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REVIEW ARTICLE

Real-World Evidence: A Primer

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Abstract
Real-world evidence (RWE) is clinical evidence on a medical product's safety and efficacy that is generated using real-world data (RWD) resulting from routine healthcare delivery. There are several sources of RWD, including electronic health records (EHRs), registries, claims/billing data, and patient-generated data, as well as those from mobile health applications and wearable devices. Real-world data from these sources can be collected and analysed through different study designs such as prospective and retrospective cohort studies, case–control studies, and pragmatic clinical trials. Real-world evidence in the form of post-marketing surveillance has been extensively used to generate pharmacovigilance data. Of late, it has been realised that, apart from safety, RWE has additional applications in different stages of the drug approval cycle, and can be used to optimize the design of randomised controlled trials (RCTs). There has been an increasing awareness and acceptance of RWE from different stakeholders, including physicians, pharmaceutical companies, payers, regulators, and patients. Several regulatory authorities have also created frameworks and guidelines for efficient harnessing of RWE while acknowledging several challenges in RWD collection and analysis. The purpose of this review is to offer an outline of the current information on RWE, its advantages and disadvantages, as well as the associated challenges and ways to overcome them, while also throwing some light on the future of RWE.

Key Points

Real-world evidence (RWE) is medical evidence generated during routine patient care.

There are multiple sources of RWE, including patient health records, pharmacy claims, registries, and even social media.

Realising the importance of RWE in health, different regulatory bodies have come up with guidelines for generating RWE.

1 Introduction

Data collection is a routine procedure during drug development. However, structured data collection from the real-world usage of the drug after marketing approval is largely restricted to regulatory safety data collection in the form of pharmacovigilance [1, 2]. Of late, it has been realised that the collection of efficacy data (in addition to safety data) in the real-world setting can generate crucial insights that can improve healthcare decision making. Such data are called real-world data (RWD) [3].

Real-world data have been in use in research for post-marketing surveillance, as well as to monitor disease progression through natural disease history studies [4]. Moreover, the rapid increase in the use of technology, such as electronic systems, biosensors, mobile and wearable devices in healthcare, has led to the accumulation of large amounts of RWD. These data can help enhance the study designing and conduct in order to address unmet clinical needs [3]. However, RWD is often vast and unstructured compared to data collected during randomised controlled trials (RCTs) [5]. As a consequence, collection, storage, and analysis of such amounts of data can often be challenging. Integration of advanced healthcare technology [such as connected devices,

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analytical methods, artificial intelligence (AI) tools] can help address the data-related challenges to some extent, while also enabling the analysis of RWD to generate real world evidence (RWE) [6]. Researchers are increasingly realising the importance of RWE to generate valuable insights into the efficacy, safety, and the pattern of usage of drugs and medical products [7]. That said, it has to be acknowledged that although RWE can generate additional information, evidence from RCTs is still considered the gold standard in research.

The interest in RWD and RWE is expanding among all relevant stakeholders across the globe, and with significant improvements in technology, the collection and analysis of RWD has become easier. However, using RWD in research can also raise some concerns, including data privacy and confidentiality, poor data quality due to unstructured data and resulting bias, and confounding, among others [8–10].

The purpose of this article is to bring together the existing knowledge on RWE, its potential applications in different areas, concerns and challenges, and future.

2 What is Real World Evidence?

Broadly, all data collected routinely (that is, not as a part of RCTs) on patient health from different sources, are called RWD. The US FDA defines RWD as "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as electronic health records (EHRs), claims and billing activities, product and disease registries, patient-generated data from in-home settings, and data from other sources, such as mobile devices" [3]. The analysis of RWD generates real-world evidence (RWE), and as per the USFDA, RWE is "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD" [3].

Another related term, real-world insights (RWI), refers to the insights generated by leveraging RWE, which is used by different stakeholders from the healthcare industry to inform internal research and business-related decisions. Real-world insight facilitates the assessment of the commercial viability of a study, identification of relevant patient subpopulations, understanding of time-based trends, and addressing better research questions [11].

Real-world evidence contrasts strongly with evidence generated from RCTs. In fact, RWE provides answers to many of the well-known disadvantages of RCTs. For instance, RCTs are conducted in selective populations in tightly controlled settings using strict inclusion and exclusion criteria to accurately quantify treatment effect. However, because of this exclusion, the RCT findings are from 'ideal' settings [12] and when considering the diverse population and situations that are seen in the real world, it is challenging to apply RCT findings of a selected population to the broader population [5]. Additionally, RCTs have a fixed design and follow a fixed treatment pattern of a homogenous study sample.

