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(REVIEW ARTICLE)

Real world evidence studies: Perspective on study design and regulatory framework for RWE

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Abstract

There is a growing need for broader information on Real-World Effectiveness and safety of any new intervention, service or protocol vs data limited by standardized and strictly controlled environment like in a RCT. RWE studies gives the freedom for analysis based on a varied and diverse database. As Real-World Studies gain higher acceptance, it is important to understand the types of RWE studies and design that can be used. Data from real-world patient experience has the potential to improve the quality and delivery of medical care, impact overall costs and outcomes. This review helps understand study designs, issues, and its implications in improving medical services. Though the RWE is challenged by diversity of information, large data sets of uncertain quality, and methodological rigor, however if utilized properly has potential to shape policies, protocols and develop programs to implement best practices.RWE has many issues including Legal, technological, data privacy, transparency, and standardization. These challenges can be and necessarily need to be addressed while planning the RWE which would then vastly enhance the acceptance of the evidence generated by RWE. Several researchers, professional societies, government agencies and multi-stakeholder initiatives worldwide have disseminated guidance, framework, and standards in this aspect which can address gaps in data standardization and improve the quality of RWD

Keywords: Real world Evidence RWE; Real World data RWD; Regulatory framework OPTIMAL; SPIFD; Pragmatic Trials; Explanatory Trials; Retrospective trials; Prospective trials; Cross sectional studies; Case control studies; cohort Studies

1. Introduction

Randomized controlled trials (RCTs) are the gold standard when it comes to evidence-based medicine.1 RCTs are conducted to assess the efficacy and safety of study drugs under well-defined, controlled clinical conditions and in selected patient populations. The design of RCTs, including features such as randomization, blinding and intention-to-treat approach minimizes confounding factors and sources of bias enabling differences in efficacy to be determined between two interventions.1,2 Consequently, RCTs are highly reliable 3 and have strong validity.1

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RCTs however have limitations. In an RCT, the conditions under which patients receive the study drug are tightly controlled, patient population is highly selective, and often not representative of the general population in real-world clinical practice. Thus, at times it has been observed that such 'real-world' patients may show different performance status and compliance to the intervention.2,3,4,5 In addition, the treatment and follow-up periods are often short, which at times does not lead to clarity on, both long-term benefits and delayed hazards associated with treatment. Another key aspect with RCTs is that they are lengthy and costly to conduct and analyze.6

RCTs thus, have limited generalizability 1-6 and the conclusions from these tightly controlled studies often apply only to the selected patient population.7

Compared with RCT, the core aspect of RWE is its practical nature rather than a tightly controlled environment. As RWE grows and expands its uses, planning of the study and the study design needs to be deliberated since there is at present no clear agreement within decision makers on any specific standards. Thus, researchers at times struggle to provide data that meets the requirements of decision makers. The other challenges researchers face is about sharing of data or database since amongst other issues is also an issue of privacy of data. Many RWD border on patient privacy. Technologically also researchers face the problems of linking database.

2. Real-World Data (RWD) and Real -World Evidence (RWE)

Real-world evidence is the clinical evidence regarding the usage and potential benefits, or risks of a medical product/intervention derived from analysis of Real-World Data RWD.8

Real-world data RWD, is data relating to patients health status and/or the delivery of healthcare routinely collected from a variety of sources.8 RWD can come from sources like, for example 8

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Electronic Health Record (EHR) includes diagnosis and prescriptions stored in a database that can be easily accessed and utilized. EHR research broadly reflects actual practice. EHR allows for the quick and systematic collection of data on the effectiveness or side effects that manifest when a specific drug has been prescribed to unspecified masses.9,10

In addition, EHR can showcase the performance or clinical output of medical staff, procedure or hospital protocols. EHR data analysis can evaluate the actual achievement rate of goals of individual medical departments or hospitals.11 For e.g., compliance of prescriptions in accordance with the guidelines. EHR can directly reflect on the behavior of the one making the prescription by analyzing data on what is being prescribed and the rationality for selecting the therapy/co-therapy. EHR studies help understand compliance with product label or treatment guidelines and Identification of suboptimal dosing or treatment.

2.1. Real-World Evidence Studies: Potential Benefits

RWE studies are valuable across product lifecycle and can provide a comprehensive understanding of how a therapeutic option works in the "real world".2-4 By using real-world evidence, one can enhance understanding of what works for diverse patient types in a larger population context. RWE allows researchers to examine the performance of drug treatments and/or interventions while also looking at other factors and variables. In addition, RWE generation is more cost effective and faster than standard RCTs.

