or a higher than anticipated incidence or severity of adverse effects' [7]. GetReal, an innovative medicines initiative (IMI), launched a study which aspires to

advance awareness of how to harmonize evidence to back efficacy and effectiveness and at proposing operational solutions [9].

Real-World Data Challenges

An in-depth and systematic literature search was performed to identify several potential challenges and risks in selected academic publications. Relevant categorized publications included the words "RWD" and/or "RWE". We found a total of forty-one challenges relating to RWD and RWE that were mentioned repeatedly. After pre-processing the results, clustering similar and removing duplicated challenges, 16 unique challenges were identified. To achieve these results, the authors allocated a one-word identifier for each challenge and used text analysis to derive the statistics about the results. In Table 1, the identified challenges are mapped to three 'classical' categories, which will be discussed in the following sections. The 'Occurrence' column indicates the overall frequency, with which a key challenge appeared in the analyzed literature.

Key Challenges	Categories	Occurrence
Data Quality	Organizational	6 (15.8%)
Bias and Confounding	Organizational	5 (13.2%)
Standards	Organizational	4 (10.5%)
Trust	People	3 (7.9%)
Data access, expertise to analyze RWD, Privacy, Regulations, Costs	People	2 (5.3%)
Security, Awareness, Coordination, Adoption, Format, Assurance	Technological	1 (2.6%)

Table 1 RWD challenges occurrence in the academic literature

To further categorize the identified key challenges that risk managers in stakeholder organizations are likely to face when RWD is discussed, we developed a criteria schema, the 'RWD Challenges Radar', as visualized in Figure 2. The RWD Challenges Radar is guided by the three classical information system perspective: firstly, the 'Organizational' view, secondly, the 'Technological' view, and thirdly, the 'People' view. Each view consists of sub-categories, originating from the literature search.

