Introduction to real-world evidence studies

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Real-world data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-world evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[1]

RWD can be generated from:

- Electronic health records (EHRs)
- Medical claims, billing data, and insurance data
- Data from product and disease registries
- Patient-generated data, including from in-home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices.[1,2]

Findings from clinical trials cannot be generalized to population at large due to the stringent eligibility criteria. RWE studies complement clinical trials by generalizing the findings from clinical trial to general population. Furthermore, RWE can provide information on other areas, such as natural history and course of disease, effectiveness studies, outcome studies, and safety surveillance.[2]

DIFFERENCE REAL-WORLD EVIDENCE STUDIES AND RANDOMIZED CLINICAL TRIALS

Randomized clinical trials (RCTs) are initial studies conducted to establish the safety and efficacy of an investigational product. RCTs are designed to focus on internal validity (capability of a clinical study to provide reliable results which are actually true and not due to an error), which may sometimes compromise generalizability to general population.[2] RCTs are conducted on very selective populations, so patients with comorbidities may be excluded. Furthermore, these studies are conducted in very controlled settings. Most of the clinical treatment guidelines are formulated based on the RCT results. However, these results do not truly represent the actual entire population, since these RCTs have many inclusion and exclusion criteria. Hence, these results from RCT require support from diverse situations that would be present in a real-world clinical scenario [Table 1].[3]

Safety evaluation is another aspect that can be influenced by the type of study design. In RCTs, small sample size, strict patient eligibility criteria, and short-term follow-up do not always allow the measurement of rare adverse events (AEs). Hence, AE rates recorded during RCTs do not correctly reflect the incidence of AEs in real-life settings. The short duration of RCTs may not allow AEs to be detected in patients who would have developed the AE after a longer period of drug exposure; the selection criteria might have excluded older patients and patients with comorbidities, so the frequency of AE reported from RCTs might have been lower.[4]

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Table 1: Randomized clinical trials versus real-world evidence[2,3]

	RCT	RWE
Setting	Experimental or interventional setting	Real-world setting or observational or noninterventional setting
Study conduct	Protocol-based, GCP compliant	Real-life clinical practice
Treatment	Fixed pattern	Variable pattern
Participant population	Strict and many inclusion and exclusion criteria	Very few inclusion and exclusion criteria
Attending physician	Investigator	Practitioner
Comparator	Placebo/selective alternative interventions	Either no control arm or standard treatment or care
Outcome	Efficacy	Effectiveness
Randomization and blinding	Yes	No

GCP=Good clinical practice, RCT=Randomized clinical trial, RWE=Real-world evidence

ADVANTAGES OF REAL-WORLD EVIDENCE COMPARED WITH RANDOMIZED CLINICAL TRIALS[2,3]

1. As compared to RCT, depending on the type of RWE, it may take much less time, less resources, and less cost
2. In RWE studies, data can be accessed rapidly and data can be retrieved easily
3. RWE studies can be used to evaluate the natural history of disease, prevalence, incidence, unmet medical need, current treatment patterns, and standard of care
4. RWE studies can be used to support patient outcomes and health economics
5. RWE studies can be used to understand current health-care services
6. Research which is not possible with RCT can be done with RWE, for example, studies on high-risk groups
7. Side effects which are less frequently seen can be studied better with a RWE study as compared to RCT since RCT is conducted in a smaller population and with a shorter duration.