Generation of RWE from RWD can solve many of the above problems. Below are some advantages of RWE: [5, 13].

- No strict eligibility criteria, and thus fewer chances of no exclusions based on concomitant medications and comorbidities.
- Quicker, cost-effective: less time required for patient recruitment/enrolment and completing the research.
- Possibility of undertaking research that cannot be done with RCT, such as that on high-risk groups like pregnant women and children.
- Ability to track real-world patient behaviour.
- Rapid and more straightforward retrieval of and access to data.
- Large sample size facilitates sub-population analyses and less common effects.
- Large sample size facilitates better generalisability and modelling.

Thus, while RCTs still remain the gold standard for assessing safety and efficacy of drugs and medical products and the evidence from RCT represents the outcome of a 'standardised' intervention used in an 'idealised' setting, RWE represents the outcome of 'variable' treatment patterns in the 'real world'. Therefore, RWE complements the RCT findings and can contribute to enhanced evidence generation. Table 1 provides a concise comparison of RCT evidence and RWE.

Thus, the evidence generated through RCTs and RWE studies provide a mutually complementary set of information, which seeks to fill in the missing gaps in the complete knowledge about the intervention [14, 15].

3 How is RWD Accumulated?

Generation of RWE depends on the fundamental principle of collecting data under real-world clinical settings from diverse sources, such as healthcare databases, registries, claims databases, health-related data from mobile devices, social media, and patient platforms [13].

3.1 Healthcare Databases

Healthcare databases are systems used by healthcare practitioners to record routine clinical and laboratory data during their day-to-day practice [16]. Healthcare databases, including EHRs, are probably the most significant sources of RWD

Table 1 Comparison of evidence generated from randomised controlled trials (RCT) and real-world evidence [5, 7]

	RCT data	Real-world data
Purpose	Efficacy	Effectiveness
Focus	Investigator-centric	Patient-centric
Setting	Experimental	Real-world
Patients	Included as per strict criteria	No strict criteria
Concomitant medications and comorbid illnesses	Only those defined in the protocol allowed	As in real practice
Attending physician	Investigator/designated representative	Many practitioners as chosen by the patient
Comparator	Placebo/standard practice, as per the protocol	As per patient profile/real-world usage of available drugs in the market, at the physician's discretion
Patient monitoring	Continuous	Changeable
Treatment	Fixed pattern	Variable, at physician's discretion
Follow-up	Designed, as per protocol	Not planned; as per usual practice

[12, 17]. Healthcare databases broadly represent the actual clinical practice, and their analysis can enable quick and systematic evidence synthesis about efficacy and safety of drugs, quality of life and other patient-reported outcomes, and the natural history of disease [12]. Data from EHRs can also help address various safety issues, especially long-term safety data, often not detected over a limited duration of III- and IV-Phase studies [12].

The USFDA's Sentinel Initiative is a system that links accumulated healthcare data from several databases in the USA for active real-time monitoring of the safety of medical products [17, 18]. The European Health Data and Evidence Network (EHDEN) project, a part of the European Union's (EU) Innovative Medicines Initiative (IMI), aims to build a merged network of databases, which will be standardised to a common data model. The purpose of EHDEN is also to facilitate the assessment of the real-world health outcomes across various healthcare systems, as well as to sustain open science partnerships in Europe [19].

3.2 Registries

Registries are organised systems that collect, analyse, and publish observational data on a patient population with specific characteristics in a prospective manner [16]. Registry data are usually collected in the form of cohort studies with a predetermined clinical or public health-related purpose. Registries have evolved from paper-based patient records to electronic databases and often contain large amounts of data, encompassing a variety of information, such as clinical information or biological samples stored in bio-banks [16]. Registries usually comprise standardised, continuous, prospective data collection in a real-world setting, where treatment and care management is at the discretion of patients and healthcare providers rather than a study protocol. Registries enrol a much larger and more diverse patient sample than an RCT, and can also be a source of recruitment of patients for RCTs [20].