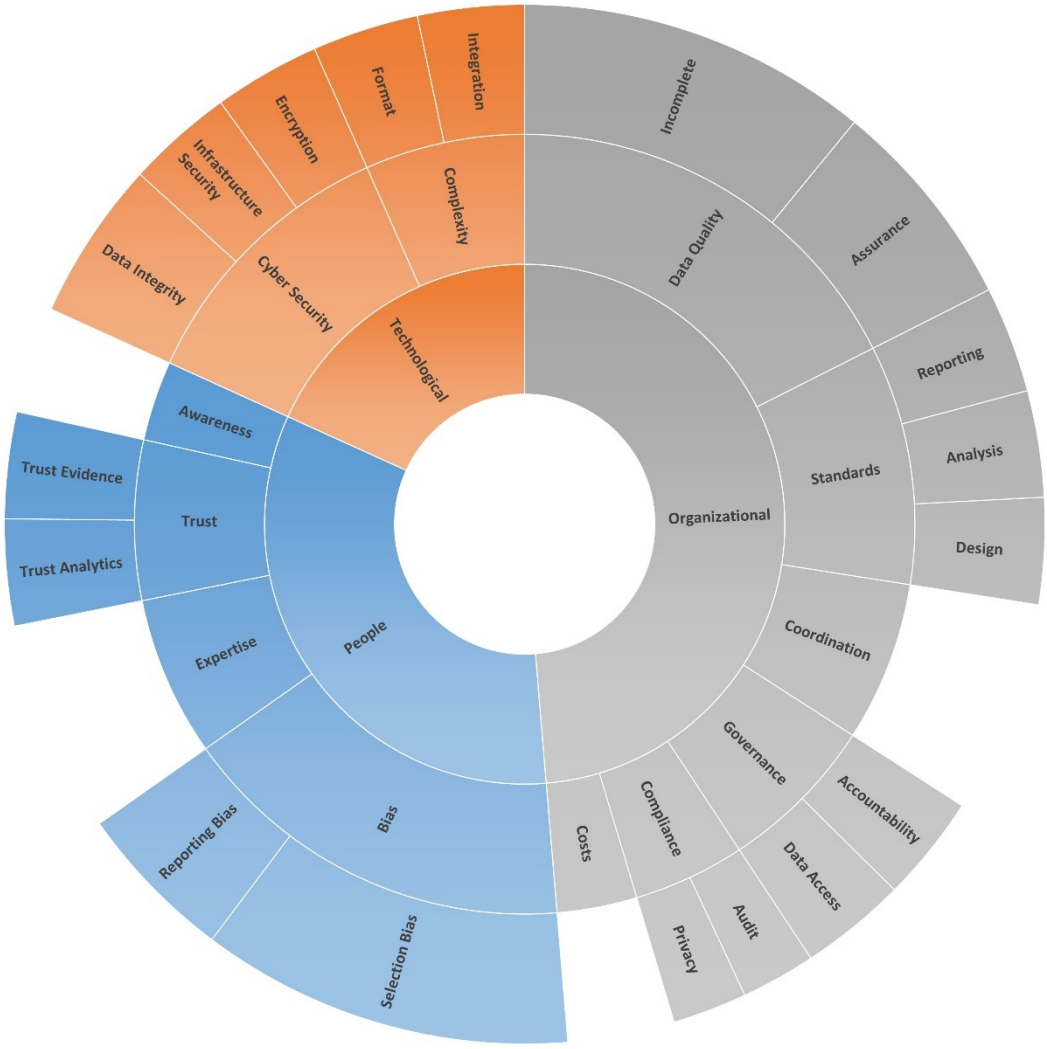

Figure 2 RWD Challenges Radar

RWD Challenges Radar

Organizational view

The process of converting RWD into RWE to be used in a regulatory context needs to be embedded in adequate organizational structures. This relates to a) governance arrangements, b) alignment with compliance requirements, c) availability of suitable standards, d) active coordination, e) availability of data quality mechanisms, and f) cost considerations.

Governance

RWD is generated by different sources such as academic institutions, hospitals and private individuals. Consequently, sought after RWD may not be accessible to all stakeholders. RWD is concentrated mostly in hospital, pharmaceutical, and university databases – entities that might not have the funding nor the interest to conduct observational research. Thus, access to these databases

might be limited from outside the respective organizations. Therefore, access to RWD sources is highly related to the type of interactions that are in place between different stakeholders in the organizations [3]. Moreover, most databases are often only accessible to researchers from academia upon request, while not being offered to other types of groups. Research suggests that this may be due to the fact that RWD is being used for reasons other than why they were initially intended [10]. Consequently, legal frameworks and governance arrangements for RWD access are vital to allow different groups to access the required data in time to optimize healthcare for patients.

Compliance

Recent changes in data privacy legislation in Europe, such as the General Data Protection Regulation (GDPR), should be considered for RWD [11]. These rules pose a challenge to the collection and analysis of RWD. For example, the GDPR's data minimization principle, which indicates that data must be 'relevant and limited to what is necessary' [12], can conflict with the objectives of research groups where an accurate analyses and results require increasingly more datasets [11]. Additional rules applied to the collection of RWD concerning ‘consent’ and ‘purpose limitation’ could restrict social media data gathering. Ethical concerns and the fear of data misusage hinder the gathering of patients' personal data. This has led to some unsuccessful initiatives, such as the Netherland’s attempt to develop a national electronic record system to facilitate the exchange of information between different healthcare entities like hospitals, insurance companies, and pharmaceutical firms [3,13]. A specific concern is that commercial organizations may misleadingly interpret the health datasets that can contradict the original aim of the project [13]. Additionally, several privacy frameworks have been built to facilitate further protect patient data, such as the OECD Privacy Framework [14]. However, due to its sensitive nature, health data is always a significant concern for regulators around the globe. Data privacy legislation will continue to be a major challenge that stakeholders must take into considerations when collecting data from any source.

Standards

Data standardization is important on a fundamental level that extends form data collection, processing, quality, terminology, design principles, the conduct of data collection, or RWE reporting [3,13,15,16]. Currently there is a large gap in data standardization between all institutions which reduces the quality of RWD compared to data originating from RCTs. Consequently, if the RWE cannot be utilized to ascertain the effectiveness of compared medical treatments, there will be less incentive to generate, gather and use RWD [13]. Nevertheless, there are some recent efforts by regulators, such as the FDA, to introduce data standards to increase the use of RWD and RWE in drug development and regulatory life cycle [17].

Coordination

There is a lack of coordination between different organizations on a national and international level regarding RWD translation into evidence. This is due to insufficient interactions between research groups, leading to inadequate evidence derivation from a limited research capacity [16]. The European Medicines Agency (EMA) has defined several challenges for existing registries to be utilized as evidence, one of which is the lack of harmonization and coordination between healthcare providers (HCPs) [18]. Additional research indicates that there is no coordination between healthcare organizations on an international level [9]. Hereby, this is one of the most significant barriers to the capture and use of RWD.