SOURCES OF REAL-WORLD DATA

Health records can be paper based or electronic. RWD can be leveraged if it is digitally recorded so that it can be aggregated and analyzed appropriately for research. Over the last 2 decades, significant progress has been made in digitalization of health records.[5] Electronic health-care records (EHRs) can be defined as an organized set of health-care data, which can be accessed electronically. They contain a diversity of data, the most frequent being medical records from general practitioners, specialists or hospitals, pharmacies, prescription data, and sometimes lifestyle-related information.[6]

RWD can be accessed from various sources as mentioned below:[7,8]

1. Claims
    i. Medical claims
    ii. Prescription drug claims
    iii. State Medicaid
    iv. Insurance companies.
2. Clinical studies
    i. Clinical trial data such as pragmatic study
    ii. Product registry
    iii. Disease registry.
3. Clinical setting
    i. EHR from clinicians/hospitals
    ii. Laboratory test
    iii. Billing data.
4. Pharmacy
    i. Sales data
    ii. Prescription data.
5. Patient powered
    i. Social media
    ii. Patient advocacy groups/patient communities.

EXAMPLE OF REAL-WORLD EVIDENCE STUDIES CONDUCTED IN INDIA

Few examples of different types of RWE studies conducted are given below:

1. Retrospective study: This is a retrospective study done to evaluate to what extent type 1 diabetic guidelines are followed in clinical practice in Sweden. These guidelines recommend quarterly or more frequent hemoglobin A1c (HbA1c) assessments in patients with uncontrolled type 1 diabetes mellitus. 5989 patients were recruited from 10 outpatient diabetes clinics in Sweden. 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[9]
2. Prospective study: LANDMARC study is a prospective, multicenter study evaluating a large cohort of people

with type 2 diabetes mellitus across India over a period of 3 years. This study will reveal the trends in complications associated with diabetes; treatment strategies used by physicians; and correlation among treatment, control, and complications of diabetes[10]

3. Cross-sectional study: This multicenter study was designed to determine the control of dyslipidemia in the Indian diabetic population treated with lipid-lowering drugs. The study was conducted in 178 sites in India. This study found that dyslipidemia control in Indian type 2 diabetes mellitus patients is very poor with almost half of them not reaching their low-density lipoprotein-cholesterol goal.[11]

CURRENT SCENARIO OF REAL-WORLD EVIDENCE IN INDIA

Recording patient data in the hospital needs time and effort. There is no legislative framework or guidelines in India, which would enable collating data from hospitals on standard indicators of quality of patient care. This could be one of the reasons for the poor quality of medical records. Many of the hospitals do not even record patient history in detail and information about treatment provided is sometimes very less. The private sector hospitals have better resources and funds as compared to public hospitals. However, in the absence of any government regulations, there is no requirement to collect these data. Furthermore, public hospitals are overloaded with patients. For RWD, well-defined formats whether in the physician's clinic or in the operation theater are required to yield data which can be analyzed appropriately. Some prestigious medical institutes in the country have developed a simple format to get structured data.[12]

WHAT CAN BE DONE NEXT

To generate RWD, it is crucial to develop brief and easy to fill computer-readable formats for collecting information at the clinic or at the hospital.[12]

India with its diverse vast population does have an advantage for conducting RWE studies, especially in areas as listed below:[2]

- Natural history and long-term complications of communicable diseases, such as drug-resistant tuberculosis, and noncommunicable diseases, such as diabetes, hypertension, and heart failure
- Registry for orphan/rare disease, such as thalassemia
- Health economics and outcomes research in government as compared to private hospitals
- Identification of unmet medical needs which would be relevant to Indian population
- Comparative effectiveness research of branded products versus generic and biologic versus biosimilar
- Comparative effectiveness research of Indian prescribed dose as compared to prescribing information.

In order that RWE studies achieve its true objectives and are designed, conducted, analyzed, and reported appropriately in India, the following needs to be done:

- Different stakeholders such as government, academicians, investigators, pharmaceutical industry, and patient support group would have to come together and encourage the conduct of RWE studies which are relevant to Indian health care
- India-specific RWE guidelines are required to be drafted
- Support in terms of data management, statisticians, and technical support for public and private hospitals so as to help them in developing structured format for collecting data and also to analyze and report RWE studies appropriately.

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Conflict of interest
Dr Deepa Chodankar is an employee of Sanofi India and might be shareholders of Sanofi.

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