Registries can be either disease (or condition) registries, focusing on populations with a particular disease or diseases, or product registries, focusing on populations using specific products, i.e., treatments or devices. Registries can be hospital based (that collect information from patients with a specific disease diagnosed and treated at a single hospital or a group of hospitals), or population-based (that collect information from all people living within a specific geographic region) [21]. For example, the European Cystic Fibrosis Society (ECFS) Registry collects demographic and clinical data from cystic fibrosis (CF) patients in Europe. These data are further used to monitor and analyse CF aspects and treatment in EU countries, improve care standards, support CF-related epidemiological research, and expedite public health policy planning [22]. Another example is the national registry of patients on biologic therapy by the British Society for Rheumatology [23]. The National Cancer Registration and Analysis Service (NCRAS) is a population-based registry for cancer in England, and is a part of Public Health England (PHE) [24]. The American Academy of Orthopaedic Surgeons (AAOS) registry programme is a hospital-based registry programme, aimed at improving orthopaedic care through collection and analysis of patient data to achieve improved outcomes [25].

3.3 Claims Databases

Claims databases include billing and other healthcare administrative data entered by pharmacies, or health insurers. Various stakeholders like health researchers, insurance companies, and health authorities use information from these databases to assess the long-term impact and effectiveness of health interventions in the 'real world'. Generally, claims databases consist of data on inpatient, outpatient,

emergency room, pharmacy services, and include data on the services received by the patient during clinical visits, surgeries, diagnostics, laboratory tests, hospitalisation and length of stay, and pharmacy filing [16].

Most of these databases are based in the USA, where Medicare and Medicaid are the prime sources of non-commercial health claims data [26, 27]. Additionally, the Sentinel Initiative by the USFDA uses claims data for safety assessment [17]. Another example is using claims data for research purposes to understand service use, drug utilisation, and drug effects in real-world populations. The Ontario Pharmacy Evidence Network (OPEN) is a database used for research on service use, i.e., data on optimising the knowledge and skills of pharmacy professionals to integrate within the more extensive healthcare system, thereby improving medication management in all healthcare domains [28].

3.4 Other Sources of RWD

Recently, social media are receiving more attention as a source of patient data. There are websites and applications that allow users to network with each other to create and share content. Social media platforms can be helpful by providing patient perspectives on various health topics, such as adverse events, reasons for treatment changes and non-adherence, and quality of life [16]. Patients usually visit social media to find information on their health conditions, connect with other patients, share experiences, and find social support. Assessment of the vast amount of content created and shared by patients on social media can facilitate research. These data are often considered a source of 'big data' [16]. Examples of social media include Facebook and Twitter, other forums, online message boards, and online patient platforms, such as PatientsLikeMe [29].

Patient-powered research networks (PPRNs) are another source of RWD. These are online platforms set up and managed by patients and patient partners, such as patient advocacy/support groups, patient-run organisations, and other stakeholders, including carers/guardians, clinicians, and researchers. Patient-powered research networks typically collect and organise data focused on either a specific disease or multiple disease areas, emphasising the comparative effectiveness of research and the use of patient-centred outcomes [16]. The PCORnet, set up by the Patient-Centred Outcomes Research Institute (PCORI) in the USA, has supported approximately 30 PPRNs across multiple disease areas [30]. PatientsLikeMe can also be categorised as a PPRN because it fosters data-sharing partnerships to contribute health data to improve products, services, and patient care [29]. Furthermore, the Accelerated Cure Project shares information (such as bio-samples and patient data) with researchers to expedite research on multiple sclerosis [31].

4 How is RWE Generated from RWD?

Different types of experimental and observational study designs can help generate RWE from RWD. The different types of RWE studies are non-interventional (i.e., observational) studies, registry analysis, claims database analysis, patient surveys, and abstraction and analysis [32, 33]. Observational studies can be in the form of cohort studies, cross-sectional studies, or case–control studies [20]. The data collection for RWE studies can be done prospectively (wherein fresh data are collected from RWD sources) or retrospectively (wherein secondary data, i.e., already collected data from RWD sources are analysed) [20].

One common factor in all RWE studies is that the treatment is prescribed as per marketing authorisation, physician discretion, and national or regional treatment guidelines, and not as per a pre-specified protocol as in the case of RCTs [20]. Often, some prospective, multicentre, observational studies are conducted as part of routine clinical practice, and such trials are called pragmatic clinical trials [33].

4.1 Cohort Studies

Cohort studies aim to assess the incidence, aetiology and risk factors, natural history of disease, disease prognosis, and treatment outcomes. They can be retrospective, involving a post hoc analysis of accumulated data [20]. Alternatively, they can be prospective, as in the XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation) study, which was an international, multicentre, prospective, non-interventional, cohort study that supported RCT findings of lower incidences of major bleeding and stroke amongst patients with atrial fibrillation who received rivaroxaban for stroke prevention in real-world settings [34].