Data Quality

Various stakeholders are concerned when it comes to the quality of RWD. Research suggests that these concerns primarily originate from low quality patients' registries [10]. Therefore, RWD quality assurance processes that are more robust are needed to facilitate the derivation of evidence from RWD. Moreover, RWD from observational studies is considered of lower quality thus less important compared to RWD from RCT studies [4,9]. Incomplete data is another factor profoundly affecting the quality of RWD. Some RWD sources are vulnerable to misclassification or systematic omissions which further extends the gap in the data (e.g., claims data that could contain information whether a patient had a test or not, does not reveal any test result details) [13]. Even though gaps or missing data could be complemented, new issues, such as bias, a challenge that is presented in a later section, could be introduced. Also claims databases may lead to quality issues as they bear the risk of incomplete and inconsistent data. For example, claims databases by nature lack information on the severity of clinical diseases and patients' lifestyles [9].

Costs

The ISPOR real-world task force’s article on 'Evidence costs money' states that the most critical question for gathering and analyzing RWE is: 'who will pay for it?' [4]. One of the tools that were suggested to evaluate the costs and benefits of RWD is the Value-of-Information (VOI) analysis, which offers an approach to determine the type and amount of time collecting the data would take and whether collecting a specific kind of data will ultimately improve the expected benefit [4]. Pfizer, one of the top ten pharmaceutical companies, mentioned that the costs of RWD analysis could be quite high, for example, in prospective non-interventional studies [19]. Other researchers recommend real-time monitoring of patients as a way to reduce costs of evidence generation; for example, the use of wearable devices such as smartwatches can routinely collect RWD [13].

Technological view

The role of technology in the generation of RWD is closely tied as ‘smart’ devices become available to the populace but technological RWD challenges also hinder the use of RWD by commercial institutions in particular in the form of ‘cyber security’ and ‘complexity’.

Cyber security

Cybersecurity is an important measure that must be considered when collecting a vast amount of sensitive data. In the case of RWD, these measures are i) unauthorized access or alteration, ii) data theft, or iii) data encryption. These are underlining factors in cyber-attacks such as the ransomware 'WannaCry' cyberattack in 2017. Research has shown that more than 40% of healthcare organizations have experienced a cyber-attack involving the WannaCry crypto-worm [20]. Data breaches are a danger to data integrity, confidentiality, and availability and, as such, are also a threat to the adoption and advancement of RWE [15]. Furthermore, data abuses can be triggered both by external factors, such as criminal cyber-attacks and by internal factors, such as internal employees. Kaspersky, a vendor for security solutions, further explains this vulnerability in the study 'How Employees are Making Businesses Vulnerable from Within' [21]. The study demonstrates the dangers of irresponsible employees and shows that 52% of businesses admit that employees are their biggest weakness in IT security. Therefore, cybersecurity should become more robust and resilient to further advance the use of RWD. Attacks on HCPs' databases are constant and pose a threat to RWD integrity and availability which can harm the reputations of data sources impeding the use of RWD [15].

Complexity

Another technological challenge that is hindering the RWD advancement is the heterogeneity of data formats between different sources and countries. The FDA recognized the importance of having a common data model (CDM), along with standard representations like coding schemes and common terminologies, to maximize the utility of RWD [17]. Some organizations, like the Institute for Clinical and Economic Review (ICER), have already started requesting drug companies to provide RWD in a specific format with the aim to increase the integration of different data types [13]. Unifying data formats from observational databases can be useful in comparative research to answer questions related to the cause of an observed effect. An initiative called Observational Health Data Science and Informatics (OHDSI) has introduced a CDM called Observational Medical Outcomes Partnership (OMOP), which enables a separate database to be systematically analyzed [22].

People view

From the People perspective many new challenges also arise in the form of ‘data bias’, the necessity of ‘expertise’ in analyzing RWD and a lack public ‘awareness’ of the positive uses of RWD that hinder the use of RWD.