RWE generates insights into how treatments perform among patient sub-groups that may have not been studied in the RCTs. For example, patients with co-morbidities, extreme age groups, or specific socio-demographic status. It provides valuable additional information to the authorities, health insurers, hospitals, pharmaceutical industry, and its associated stakeholders. It can include patient-reported outcomes (PROs) describing the impact of a treatment on patients' daily activities, symptoms and quality of life as well as clinical or economic outcomes. The FDA uses real-world data and RWE to monitor post-marketing safety and adverse events, and in support of its regulatory decisions.8

RWE can be utilized for product development, to understand the natural history of disease – prevalence, incidence, and unmet medical need. RWE can also help generate hypotheses for prospective trials. One of the key uses of RWE studies

have been for safety surveillance and to develop evidence to support health outcomes, and patients' acceptability. RWE studies also help in further understanding of detection of untreated/undiagnosed patients ("unmet need") comparative effectiveness and health outcomes.

Thus along with data integration and insights gained from existing data, or as a by-product of clinical care, RWE can

- support regulatory filings
- expand patient access
- drug safety surveillance
- protocol feasibility assessment,
- identify at-risk patient factors
- historical controls
- Governance of care processes and their outcomes
- Health emergencies

2.2. Types of RWE Studies

RWE research can be divided into two types: primary data, collected specifically for research purposes and secondary data, collected for other purposes.12 Primary data is generally obtained from study-specific case report forms, electronic medical and health records, and/or clinical outcomes assessments. This data is collected in interventional Phase IV studies and in non-interventional prospective observational studies, patient registries and health surveys. Secondary data is obtained from clinical chart reviews, registries and/or insurance claims databases, and are used in retrospective database studies or as an input to prospective study design or hybrid studies.12

2.3. RWE Study Designs

RWE studies are mostly categorized based on a) assignment of intervention and requirement of the comparison group or b) Pragmatic Trial, which seeks to examine whether a treatment/intervention works or not. This is based on timings of studies for e.g. prospective which is future facing and generally require primary data collection, or retrospective studies which use secondary data to look back in past or cross-sectional studies, which involve the assessment of a homogenous group of patients at a point in time, during which treatment and outcomes can be determined simultaneously.

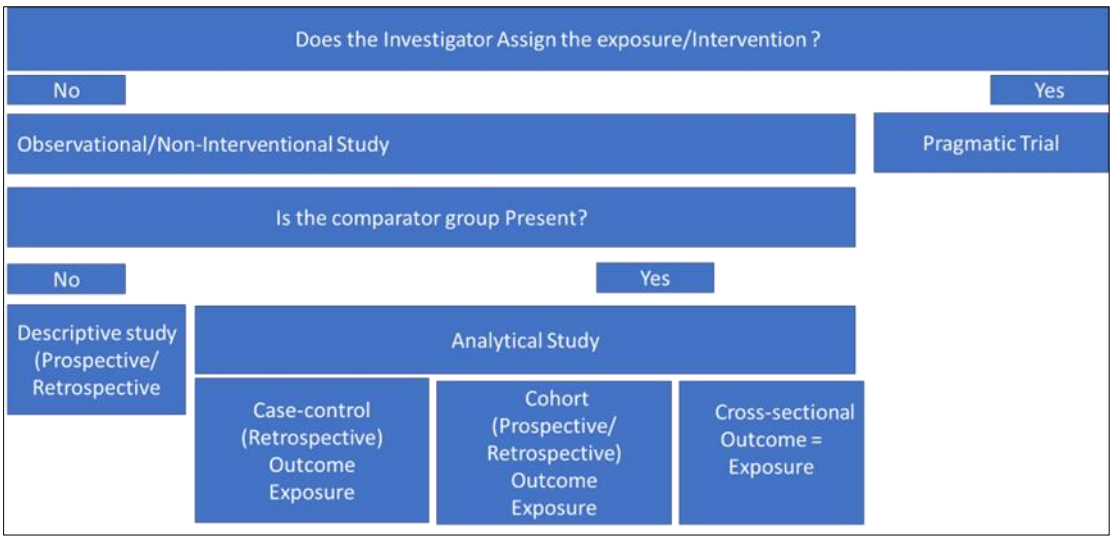

Figure 1 Types of RWE Studies [3]

2.4. Case control studies

The approach with Case control studies is to identify the patient with the disease of interest and then evaluate for risk factors that could have caused it. Thus, typically they are retrospective in nature. Case–control studies help answer the research question leading to hypothesis generation.13

Advantages of case control studies are that they can simultaneously assess multiple etiological/risk factors. Such studies are also suitable for diseases with long latency period between exposure and disease.

The key disadvantage is that incidence and prevalence can't be estimated since they do not cover information about the base population from which the cases are drawn

2.5. Cohort studies

Cohort studies evaluate the association between a particular exposure or a risk factor and subsequent development of disease. 13 They can be prospective when information on risk factor has been collected or retrospective when exposure information has already been collected prior and now patients are being assessed in the present to determine the presence or absence of disease.13

Cohort studies help to provide information regarding the natural course of the disease and help in estimating incidence, relative risk and in studying the relationship between exposure and diseases outcome.