4.2 Cross-Sectional Studies

Cross-sectional studies aim to assess disease prevalence and outcomes, wherein they consider a single group of patients at a time with concurrently studied treatment and outcomes. These are quick, and are most valuable when studying disease prevalence [20]. This study design has been used to gain insights into the prevalence of underdosing or achieving appropriate dose selection among real-world populations [35].

4.3 Case–Control Studies

Case–control studies are generally conducted in a retrospective manner, meaning they first identify the cases, i.e., persons with a disease, and then retrospectively analyse the associated causal factors [36]. They aim to assess a single

outcome and causality, and are valuable for rare conditions or those with a long gap between exposure and disease occurrence. These are also useful in simultaneous assessment of multiple variables and can identify potential outcome predictors case efficiently [20]. For example, a 2022 case–control study concluded that neuromuscular electrical stimulation (NMES) did not result in a significant improvement in muscle strength, functional capacity, daily activities, or length of stay in the hospital among patients who received live donor liver transplant (LDLT). The control group in this study were LDLT recipients from the same centre who did not undergo NMES [37].

4.4 Registry Analysis

Registry analyses provide information on specific patient populations, and are usually retrospective in design on a prospectively collected data [38]. For example, a recently reported audit of Taiwan cancer registry over a period of 10 years provided insights into the epidemiology and trends of acute myeloid leukaemia (AML). This was especially valuable considering that literature on epidemiology of AML was limited in Asia [39].

4.5 Claims and EHR Database Studies

Claims database studies are typically retrospective, longitudinal, and cross-sectional analyses of data from healthcare and administrative databases, such as treatment and clinical data, diagnosis codes, and hospital admission and discharge information. These studies usually aim to analyse healthcare resource utilisation (HCRU) and costs. Electronic health records database studies are retrospective, observational analyses of data from medical records and charts that aimed to assess clinical treatments and outcomes [20]. For example, a retrospective cohort study using data from over 25,000 Medicare beneficiaries from the United States Renal Data System with dialysis-dependent end-stage kidney disease (ESKD) and concomitant atrial fibrillation (AF) concluded that apixaban is associated with a lower bleeding risk compared to warfarin in this patient subgroup. This provided valuable insights into the safety of apixaban because its use was not evaluated through RCTs in this patient population [40].

4.6 Pragmatic Clinical Trials

Pragmatic clinical trials are typically used to inform a clinical or policy decision as they provide evidence for adoption of the drug/medical product into real-world clinical practice [33]. Pragmatic trials can be prospective or retrospective in nature and can provide results that can be generalisable in the real-world settings [41]. For instance, a recent multicentre pragmatic trial reported that treatment with erythropoietin (EPO) did not impact the need of transfusion, renal recovery, or mortality among anaemic acute kidney disease patients. In this trial, after patients were randomised to EPO and control groups, the investigators were allowed to manage the patients based on their usual real-world practice [42].

5 Uses of RWE

Real-world evidence studies have been used to explore different aspects in health and disease, such as epidemiology, disease burden, treatment patterns, safety, treatment outcomes, long-term outcomes, and patient-reported outcomes such as satisfaction, quality of life, medication adherence, and patient experience. They can also provide valuable insights into the economic aspects of a medical product. Implementing RWE in early stages of drug development can result in a shorter duration of trials and cost savings. It can also strongly complement the evidence gathered from RCTs, thus filling gaps in existing clinical knowledge [43].

It has been well known that RCTs by themselves cannot give a complete picture of safety of any medical product, and adverse effects that are not reported in RCTs are often encountered in routine clinical practice [44]. This is the rationale behind regulatory authorities mandating the manufacturer to collect safety-related information after marketing approval in the form of Phase IV or post-marketing surveillance (PMS) studies, which are in fact RWE studies. Moreover, data from EHRs and patient-generated sources (e.g., social media platforms or PPRNs) are more challenging to analyse than the structured data. Yet, they are more expressive in that they can potentially give away more unfiltered information about unexpected side effects of medical products [8]. For instance, data from social media sources were used in pharmacovigilance in a 2019 study on the identification of cutaneous adverse drug reactions to cancer drugs about seven months before they were published in the literature. This study also reported new side effects that were not previously reported [45].

