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Abstract

Real world evidence: An Indian perspective

Randomized controlled trials (RCTs) are the gold standard for measuring the safety and efficacy of drugs. However, they are being challenged by payers and health care providers since they are looking for real world evidence (RWE) to validate whether the new intervention provides similar safety and efficacy as reported in RCT data. RWE uses real world data (RWD) to generate insight, foresight, and explorative findings on diseases, products, and patient populations. There are varied sources of RWD such as administrative data, large pragmatic trials, registries, electronic health records, and health surveys. RWE approaches are increasingly becoming the normal practice in developed countries to bring a product to the healthcare market and to ensure its significance in clinical practice. The Indian healthcare sector is growing at a brisk pace and is grasping up with the principles of health economics and outcome research, thereby exhibiting the value of real-world insights in healthcare decision. India has taken a step toward RWE by developing a framework to assist health care providers in harmonizing RWD for economic, clinical, and humanistic outcome.

Key words: Clinical outcome, health economics, health technology assessment, humanistic outcome, real world data, real world evidence

BACKGROUND

Pharmaceutical manufacturers invest considerable time and money during preauthorization drug development phases, especially in conducting phase-III clinical trials to provide robust data on the safety and efficiency of their products. Such studies are planned as randomized controlled trials (RCTs) which are considered gold standard for research to prove safety and efficacy of product with high validity but within firmly regulated boundaries of

clinical trials. However, the results of the RCTs, whose primary purpose is usually regulatory, cannot always be generalized to an average patient seen in the real world settings.^[1] Healthcare payers, regulatory authorities, and health technology assessment (HTA) agencies face the issue of making decision on relative efficacy of the new products based on evidence generated from RCTs, with inbuilt fears on the aspects of real world effectiveness.^[2] Regulatory and HTA agencies are looking for evidence for clinical value of

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the product in a real world environment. Patients are seeking for a better end result with their treatment and providers for the data-oriented proof of the prescribed drug to optimize patient treatment, cost efficiency, and better profit margins. Payers (both government and private) are enquiring providers and manufacturers to prove the benefits that they will reimburse for in their health care systems. With all these pressure, pharma manufacturers are forced to think of “evidence” -and the time has come to think ahead of the controlled environment of clinical trials. RCTs need to be supplemented with the combatively new standard, called real world evidence (RWE), as it alone cannot adequately answer questions about the long-term effectiveness and safety of the product, which is an increasing focus of regulators, providers, patients, and payers.^[3]

WHAT IS REAL WORLD EVIDENCE?

RWE is organized information that derives conclusion or judgment based on real world data (RWD). RWE uses observational data to generate insight, foresight, and extrapolative findings on disease, products, and in patient populations.^[4]

RWD is the data used for decision making by health care industry that are not collected in conventional RCT setting, but in a nonexperimental, noncontrolled observational setting. RWD provides useful information on comorbidity profiles of the target populations as well as confirm a decision on market access, new indications and related conduit investments. In addition, they can provide supporting evidence on the financial value of interventions to patients, government health agencies, and payers.^[4]

REAL WORLD DATA SOURCES

RWD can be collected prospectively or retrospectively depending on the aims of a particular study (phase IV trials, pragmatic trials, registries, postauthorization safety/efficacy studies, observation studies, pharmacoeconomic (PE) studies, etc.). Examples for RWD sources include supplementary information collected during RCTs, large pragmatic trials, administrative data, registries, review of electronic health records and medical charts, and health surveys.

Supplements to randomized control trials

Along with standard clinically focused RCTs, researchers often congregate information on variables such as patient-reported outcomes (PROs), therapeutic resource use, and costs. These information can provide valuable RWD. Such efforts can provide significant evidence on

treatment patterns for common events (e.g., doses of drugs used to treat rejection in kidney transplantation).^[5]

Large pragmatic trials

Furthermore, called “large simple trials” or “practical clinical trials,” they include prospective, randomized task but aim at larger more diverse real world population.^[6] This type of trial may have a role in the evaluation of effectiveness (i.e., the extent to which a drug does what it is intended to do for a specified population when used in routine circumstances) because confounding by indication is inherent in observational analyses of efficacy due to medical practitioner prescribing the drug that they think will most benefit their patients.^[4]

Administrative data

Furthermore, known as claim databases, administrative databases are typically retrospective or real-time in nature. The data are collected primarily for reimbursement, but contains some clinical opinion and process use with detailed information on charges. Administrative databases provide themselves to retrospective longitudinal and cross-sectional analyses of economic and clinical results at the patient, group, or population levels. This type of analyses can be performed at overall low cost and in a short period. With the administrative databases, researchers can gain insights into association between intervention, patient, and economic outcomes.^[4] Administrative databases (e.g., Medicare, Medicaid) predominate in North America and other parts of the world where a fee-for-service healthcare environment exists.^[7]