The key disadvantage of such studies is that they are longer in duration thus difficult in maintaining consistent study method. They also require large sample size.

2.6. Cross-sectional studies

Cross-sectional studies are used in evaluating prevalence and cause/effect relationship and thus help assess exposure and outcomes in a specified cohort of patients at any given point in time. 14 The important thing in such a study design is to define the cohort of the patient and the specific characteristics being considered. The definition of the condition and health characteristics under study should be standardized, reproducible, and feasible to apply on a large scale. 14

The advantages of such studies are that they are relatively quick and inexpensive and can assess variety of exposure and outcomes.

The key disadvantage of such studies is that they are susceptible to selection bias. They are also unsuitable for rare disease or diseases of short duration mostly due to low prevalence at a single point in time.

2.7. Pragmatic and Explanatory Trials

Studies with healthcare interventions are described as either pragmatic or explanatory.

Pragmatic randomized clinical trials measure effectiveness and treatment benefit in routine clinical practice. A pragmatic trial reflects variations between patients that occur in real clinical practice and aims to inform choices between treatments, as in Table 1.

Pragmatic trials offer a scientific method of research for policymakers and clinicians, and serve as real-world evidence sources for decisions, such as for funding, regulations, policy, and organizational changes.15

Explanatory trials are specialized as they specify and evaluate a uniform population to evaluate treatment benefit under an ideal condition. This is different as compared to pragmatic trials consider the realities of the diverse patients.15,16

Table 1 Comparison of Pragmatic vs Explanatory Trials[15,16]

Pragmatic Trials	**Explanatory Trails**
High External Validity	High Internal Validity
Large Sample Size	Smaller Sample Size
Simple Design	Sophisticated design
Diverse Setting	Controlled Environment
Mostly Phase IV	Mostly Phase I-III

RWE studies are also classified based on the time perspective on evidence that is being sought.

RWE studies hence include both retrospective, cross-sectional, and prospective designs. 3,4

Table 2 RWE studies based on Time of Initiation 17

Retrospective	**Present**	**Prospective**
Non-interventional Case-control Cohort	Cross-sectional Study	Non-interventional cohort study with primary data
Non-interventional cohort study with secondary data		Registry
Administrative or claims database study		
Electronic Health Record Study		

2.8. Prospective Studies

Prospective studies are conducted from present into future and thus participants are followed up for outcome to an intervention or exposure. Prospective studies carry the advantage of methodology for collecting specific data. Prospective design studies generally require primary data collection and hence allow a high degree of control over data elements collected and have the advantage of being tailored to collect specific exposure data. They provide information on long-term data on the natural history or disease progression. The disadvantage of a prospective studies could be the long follow-up period while waiting for events/diseases to occur. This study design is inefficient for investigating diseases with long latency periods and is vulnerable to a high drop-out rate to follow-up rate

Examples of such studies include:

- Registries
- Health surveys
- Prospective observational studies
- Post-authorization safety study.

2.9. Retrospective Studies

In retrospective observational study, both exposure and outcomes have already occurred. Retrospective studies are conducted from present but observe the past to examine outcomes or events. Retrospective database studies look backward in time using secondary data, having the potential to generate large, real-world sample sizes quickly and efficiently. The advantage of these studies is that there is a readily available data and thus it is economical and fast to conduct. They can be customized to analyze specific events and factors associating with those events. The key disadvantage of such studies is limited control over data collection. The data existing, however could be incomplete, inaccurate, inconsistently measure between subjects and unstandardized.

Examples of such studies include:

- Clinical/hospital record/chart review
- Administrative data/insurance claim data
- Electronic medical records (EMRs).

2.10. RWE Challenges

There are several challenges in interpretation and in utility of RWE studies. The most important challenge is validity – Open, unblinded, and nonrandomized designs used in RWE studies raise questions about their validity.18,19 Quality of data – Most of the sources for RWE studies are data collected to support clinical care and reimbursement. These data are not gathered to support any specific research question. Hence, there are gaps in the accuracy, completeness, and quality of Real-World data.18,19,20 The challenges with RWE can be categorized broadly in legal, regulatory, technical and acceptability of data/inferences. Legal and regulatory issues relate to data quality, safety, ownership, and access to data. At times RWD sources impinge on personal data thus access and sharing of this data can border on privacy issues. Technologically the challenge for RWE is to relate digital linking of different RWD sources. It needs to be acknowledged that many databases lack the quality controls and rigor required by researchers. This potentially confounds interoperability, harmonization and access, limiting their use. Finally, there is also at present no clear agreement within

decision makers on any specific standards thus researchers at times struggle to provide data that meets the requirements of decision makers.