Of late, RWE is increasingly being utilised to support clinical and regulatory decisions including approval of medical products [46]. Traditionally, the regulatory decisions regarding new drug approvals have always been based on RCT findings. Of late, there are numerous examples where RWE was leveraged to make regulatory decisions surrounding new drug approvals, supplementary approvals, and to support label revisions. For example, in 2019, palbociclib, a CDK4/6 inhibitor, approved only for treating women with ER+/HER2− breast cancer, was approved in men based on EHR outcomes data related to its off-label use among men [47]. The USFDA has developed accelerated regulatory

pathways to aid the production of biologics and biosimilars, based on several RWE studies showing their efficacy and safety, along with non-inferiority to the pharmaceutical comparators [8]. In March 2017, the USFDA used RWE data in the form of historical control arm to grant marketing approval of avelumab for treating Merkel cell carcinoma, marking the first instance of use of RWE for original drug approvals [48, 49]. Table 2 provides a list of recent use of RWE in different stages of drug approval cycle.

Real-world evidence can also help in the better conduct of RCTs. For example, when planning RCTs for rare diseases, randomising patients into control arm can be complex. Moreover, these studies can be expensive, have difficulty enrolling patients, and take longer to finish, thus extending pre-specified regulatory timelines. In such cases, the alternate approach is implementing a single-arm experimental or synthetic control design, i.e., taking historical information or data from EHRs and other RWD sources in the control arm. Although this study design is controversial owing to the issues related to unpredictable outcomes, it has been implemented in cases with a well-understood course of the disease and predictably rapid and significant treatment effects [8, 50, 51]. Payers have also used synthetic controls to support coverage decisions. For instance, findings from two single-arm Phase II studies led to the approval of alectinib, an advanced anaplastic lymphoma kinase (ALK) inhibitor for treating ALK+ non–small cell lung cancer (NSCLC) in the USA and Europe [52]. However, European payers further requested additional evidence on the drug's comparative efficacy with ceritinib. As a result, the sponsor, recruited a synthetic control group of 77 patients to fulfil the coverage requirements, which was followed up with an RCT that confirmed similar findings between propensity-matched synthetic control and the ceritinib group [8, 52, 53].

Evidence from literature also shows that RWE is increasingly being used to inform clinical study designs and optimisation [8, 54]. For instance, RWD, especially EHR data, can facilitate the identification of unmet clinical needs, thus aiding the recruitment of clinical cohorts that would most likely benefit from novel treatments. Real-world evidence can also refine study inclusion criteria and identify potential study sites, thus helping with patient enrolment and retention. Real-world evidence can help researchers identify the most relevant variables, thereby saving costs and time in data collection [8]. Real-world data, in the form of registries, can also be used to quickly source patients to conduct RCTs, a concept known as registry-based RCTs. This is especially valuable for rare diseases, where finding suitable patients can be challenging [55].

6 Challenges with RWE Generation and Overcoming Challenges

The most commonly reported challenge in using RWE is missing data and lack of randomisation, and the resulting bias in patient selection. The inherent principle of using RWE is based on the analysis of routinely collected patient data, which, if not managed appropriately, can lead to bias [8]. Also, inconsistent data collection can lead to missing data, which can further restrict data analysis and also lead to bias, impacting negatively on analytical outcomes.

Table 2 Recent examples of the use of real-world evidence in drug approvals

Name of the drug/biologic/device	Source of RWE	Agency involved in regulatory decision making	Month/year	Regulatory action supported
Avelumab	EHR data as historical control for efficacy	USFDA	March 2017	Original marketing application approval
Pembrolizumab	Expanded access study data to support clinical efficacy	USFDA	May 2017	Supplementary indication approval
Lutetium Lu 177 dotatate	Expanded access study data to support clinical efficacy, safety	USFDA	January 2018	Original marketing application approval
Blinatumomab	Retrospective data from clinical sites as historical control for efficacy	USFDA	March 2018	Supplementary indication approval
Palbociclib	EHR data, claims data, post-marketing safety reports to support clinical efficacy, safety in new patient population	USFDA	April 2019	Supplemental indication approval
Tacrolimus	Retrospective observational study of data from the US SRTR	EMAF	July 2021	Supplemental NDA approval

EHRs electronic health records, *EMA* European Medicines Agency, *NDAs* new drug applications, *RWE* real-world evidence, *SRTR* Scientific Registry of Transplant Recipients, *USFDA* US Food and Drug Administration

Techniques such as data imputation can predict missing values by close estimation methods based on data context. However, certain imputation methods can, in fact, lead to biased assumptions [56]. Moreover, missing data and lack of quality control can lower the statistical validity of study findings and impact how the research question is addressed [9, 57]. Selection bias can also occur due to different prescriptions or dosing to different patients as per disease severity and other characteristics [58].