Bias

Credible evidence generated from RWD must be of high quality and free from any form of bias through the entire process of translating data into evidence. Bias was, with around 13%, one of the most recurring challenges mentioned in the academic literature (see table 1). Even if data quality is ascertained and privacy concerns are addressed, the selection bias is still regarded as the most known and challenging risk that is facing the adoption of RWD [4]. Earlier research revealed proof of reporting bias in several disease areas such as depression, bipolar disorder, and many others through denying study data of drug manufacturing and regulatory bodies [23]. As such, bias is an issue known in data analysis for decades. Further forms of bias in observational studies can manifest itself as selection bias, information bias, or reporting bias. In their framework, the FDA stated that randomization is the key to prevent bias when allocating interventions via making 'study groups balanced for risk factors for the targeted outcome' [17].

Expertise

To rely on evidence from RWD, one must first be able to understand the data and have the skills to analyze it and generate valuable information that can be used in a decision-making process. However, research shows that the skills needed to exploit the maximum benefits of RWD are not in 'abundant supply within the pharmaceutical industry' [15]. These skills must include domain knowledge, healthcare information technology, and methodological and technical expertise [15]. A further study, in which interviews were conducted with several healthcare stakeholders, confirmed that there is a lack of expertise in the RWD analysis domain, giving the example of ’innocent misinterpretation‘ in which analysts misunderstood relationships as causality [13]. It is indeed vital to mention that an excellent understanding of accessible databases supports the assumptions of the validity of these databases [3,13]. Research also referred to the lack of higher education programs on data analysis of RWD and the insufficient research capacity as a significant challenge that is facing RWD [16]. Nevertheless, several initiatives aim to combine expertise from information technology and healthcare to analyze different databases and facilitate a fruitful collaboration between other HCPs [3].

Awareness

An important area requiring collaboration for the adoption of RWD is raising the public awareness of health data and its benefits [24]. This naturally comes side by side with educating the public about privacy and data protection. Moreover, awareness among healthcare professionals is just as important. Research reveals that the lack of awareness among health data controllers can be detrimental to RWD access and use. An example of the French personal health record, the Dossier Medical Personnel, highlights this concern, 'by the end of 2013, the target number of health records was not reached due to a lack of political visibility of both patients and professionals' [3]. Nevertheless, several firms currently seem to promote easy access to electronic health data and registries around the globe. Thus, the awareness of RWD is increasing along with the number of research groups specializing in analyzing it [25].

Conclusion

In today's digital world the unprecedented access to vast amounts of RWD has led to an irrevocable interest by the life science industry to explore new possibilities in providing clinical evidence for the development and approval of drugs, treatments, and therapies outside the context of 'traditional' RCTs. However, our study shows that numerous different challenges must be considered when using RWD. The term RWD must be placed in the context of the application field and the associated industry. In particular, the evidence associated with RWD − RWE − needs to be considered and aligned with the related industry. Further, there are currently no established and globally accepted instruments and standards. Concerning the use of RWD in the health and life science industry, it is also essential to consider the EEG (Efficacy Effectiveness Gap) and to develop solutions or controls for it. An important finding is that the regulatory landscape must be carefully assessed before utilizing RWD. As there are constant changes and adjustments, both nationally and internationally, regulatory requirements need to be systematically reviewed, and their implementation monitored. While for the fulfillment of the regulatory requirements, the monitoring of potential associated risks is vital, other areas that deserve special attention could be identified. We categorized them with a focus on organizational, technological, and people-oriented challenges; for each of the categories, the outlined units of analysis stand for future research tasks. The prototypical RWD Challenges Radar (Figure 2) we have developed is a first attempt to visualize the relevant aspects for decision-makers and other stakeholders, as seen from an organizational, technology and people perspective. Further research activities that we pursue relate to automatization of the prototypical RWD Challenges Radar into a RWD Challenges Cockpit. This dashboard type solution automatically captures, classifies, assesses, and visualizes the quality of the RWD enabling the user to be fully aware of the challenges and risks related to the data, whilst taking full advantage of the RWD potential.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The research for this work was financially supported by the foundation ´Stiftung FHNW` (www.stiftungfhnw.ch).

Author Contributions

F.G., P.M.A, B.S., E.M., L.B., and A.H. made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. F.G., P.M.A, B.S., E.M., L.B., and A.H. drafted this work or revised it critically for important intellectual content. F.G., P.M.A, B.S., E.M., L.B., and A.H. gave final approval of the version to be published. F.G., P.M.A, B.S., E.M., L.B., and A.H. agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure Legends

Fig. 1. Risk fields in the Context of RWD.

Fig. 2. RWD Challenges Radar.