2.11. RWE studies: Revelations & Implications

Post-marketing RWE studies, confirm the therapeutic value of a drug/intervention in clinical practice. This includes the availability of adequate care to achieve specific outcomes in the individual patient, achievement of the best possible results with available resources, a fair distribution of resources among all patient groups and the contribution of healthcare system and protocols. This is of fundamental importance especially for those drugs for which there is little information, wide regional differences, fears about prescription independence and therapeutic continuity, as in the case of biosimilars and generics. For biosimilars/generic drugs, collection of data from the real-world can help confirm their overlap with the respective originators, compare the effectiveness and tolerability profile of drugs belonging to the same homogeneous therapeutic class.

A RWD study, analyzed regimens followed by hematologist/s in managing acute lymphoid leukemia (ALL). The dosing, safety and the effectiveness achieved by biosimilar pegaspargase was noted and showed overlapping findings between the biosimilar and the originator. This supported the local use of biosimilar pegaspargase in acute lymphoid leukemia(ALL) patients and help build the confidence of the treating physicians on the biosimilar product.21

A Retrospective review from the CESQIP(The Collaborative Endocrine Surgery Quality Improvement Program)registry of 8381 thyroidectomy patients by 173 surgeons at 46 institutions analyzed a total of 7142 ER (Emergency Room) visits and 7265 HR (Hospital Readmission).22 The study revealed that rates of all ER visits were 3.4% (n = 250) and all HR were 2.3% (n = 170) within 30-days of surgery. The visits were linked to 3 key associated risk factors. Hypocalcemia was linked with 21.9% of ER encounters and 36.4% of HR, BMI >40 kg/m2 was a risk factor for both ER visit (OR1.86) and HR (OR 1.94) and the 3rd risk factor was of surgical duration (>3 hrs, OR 2.63, and transection of recurrent laryngeal nerve OR 4.58). These were risk factors for HR. The study thus identified risk factors which influenced ER and HR, suggesting that strategies to manage these risk factors could potentially improve post-thyroidectomy outcome. Programs should be directed towards managing these 3 risk factors to evaluate the potential to reduce ER and HR visit.22

Another retrospective study of 5989 patients across 10 outpatient diabetes clinics in Sweden evaluated adherence to guidelines in type 1 diabetic patients.23 . Diab-Base electronic medical record database was used for data collection. Data on patient characteristics, including treatment, general risk factors for diabetic complications, and frequency of HbA1c measurements, were retrieved for all patients. This study provided important insight into HbA1c measurement in routine clinical practice in Sweden. It was found that the measurements were done less than that recommended by guidelines recommend. Guidelines recommend quarterly or more frequent hemoglobin A1c (HbA1c) assessments to be monitored in patients with uncontrolled type 1 diabetes mellitus. The study thus highlighted the need for intervention at the practitioners being educated on the guidelines and at interventions which could help push for a better practice of the guidelines and in turn Diabetes control.23

A similar but a Prospective Longitudinal data LANDMARC study evaluated management and progression of type 2 diabetes mellitus patients over a period of 3 years.24 This analysis was to reveal the trends in complications associated with diabetes; treatment strategies used by physicians and correlation among treatment, control, and complications of diabetes. Participants from metropolitan and non- metropolitan cities showed similar decrease in glycemic levels (mean change in HbA1c: -0.5% vs. -0.5%; p = .8613). Among diabetic complications, neuropathy was the predominant complication (815/6236, 13.1% participants). Microvascular complications (neuropathy, nephropathy, and retinopathy) were significantly (p < .0001) higher in non-metropolitan than metropolitan cities. Hypertension (2623/6236, 78.2%) and dyslipidemia (1696/6236, 50.6%) continued to be the most reported cardiovascular risks at 1 year. At 1 year: 4045/6013 [67.3%]), while the proportion of those taking insulin along with OADs increased (baseline: 1498/6236 [24.0%] vs. 1 year: 1844/6013 [30.7%]). Thus, the real- world study gave a panoramic view of what can be anticipated as changes in patients and what physicians need to look out for in their patients.24

An example of analyzing EHR is the RWE study which examined the association of the Hospital Readmissions Reduction Program (HRRP) with readmission and mortality outcomes among patients hospitalized with heart failure within a prospective clinical registry.25This study included 115245 fee-for-service Medicare beneficiaries across 416 US hospital sites participating in the American Heart Association Get with The Guidelines-Heart Failure registry. The 30-day risk-adjusted readmission rate declined from 20.0% before the HRRP implementation to 18.4% in the HRRP penalties phase. In contrast, the 30-day risk-adjusted mortality rate increased from 7.2% before the HRRP implementation to 8.6% in the HRRP penalties phase. The 1-year risk-adjusted readmission and mortality rates

followed a similar pattern as the 30-day outcomes. The 1-year risk-adjusted readmission rate declined from 57.2% to 56.3% (HR, 0.92; 95% CI, 0.89-0.96; P < .001), and the 1-year risk-adjusted mortality rate increased from 31.3% to 36.3% (HR, 1.10; 95% CI, 1.06-1.14; P < .001) after vs before the HRRP implementation.25 Implementation of the HRRP was thus temporally associated with a reduction in 30-day and 1-year readmissions but an increase in 30-day and 1-year mortality. This finding may thus require reconsideration of the HRRP in heart failure