Real-world evidence studies can also suffer from other types of bias, such as information bias (e.g., ad hoc collection of unstandardised data), recall bias (i.e., data resulting from a selective recollection of events by patients/caregivers), and detection bias (i.e., likelihood of an event being captured in one treatment group than in another) [58]. Carefully designing the cohorts and limiting the representativeness to include just enough patients from the target population would help solve the issues of missing data. Bias can be avoided or managed with biostatistical analytical methods, including estimation and correction [8].

Accessing the collected data can also be challenging. Especially in countries like the USA, where there is increasing awareness about the protection of digital privacy and confidentiality of data, accessing patient data to gain crucial insights can be difficult owing to the risk of data theft and manipulation. Although RWD collection from sources complying with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) can address privacy and confidentiality concerns to some extent [59], several other solutions have been explored, such as tokenisation and other de-identification methods, synthetic cohorts and federated data networks that can avoid the actual data transfer, and so on, to improve data access without compromising confidentiality [11].

Moreover, data repurposing, i.e., using data that were collected for one purpose for another purpose, can affect the research outcomes and lead to measurement biases. Analytical methods of recruiting mixed-effect or errors-in-variables models can be recruited to solve this problem. With the possibility of the same patient's health data being captured in multiple RWD sources (such as EHRs, claims data, pharmacy data, social media, etc.), there is a genuine risk of data duplication [8]. Data tokenisation, i.e., using unique patient tokens to link different data sources, is gaining increasing importance in addressing this issue, which would help in a thorough understanding of care delivery. Several digital health companies are working to create patient 'tokens' that would identify them across varied RWD sources, thus avoiding their reidentification/data recall [11].

Several other challenges with RWE include source and format discrepancy among different regions, differences in data terminology and exchange, dataset building methods, and overall data quality. These challenges continue to limit the applicability of RWE despite its advantages and noteworthy data capabilities.

To address these challenges and facilitate RWE uptake, regulatory authorities, such as the USFDA and the European Medicines Agency (EMA) are now in the process of laying down the standards and processes for generating RWE for its greater use [3]. The USFDA has released draft guidance outlining guidelines for sponsors to follow during drug approval submissions with RWD [48]. Similarly, the Professional Society for Health Economics and Outcomes Research (ISPOR), in association with the International Society for Pharmacoepidemiology, the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council, have launched the Real-World Evidence Transparency Initiative [13]. This initiative aims to promote health economics and outcomes research (HEOR) excellence, enhancing informed decision making concerning global healthcare delivery. Furthermore, ISPOR believes that this initiative will enhance and promote the culture of transparency for analysis and hypotheses reporting for assessing RWE studies [60, 61]. This initiative launched the RWE Registry in October 2021 to further improve transparency and reliability of RWE studies [60, 62]. The RWE registry aims to provide a platform to the researchers to prospectively register their study designs before initiating data collection and to implement open, integrated workflows to boost collaboration and facilitate the transparency needed to validate study results [62].

7 Why RWE is Important: Stakeholders Perspectives

7.1 Pharmaceutical and Medical Device Companies

Evidence from literature shows increased uptake of RWE by pharmaceutical and medical device companies in the last few years. Real-world evidence has been used throughout the product lifecycle to inform trial designs, improve clinical guidelines and disease understanding, facilitate financial discussions and reimbursement decisions, support regulatory decisions, and promote further uses for products already in the market [63, 64]. In many pharmaceutical companies, the RWE capabilities are primarily centralised and revolve around data acquisition and related standards and procedures. Many companies have constantly optimised RWE to gain insights into the impact of certain drugs in a target population. For instance, findings of an RWE study in 2020 reported substantially higher patient adherence and longer persistence with dulaglutide injection when compared with weekly semaglutide or exenatide injections in patients with type 2 diabetes [65].

7.2 Healthcare Providers

Physicians rely on EHRs extensively for physician-led research, since massive patient data becomes easily accessible. The hospital and healthcare system partnerships in the USA have led to centralised prescribing control. The National Health Service (NHS) is already encouraging value-based pricing for specific treatments in the UK [64]. For instance, an RWE study enabled the NHS to negotiate with the manufacturers of simeprevir to rebate the cost if patients with hepatitis C receiving the drug are not cured after 12 weeks of treatment [66]. Moreover, in many instances, prescribers resort to off-label uses of products as their daily patient population visiting their offices does not fit into a particular study inclusion criteria. Advanced analytical methods leverage RWE to provide customised supporting tools for patients and physicians to make informed shared decisions. For example, the Michigan Bariatric Surgery Collaborative uses a tool based on individual patient features to predict their response to different types of bariatric surgery [67].