Registries

Registries are prospective, an observational collection of data of patients who have a particular disease and are receiving an intervention. Analysis of registries can help in understanding natural history, and for assessing real-world safety, effectiveness, quality of care, and provider performance.^[4] The most effective registries are those that are disease-based, maintain good data quality, and engage physicians and patients in their development and continuity. An example of registry is the Global Registry of Acute Coronary Events, which tracks outcomes of patients with acute coronary syndromes, myocardial infarction, or unstable angina in hospitals in North America, South America, Asia, Europe, and Australia.^[8]

Electronic health records and medical chart review

This is a vital source for RWD for a wide range of clinical settings throughout the world. The development of electronic data capture is effectively reducing the cost of medical chart reviews. Examples of databases used as RWD sources are the Clinical Practice Research Datalink^[9]

and The Health Improvement Network^[10] in the UK and the Kaiser Permanente, Geisinger and Marshfield Clinic health systems in the US.^[11] These databases are designed to provide a resource for pharmacoepidemiology, PEs, outcomes research, and risk-benefit analysis.^[9]

Health surveys

Health surveys are planned to gather descriptions of health status, utilization of health care system, treatment protocol, and health care expenses from patients and providers. Health surveys are methodologically meticulous and collect data on representative individuals in the population of interest (patients, physicians, or general population). With such designs, surveys can offer information about all members of the target population, not just those who are involving in a given RCT, or members of a specific health plan.^[4] Although surveys can provide valuable data, preoccupation with RCTs as the predominant source for evidence generation has pushed surveys into a shadow.^[12]

APPLICATIONS OF REAL WORLD EVIDENCE

There are many applications of RWE in the healthcare sphere. In addition to being utilized as a means to improve healthcare quality, the RWD may augment RCT data on the efficacy and safety of new drugs and medical devices. Data on the use of more heterogeneous (real world) sets of patients may create greater precision and clarity as to the safety and efficacy profile of new products, thus improving the labeling and approved indications of products.

The analysis of the usage of various products after their regulatory approval provides valuable information about the rate at which products prove their value to patients, providers, and payers. Further, it will enable a more precise identification of safety risks and risk/benefit trade-offs, and will allow an identification of heterogeneous responses, sub-population effects of products, the value of products when used among complex and comorbid patients, and value derived when products are delivered in diverse practice settings.

RWD collection facilitates long-term study of patient outcomes and health care utilization, helps in the generation of research hypotheses and research questions that can be tested in RCTs, and the sources for RWD can be utilized to identify and recruit patients for RCTs.^[13]

REAL WORLD EVIDENCE SCENARIO IN INDIA

Current healthcare status

The healthcare sector in India is growing at a rapid pace due to its services, strengthening exposure, and escalating

expenditure by private as well as public domains. Healthcare delivery system in India has two major components-public and private. The Government, i.e. public healthcare system comprises partial secondary and tertiary care institutions in major cities and focuses on offering basic healthcare facilities in rural areas. The private sector offers majority of secondary, tertiary and quaternary institutions of care with a major concentration in metros, tier I and tier II cities. As compared to Western countries, India is cost-competitive. The healthcare market of India is worth US\$ 100 billion and is anticipated to rise to US\$ 280 billion by 2020, a composite annual growth rate of 22.9%. The overall market constitutes 65% which includes healthcare delivery, (hospitals, nursing homes, and diagnostics centers), and pharmaceuticals.

With growing of healthcare expenditure as a percentage of Gross Domestic Product, there is a significant scope for enhancing healthcare services. Rural India is set to emerge as a potential demand source as it accounts for over 70% of the population. With increased accreditation of most of the hospitals, with awareness to develop quality to meet international standards, India aims to become India's healthcare core in 5 years. The data released by Department of Industrial Policy and Promotion reflected that many hospital and diagnostic centers attracted Foreign Direct Investment worth US\$ 3.21 billion between April 2000 and September 2015.^[14] However, we still need to focus on many issues of health care system.