Another example, wherein Hospital records were analyzed for In-hospital mortality, mortality or hospice, major complications, and venous thromboembolic events.This was compared between hospitals who had a Trauma quality program MTQIP (Michigan Trauma Quality Improvement Program), compared with ACS TQIP (The American College of Surgeons Trauma Quality Improvement Program)and compared with hospitals who did not have any such program.26A total of 2373130 trauma patients, 16 years or older with an Injury Severity Score of 5 or more were identified from 98 ACS TQIP hospitals, 23 MTQIP hospitals, and 429 nonparticipating hospitals, based on program participation status in 2011.Hospital participation in either ACS TQIP or MTQIP was associated with improvement in mortality or hospice (ACS TQIP vs nonparticipating: OR, 0.90; 95% CI, 0.87-0.93; MTQIP vs nonparticipating: OR, 0.88; 95% CI, 0.81-0.96). Hospitals participating in MTQIP achieved the lowest overall risk-adjusted mortality in the postenrollment period (4.2%; 95% CI, 4.1-4.3). This study demonstrates that hospital participation in a collaborative quality improvement program is associated with improved patient outcomes beyond benchmark reporting alone while promoting compliance with processes of care.26

Retrospective, comparative analysis of prospectively collected data was analyzed. This was comparing laparoscopic and robotic-assisted elective ventral hernia repair (VHR) procedures reported in the multi-institutional AHSQC database. 27 Up to 28% of patients who have undergone laparotomy can develop a ventral hernia. There is increasing interest in robotic-assisted VHR (RVHR) as a minimally invasive approach to VHR not requiring myofascial release and in RVHR outcomes relative to outcomes associated with laparoscopic VHR (LVHR). The RWE study hypothesized that real-world evidence from the Americas Hernia Society Quality Collaborative (AHSQC) database would indicate comparable clinical outcomes from RVHR and LVHR approaches not employing myofascial release. A one-to-one propensity score matching algorithm identified comparable groups of patients to adjust for potential selection bias that could result from surgeon choice of repair approach. 27

The analysis revealed significant differences amongst the 11 outcomes that were pre-specified. Operative time tended to be longer for the RVHR group compared to the LVHR group ($p < 0.001$). Length of stay, LOS differed between the two groups; while both groups had a median length of stay of 0, stay lengths tended to be longer in the LVHR group ($p < 0.001$). Rates of conversion to laparotomy were fewer for the RVHR group: < 1% and 2%, respectively ($p = 0.007$). Through 30 days, there were fewer RVHR patient-clinic visits ($p = 0.038$).Differences favored RVHR in terms of shorter LOS, fewer conversions to laparotomy, and fewer postoperative clinic visits; differences favored LVHR in terms of shorter operative times. 27

Data from real-world studies can also identify whether routine clinical practice differs from current guideline recommendations and whether there are any regional differences in patient management strategies. Guidelines recommend testing for EGFR mutation at diagnosis of advanced non–small-cell lung cancer to guide treatment. A large, international retrospective survey (conducted in Canada, France, Germany, Italy, Japan, South Korea, Spain, Taiwan, the UK and the USA) reported similar findings, with mutation testing requested in 77.0–84.0% of patients prior to selection of first-line treatment in 2016. 28 However, substantial regional variation reported, with the multinational retrospective PIvOTAL study demonstrating that rates of EGFR testing ranged from 42.9–85.3% of patients with advanced NSCLC across Australia, Brazil, Germany, Italy, Japan, Korea, Spain and Taiwan. 29,30 This substantial variation among countries in testing percentages, treatment patterns, and survival outcomes suggest that more efforts are needed to optimize molecular testing rates which should be implemented in the context of each country's health care scenario. 30

2.12. Frameworks and Regulatory Guidelines of RWE

RWE has been widely accepted in Post approval safety surveillance studies, however its integration in early development effectiveness during other phase of drug life cycle is only recently gaining traction by regulators.

In 2018-2019 RWD was utilized in 40% applications for Marketing Authorizations and for 18% of extensions of indication filings by European Medicines Agency (EMA).

As early as in 2018 December, US Food and Drug Administration (FDA) published its framework for RWE reinforced by three pillars 31

- Are RWD fit for use?
- Can the study design provide adequate evidence?
- Can the study conduct meet regulatory requirements?