7.3 Patients

Patients today are more aware of their health than ever before and actively participate in their health and fitness. As a result, they are using social media and many other platforms, such as patient support groups and networks, to log their health data and look for solutions. New promotional claims, which are a result of studies that have used RWE gathered from social media, have been accepted by organisations such as the Proprietary Association of Great Britain (PAGB) and the Medicines and Healthcare products Regulatory Agency (MHRA). In the UK, such RWE was successfully used to strengthen product claims for two products, viz. Infacol and Sudocrem [68]. Moreover, tokenisation and federated data networks allow patients to share and monetise their health data without concerns of data privacy and loss of data ownership [69].

7.4 Payers

Payers are leveraging claims data to enhance aspects of healthcare affordability. Payers in the USA are increasingly implementing outcomes-based contracts with prescribers and healthcare providers. In the UK, the National Institute for Health and Care Excellence (NICE) uses health technology assessments (HTA), which use RWE, to compare patterns of treatment and inform pricing and reimbursement decisions [64]. For instance, the UK's Systemic Anti-Cancer Therapy (SACT), established in 2011, documents chemotherapy data across the country, which is then used to support treatment choices and obtain essential insights on treatment patterns and outcomes [70].

7.5 Regulators

Regulators have been using RWE to monitor the safety of marketed products through traditional pharmacovigilance methods, such as periodic safety update reports (PSURs) [64]. Today, they are also leveraging the new digital systems, such as the Sentinel Initiative, a surveillance system by the USFDA to monitor post-marketing safety outcomes [17]. There is a growing need among regulators to make RWE a central part of decision-making activities. As a result, many regulators, such as the USFDA, are trying to develop pathways to integrate data collected from various sources into a cohesive safety monitoring system. Moreover, a National Institute of Health (NIH) Common Fund is in place to create infrastructure for strengthening operational knowledge and capabilities for pragmatic research. This fund will facilitate the dissemination of integrated data from various sources to identify patient populations of interest and advance study designs [64, 71].

8 Regulatory Aspects of RWE

Regulatory bodies have recognised the importance of RWE and are now developing guidelines to integrate it throughout the product lifecycle and regulatory approvals [9].

The 21st Century Cures Act in the USA, passed in December 2016, has promoted partnerships between public and private health entities. This act aims to collect patient data and further enhance disease understanding, support patient-centred drug development, and reform the clinical study designs and their analyses [64]. Moreover, the USFDA RWE framework (2018) outlines recommendations for submitting RWD and RWE for regulatory approval and is proving to be highly beneficial for regulatory submissions for investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) [48, 72]. Subsequent to the issue of these guidelines, the USFDA approved 85% of (116 of 136) NDA and BLA submissions that were backed by RWE, in the period between January 2019 and June 2021 [73, 74]. In October 2022, the USFDA also announced an Advancing Real-World Evidence programme, to improve the quality and appropriateness of RWE-based approaches to support new intended labelling claims, such as approval of new indications of existing products in the market or to fulfil post-approval study requirements [75]. This programme is aimed at giving an opportunity to the selected sponsors to meet with the FDA staff before study initiation or protocol development to

discuss the possible RWE benefits and uses in a particular study [75].

In Europe, the EMA has launched the vision statement for 2025 to facilitate using RWE for regulatory decision making and to improve and monitor medicines [76]. This statement by the European regulators explains how they will deliver this vision by creating the "Data Analytics and Real-World Interrogation Network (DARWIN EU)" [76, 77]. This network is expected to enable access to and analysis of the healthcare data from across all the countries in the EU. It was launched in February 2022 in pilot mode and is expected to be completely functional by 2024 [78]. The researchers believe that RWE and RCTs should be considered complementary, each having advantages and disadvantages, and their relative importance is based on the regulatory question [76, 77].

In the UK, the NICE launched an RWE framework in June 2022 for optimising RWD to fill the knowledge gaps, thus making innovative care accessible to patients [79].

In Canada, Health Canada, together with the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute of Excellence in Health and Social Services launched an initiative in 2018 for utilising RWE during HTAs and price negotiations at a national level [80, 81].

Additionally, the International Council of Harmonization (ICH) has introduced a "structured template for planning and reporting on RWE study implementation" (STaRT-RWE) for safety and effectiveness reporting in RWE studies. This template facilitates the designing and conduct of reliable RWE studies, setting standards for transparency, improving specificity, enabling data availability, and accelerating reproducibility and validity assessment. It is aimed to be used in the effectiveness and safety studies of medical products. This template is applicable for several study designs, data sources, reporting guidelines, and methods for bias assessment [82].