Claims data in India are inadequately used for health outcomes research since the penetration of health insurance is not up to the mark. It is expected that in the near future health insurance will become more popular in India since its health care expenditure is predominantly out-of-pocket, and the healthcare costs are escalating day-by-day. More and more Indian adults understand the value of health insurance and many corporate hospitals have empanelled various insurance schemes. Various government-sponsored insurance schemes have been initiated at state levels (e.g., Tamil Nadu) and also central level (e.g. PMSSY). The claims information should capture treatments across different Indian Systems of Medicine, and the proper methodology could avoid duplication of data.^[15]

The use of EMRs is gradually rising in India. There is Health Management Information System HIMS (Government sponsored project) in some of the states of India, which have come up in the past decade. Electronic recording of patients' information is utilized in some major corporate hospitals, but these furnish only to a small percent of the country's population. The Tata Memorial Centre for the research, education, prevention, and treatment in cancer, has recently started using E-medical records.^[16]

The physicians in India depend on disease-related outcome measures to support their clinical decisions with minimal importance to patient related outcome measures. A similar attitude is observed even in clinical studies wherein patient-related outcomes (PROs), if used, are only secondary to disease-related outcomes. Data obtained from PROs in clinical trials can be useful in making health-related decisions at all levels in India. However, the concept of patient-centered outcome researches has yet to catch up in India.^[17]

While the developed world has realized the value of registries in epidemiology and research, India still lags in the number of registries and the information stored in them. Very few established registries exist such as the National Cancer Registry, The Indian Transplant Registry, etc., In India, as healthcare is not financed by the government, it sees slight incentive in assessing healthcare technologies and building systems to generate the relevant data. As a result registries, databases, medical records, and other sources of RWD have remained undeveloped in our country. Hence, in India, we are losing out on the tremendous wealth of RWD, which could have been generated, had our population been exposed to appropriate clinical registries. Awareness, training, and development of tools to capture RWD are the need of the hour for establishing an HTA system in India.^[18]

Approaches toward real world evidence

The Indian chapter of ISPOR has already drafted the proposed PE guidelines for India. PEs analysis helps the decision makers of a healthcare system (Ex. Clinicians, hospital administrators, health insurance providers, or the government) to optimize the resources in health and provides means for assessing costs and consequences of all available pharma products. Most of the existing protocols and guidelines in HTA and health economics and outcome research (HEOR) have been developed in the western world. While devising similar guidelines for India, due care has to be given to the prevalent socioeconomic situations, healthcare systems, medical practices, cultures, and values systems in India which are significantly different from those in the western world.^[19,20] Some of the key investments in the Indian healthcare industry are IBM (American multinational technology and consulting corporation) has announced that Manipal Hospitals' communal and training facilities will implement a cognitive computing platform "Watson for Oncology," guided by Memorial Sloan-Kettering that analyses data to recognize evidence-based treatment options, helping oncologists to offer cancer patients with personalized healthcare. San Francisco-based Fitbit Inc. has launched fitness-tracking wristbands across 300 towns in India. A Chennai-based healthcare technology firm (Attune Technologies Pvt

Ltd), has raised US\$ 10 million in a Series B funding from Qualcomm Ventures and Norwest Venture Partners in array to expand its digital healthcare solutions from the 200 hospitals and laboratories to 25,000 facilities globally. Some of the main initiatives taken by the Indian Government to promote healthcare industry are launching of "Sehat" (Social Endeavour for Health and Telemedicine) to empower rural citizens by offering access to information, skills, and other services in different sectors though the intervention of digital technologies, providing diagnostic treatment, free drugs along with insurance cover to treat serious diseases under the National Health Assurance Mission. The E-health initiative, which is a part of Digital India drive, aims at offering economical and effective healthcare services to all citizens. This program can help to facilitate people to maintain health records using eKYC data of Aadhaar number.^[14]

There are concerns regarding the variable quality of the RWE data; in fact, this is the biggest challenge in credible RWE generation.^[21] Other challenges include including timely data collection, the investment required for data collection, dealing with missing data, and any bias in the data.^[22] Possible solutions to improve data quality include careful design and testing of data collection tools, and providing proper training for site coordinators to ensure data quality.^[22]

CONCLUSION

We have already taken a baby step for approaching toward RWE but still require many arms of Indian healthcare system to strengthen and take giant leap to implement RWE in India. RWE pervades clinical and commercial conclusions with the insights and scientific proof points which are vital for success in today's healthcare environment. The Indian market is grasping up with the principle of HEOR, thereby exhibiting the value of real-world insights in healthcare decision making. A confounding amount of healthcare data is already generated in India from its government-private hospitals, primary health centers, and health insurers. The data, however, need to be classified to standard formats to maintain privacy, security, intellectual property. Big data can enable identification of gaps in the Indian healthcare system and bring down costs. An ideal shift in the Indian healthcare industry can thus be expected. Standardization and synchronization across different RWD resources could be achieved by collaborative partnerships within the healthcare industry to make it more prolific and industrious.

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Conflicts of interest

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