The FDA framework outlined what was important to include and evaluate a RWE in regulatory submissions and regarding effectiveness and safety of the products. FDA has used RWD primarily in the evaluation of drug safety via efforts such as Sentinel Initiative to make many regulatory decisions, including eliminating the need for an industry-sponsored post-marketing study.31

Following the FDA framework, the European Union, published the OPTIMAL framework in 2019 on RWE focusing on 3 key aspects: 32

- Operation
- Technical, and
- Methodology

European Medicines Agency, EMA in 2020 developed draft guidelines on studies based on registry data as one source of RWD to address access to RWE due to multiple sources and interoperability.33

To further improve transparency, the International Society of Pharmacoepidemiology (ISPE), formed a RWE taskforce to provide guidance and develop protocols for study investigations and data extraction procedures 33 and in October 2021, launched the Real-World Evidence Registry in co-operation with the Real-World Evidence Transparency Initiative, where RWE studies can be pre-registered.

National Institute for Health and Care Excellence (NICE) UK in June 2022 published its real-world evidence (RWE) framework.34 The NICE RWE framework gives guidance and aligns with initiatives from the European Union (EU), US and Asia in recent years, collectively demonstrating the global drive towards improving the collection, interpretation, and impact of RWE. NICE foresees RWE researchers to transparently justify the selection of the real-world data (RWD) source using previously published frameworks, like Structured Process to Identify Fit-for-Purpose Data (SPIFD), or using NICE's DataSAT. NICE recognizes that tools like SPFID can help researchers both identify and justify the selection of the dataset. 34

Reporting guidelines had been developed since 2007to structure reporting for a range of study designs and contexts and are associated with improved quality of reporting. Both STROBE and RECORD are intended for application to observational research studies.35

RECORD was created as a guide for authors, journal editors, peer reviewers, and other stakeholders to encourage transparency and completeness of reporting of research conducted using routinely collected health data. RECORD can improve transparency, reproducibility, and completeness of reporting of research conducted using routinely collected health data.

Regulators have been increasingly calling for high levels of transparency and reproducibility as an integral part of the science of RWE. These frameworks were developed in response to concerns over wider adoption of RWE in regulatory and reimbursement decision-making with an implication that researchers could be disincentivized from conducting RCTs and healthcare decision-makers could be forced to rely on 'inferior' evidence as seen in by retraction of many studies including the recent retraction of COVID-19 RWE study from major journals.36With the advent of these framework and regulatory guidelines, it would improve quality of RWE and provide tools and formats to researchers.

In February 2023, Canadian health authorities published a Multi-Criteria Decision Analysis (MCDA) developed through a collaboration between the Canadian Institutes of Health Research and partnerships with the Canadian Centre for Applied Research in Cancer Control and Cancer Care Ontario. This collaboration, known as CanREValue, was established to create a framework for generating and utilizing real-world evidence (RWE) to enhance decisions regarding cancer drug funding. The CanREValue collaboration will focus on the generation of RWE using RWD collected from existing population-level administrative health databases, such as cancer registries, hospital records and insurance claims. CanREValue's framework provides a process for evidence-based reassessment of cancer drug funding recommendations by health technology assessment (HTA) organizations. The MCDA rating tool was created through a stepwise approach that involved selecting criteria, developing rating scales, applying weights to each criterion, and validating the tool through testing and making necessary adjustments. MCDA can facilitate transparency in decision-making processes and improve the quality and consistency of decisions. Its use in healthcare is increasing, given its

usefulness as a decision aid in complex decision-making. MCDA has been utilized by various international HTA agencies, including IQWiG in Germany and INESSS in Quebec, Canada, to support HTAs for regulatory or reimbursement decisions and in clinical decision-making at the patient-level.37

Multi-criteria decision analysis helps support decisions in Health Policy through the collaboration of Canadian Institutes of Health Research and through partnerships with the Canadian Centre for Applied Research in Cancer Control and Cancer Care Ontario. This Collaboration, CanREValue,(The Canadian Real-world Evidence for Value) in Cancer Drugs, was established with the aim of devising a structure for generating and utilizing real-world evidence (RWE) to bolster decisions regarding funding for cancer drugs. CanREValue's framework provides a process for evidence-based reassessment of cancer drug funding recommendations by health technology assessment (HTA) organizations. The MDCA rating tool was developed in a stepwise approach: (1) selection of criteria to assess the importance and feasibility of an RWE question; (2) development of rating scales, application of weights to each criterion, and calculating aggregate scores and validation testing of the MCDA rating tool and making adjustments, as necessary. Through a structured approach, MCDA can facilitate transparency in decision-making processes and improve the quality and consistency of decisions. MCDA use in health care is increasing given its utility as a decision-aid in complex decision-making. For example, MCDA has been used in health policy to support HTAs for regulatory or reimbursement decisions as well as in clinical decision-making at the patient-level and has been adopted by many international HTA agencies (e.g., IQWiG (Germany), INESSS (Quebec, QC, Canada).

3. RWE outlook

RWE studies are increasing in number and are more likely to gain further importance as healthcare decision-makers become increasingly aware of what it offers. Due to the issues of applicability, heterogeneity, accessibility, and completeness of these secondary data resources, under many circumstances, researchers may need to collect or recollect study data purposefully, either prospectively or retrospectively. The process of data collection should be a key component of study design, what data elements from which sources tools etc should all be clearly planned at study design stage. Moreover, necessary data management procedure and quality control measures should also be taken to ensure the quality of study data, so that data analysis is facilitated.