9 RWE in Low- and Middle-Income Countries

In high-income countries (HIC) the uses of RWD have evolved to be straightforward, but they can be quite complicated in resource-limited, low- and middle-income countries (LMICs). In HICs, RWD and RWE use is more prevalent, which is not the case for LMICs. The challenges include different standards of care, diverse populations, societal structures, and adherence issues, among others. Moreover, missing or lack of data or data availability and its accessibility are other major concerns. The difference in availability of RWD between HICs and LMICs can be attributed to the lack of proper infrastructure in LMICs. Poor frameworks for collecting data or conducting routine clinical care, overburdened healthcare staff and systems, and inadequate regulatory systems are some prominent challenges in LMICs that may contribute to the lack of availability or poor uptake of RWD/RWE phenomenon. Many LMICs simply lack the sources to collect RWD, which include EHRs, claims databases, health surveys, patient registries, health applications and wearables, data from social media, etc. [83].

However, the trend is rapidly changing with improving healthcare scenario in LMICs, thanks to factors such as regulations surrounding in-house pharmaceutical manufacturing and marketing of drugs/products, low-cost systems for electronic health recording, changing demographics and disease epidemiology, and increasing importance given to the regulatory compliances, as well as to resolving complexities surrounding RWE uptake [84].

10 Recent Developments and the Way Ahead

Despite its advantages and increasing acceptance by various stakeholders, the biggest challenge of RWE is the diversity and uneven quality of the RWD sources, which make data organisation and incorporation critically important.

Techniques of artificial intelligence (AI), such as natural language processing (NLP), semi-automated biomedical curation, machine learning (ML), and deep learning, can be incorporated to analyse medically related free text (i.e., unstructured data) from RWD sources including EHRs, social media platforms, and other sources [8]. Furthermore, advanced analytics are now in place to channel these unstructured data. One study even reported successful prediction of multiple medical events when ML tools were applied to EHR data from various centres [85]. Techniques of ML can also be instrumental in analysing data from wearables to track abnormalities in health parameters, such as heart rate and even seizures among patients with poor disease prognosis [86]. Moreover, innovative algorithms in RWD have been used to improve study designs that would increase the generalisability of findings. For instance, the Trial Pathfinder computational framework has been used in the analysis of EHR data of 61,000 NSCLC patients, which found the common trial eligibility criteria that often led to the exclusion of patients most likely to benefit from the study treatment [87].

COVID-19 posed unprecedented challenges globally, especially to the healthcare industry. Consequently, certain systems and applications came into existence to get health products into the market through emergency use authorisations or narrow-use approvals. USFDA has launched one such programme to leverage RWE for overall medical countermeasures (MCMs) related to COVID-19, as well as to better propagate COVID-19 precautions, therapies, and diagnostic tools [88].

Concerns regarding the utilisation of non-interventional, non-randomised RWE for assessing the effectiveness of the drugs gave rise to RCT DUPLICATE (Randomised Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) initiative [89]. This initiative applies a structured method to design RWE studies that would help emulating RCTs and comparison of results. The aim of this initiative is to strengthen the validity of future RWD analyses that may be performed in the absence of evidence from RCTs [89, 90].

In the future, RWE will continue to impact healthcare decisions across multiple systems, thus improving overall patient care. However, broadening the use of RWE would need actions taken by numerous stakeholders on different factors. Drug and device manufacturers will need to understand the RWE capabilities and analytics and its dispersal across several functions, such as medical affairs, R&D, commercialisation, HEOR. This means that these stakeholders will also need to implement the risk management processes, such as an integrated ecosystem that collates data across regions to pool all the insights and outcomes. Researchers and regulators can also encourage partnerships between data analytics experts and companies to build rapid, low-cost RWE capabilities and monitor their public health benefits, which can then facilitate higher-quality RWD databases and augmented access to them. All of these steps can help create the culture for RWE innovation [64].

11 Conclusion

The significance of RWE in the healthcare industry is increasingly becoming well known. All stakeholders are looking at novel methods to harness the potential of RWE to improve patient access of efficacious and safe medicines that are also cost effective. Technological advancements will facilitate RWE uptake, although with certain challenges. The awareness and acceptability of RWE is increasing among all stakeholders, and strategic communications and partnerships between these stakeholders can result in efficient gathering of RWD, and production of utilisable and generalisable RWE, thereby ensuring quicker and cost-effective patient access to medications.

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