4. Conclusion

Pharmaceutical companies and CROs need to focus and further RWE, data sources, analytic techniques, and study methodologies to ensure they can optimize patient access. Aiming to improve the quality and reliability of RWE, researchers, professional societies, government agencies and multi-stakeholder initiatives have issued numerous recommendation documents, white papers, peer-review publications, and position papers to set standards for generating high-quality RWE. RWE and RCT research are not competing in terms of which is better. RWE is appealing since it comes at a lower cost and the data analysis could examine millions of people instead of hundreds. Recognizing the advantages/drawbacks of RWE in comparison to RCTs is necessary to appreciate the importance of both these studies.RWE has potential to shape policies, protocols and develop programs to implement best practices. Determining validity and reliability of the RWD against its source or set of standards will therefore be essential. Extensive data hygiene practices and tools developed for using claims data (e.g., through Sentinel, Observational Medical Outcomes Partnership, Observational Health Data Sciences and Informatics, Electronic Data Methods Forum, etc.) may help to bridge the data methods gaps between such RWD sources. With advances in AI and data analytics, it is expected that there would be further increase in the usefulness of RWE studies in all phases of the product lifecycle.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

References

[1] Spieth PM, Kubasch AS, Penzlin AI, Illigens BM, Barlinn K, Siepmann T. Randomized controlled trials – a matter of design. Neuropsychiatr Dis Treat. 2016 Jun 10; 12:1341-9.https://doi.org/10.2147/NDT.S101938

[2] Stang A. Randomized controlled trials: an indispensible part of clinical research. DtschArzteblInt 2011; 108(39): 661–2. doi: https://doi.org/10.3238%2Farztebl.2011.0661

[3] Kim HS, Lee S, Kim JH. Real-world evidence versus randomized controlled trial: clinical research based on electronic medical records. J. Korean Med. Sci. 33(34), e213 (2018). https://doi.org/10.3346/jkms.2018.33.e213

[4] Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. Clin. Pharmacol. Ther. 103(2), 202–205 (2018). https://doi.org/10.1002/cpt.946

[5] Nazha B, Mishra M, Pentz R, Owonikoko TK. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. Am. Soc. Clin. Oncol. Educ. Book 39, 3–10 (2019). https://doi.org/10.1200/edbk_100021

[6] Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. J. Natl Cancer Inst. 109(11), 2017. https://doi.org/10.1093/jnci/djx187

[7] Roche N, Reddel H, Martin R et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann. Am. Thorac. Soc. 11(Suppl.2),S99–104;2014. https://doi.org/10.1513/annalsats.201309-300rm

[8] https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence last accessed on 28th Sept 2022.

[9] Kim HS, Kim H, Jeong YJ, Lee H, Yim HW, Kim JI, et al. Comparative analysis of the suspected heparin-induced thrombocytopenia level in Korea. Basic Clin Pharmacol Toxicol. 2017;121(4):360–367. https://doi.org/10.1111/bcpt.12791

[10] Kim HS, Lee SH, Kim H, Lee SH, Cho JH, Lee H, et al. Statin-related aminotransferase elevation according to baseline aminotransferases level in real practice in Korea. J Clin Pharm Ther. 2016;41(3):266–272. https://doi.org/10.1111/jcpt.12377

[11] Kim HS, Kim H, Lee H, Park B, Park S, Lee SH, et al. Analysis and comparison of statin prescription patterns and outcomes according to clinical department. J Clin Pharm Ther. 2016;41(1):70–77. https://doi.org/10.1111/jcpt.12350

[12] Mack C, Lang K. Using Real-World Data for Outcomes Research and Comparative Effectiveness Studies. *Drug Discovery & Development*. Nov. 4, 2014.

[13] Johnson LL. Principles and Practice of Clinical Research. 4th ed. Academic Press: Elsevier; 2018. Design of observational studies; pp. 231–48

[14] Camm AJ, Fox KA. Strengths and weaknesses of 'real-world' studies involving non-vitamin K antagonist oral anticoagulants. Open Heart. 2018 Apr 21;5(1). https://doi.org/10.1136/openhrt-2018-000788

[15] Kowalski CJ and Mrdjenovich AJ. Studying group behaviour: cluster randomized clinical trials. *American Journal of Clinical and Experimental Medicine*. Vol. 1(1), 2013: 5-15

[16] Maclure M. Explaining pragmatic trials to pragmatic policy-makers. *CMAJ*. May 12, 2009;180(10): 1001-10003

[17] Taur SR. Observational designs for real-world evidence studies Perspect Clin Res. 2022 Jan-Mar; 13(1): 12–16. https://doi.org/10.4103/picr.picr_217_21

[18] Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-world evidence – What is it and what can it tell us? N Engl J Med 2016; 375:2293-7. https://doi.org/10.1056/nejmsb1609216

[19] Ziemssen T, Hillert J, Butzkueven H. The importance of collecting structured clinical information on multiple sclerosis. BMC Med 2016; 14:81. https://doi.org/10.1186/s12916-016-0627-1

[20] Mentz RJ, Hernandez AF, Berdan LG, Rorick T, O'Brien EC, Ibarra JC, et al. Good clinical practice guidance and pragmatic clinical trials: Balancing the best of both worlds. Circulation 2016; 133:872-80. https://doi.org/10.1161/circulationaha.115.019902

[21] https://www.linkedin.com/pulse/real-world-data-rwd-evidencerwe-driver-change-medical-dr-apurba/ last accessed on 3rd Oct 2022

[22] Taye Aida, Inabnet W B, Pan S et al. Post-thyroidectomy emergency room visits and readmissions: Assessment from the Collaborative Endocrine Surgery Quality Improvement Program (CESQIP) Am J Surg 2020 Oct;220(4):813-820. https://doi.org/10.1016/j.amjsurg.2020.02.036

[23] Matuleviciene V, Attvall S, Ekelund M, Clements M, Dahlqvist S, Fahlén M, et al. A retrospective study in 5,989 patients with type 1 diabetes in 10 outpatient diabetes clinics in Sweden of the frequency of measuring HbA1c in clinical practice. J Diabetes Metab. 2014;5:5. http://dx.doi.org/10.4172/2155-6156.1000377

[24] One-year trends from the LANDMARC trial: A 3-year, pan-India, prospective, longitudinal study on the management and real-world outcomes of type 2 diabetes mellitus. Endocrinol Diabetes Metab. 2022 Jan;5(1): :e00316.doi: 10.1002/edm2.316. Epub 2021 Dec 1. https://doi.org/10.1002%2Fedm2.316

[25] Gupta A, Allen L A, Bhatt D et al. Association of the Hospital Readmissions Reduction Program Implementation With Readmission and Mortality Outcomes in Heart Failure. JAMA Cardiol. 2018 Jan 1;3(1):44-53.doi: 10.1001/jamacardio.2017.4265

[26] Association of Hospital Participation in a Regional Trauma Quality Improvement Collaborative with Patient Outcomes. JAMA Surg. 2018 Aug 1;153(8):747-756. https://doi.org/10.1001/jamasurg.2018.0985

[27] LaPinska M, Kleppe K, Webb L. Robotic-assisted and laparoscopic hernia repair: real-world evidence from the Americas Hernia Society Quality Collaborative (AHSQC). Surg Endosc. 2021 Mar;35(3):1331-1341. https://doi.org/10.1007/s00464-020-07511-w

[28] Peters M, Kim ES, Hirsch V. Clinical use of epidermal growth factor receptor testing in patients with advanced lung cancer by physicians: survey of US and international patterns. *J. Glob. Oncol.* 2009;5, 1–7. https://doi.org/10.1200/jgo.18.00057

[29] Lee DH, Isobe H, Wirtz H et al. Health care resource use among patients with advanced non-small cell lung cancer: the PIvOTAL retrospective observational study. *BMC Health Serv. Res.* 2018;18(1), 147. https://doi.org/10.1186/s12913-018-2946-8

[30] Lee DH, Tsao MS, Kambartel KO et al. Molecular testing and treatment patterns for patients with advanced non-small cell lung cancer: PIvOTAL observational study. *PLoS ONE* 2018;.13(8).https://doi.org/10.1371/journal.pone.0202865

[31] Arlett P, Kjaer J, Broich K et al. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Clinical Pharmacol and Therapeutics. 2022;111(5);21-23.

[32] Burns L, Le Roux N, Kalesnik-Orszulak R et al. Real-World Evidence for Regulatory Decision-Making: Guidance From Around the World. Clinical Therapeutics; 2022;44(3);420-437.

[33] Schad E, Thronicke A. Real-World Evidence—Current Developments and Perspectives. *Int. J. Environ. Res. Public Health* **2022**, *19*(16)

[34] National Institute for Health and Care Excellence. NICE real-world evidence framework. https://www.nice.org.uk/corporate/ecd9/chapter/overview Last accessed Dec 2022.

[35] Benchimol I E, Smeeth L, Guttmann A et al. The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement. PLos Medicine Oct 6th 2015. Doi 10.1371/journal.pmed.1001885

[36] Peterson J C, Alexander R, Nugent K. COVID-19 article retractions in journals indexed in PubMed.Am J Med Sci. 2022 Jul; 364(1): 127–128.

[37] Chan K, Nam S, Evans B et al.Developing a framework to incorporate real-world evidence in cancer drug funding decisions: the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration.. BMJ Open 2020;10:e032884. doi:10.1136/bmjopen-2019-032884.