



Scope of patient registries for rare diseases in India

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ABSTRACT

Rare diseases are difficult to treat and research upon and signify a global medical concern. There have been crucial advances in research and funding on rare diseases in several countries. The challenge is immense for India because of its large population and the extensive geographical territory, hence it is essential to understand the natural history and long term treatment outcomes associated with these diseases to tackle the challenges on related research and reforms on a global scale. Patient registry is one of the viable and robust tools to achieve these objectives.

Keywords: Patient Registries, Rare Diseases, Randomized Controlled Trials (RCT), Patient-Centered Outcomes Research (PCOR).

INTRODUCTION

Definition of rare disease: There is no universally accepted definition for rare disease. Some definitions are based on the number of people alive with a disease, and other definitions consider factors such as treatments options or the severity of the disease. A generally acceptable definition of a rare disease is “a disease with less than 100 patients per 100,000 population”. A rare disease with less than two patients per 100,000 population is described as an ultra-rare disease. Rare and ultra-rare diseases are also known as orphan and ultra-orphan diseases respectively^[1].

Worldwide burden: There are more than 7000 types of rare diseases and disorders identified worldwide. Thirty million people each in the United States and Europe are afflicted with rare diseases. As per estimates, 350 million people worldwide suffer from rare diseases. Most of the rare diseases (80%) are genetic in nature and affect a person's entire life, even if symptoms do not appear immediately^[2]. Despite efforts, in most countries, sufficient data to predict prevalence and describe associated morbidity and mortality of rare disease is not readily available. In such a scenario, the economic burden of most rare diseases is unknown and cannot be adequately estimated from the existing data sets^[3].

Indian scenario: India is the second highly populated nation in the world. Therefore, there are many patients with rare diseases seeking treatment. It was statistically estimated that, in India, the rare disease and disorder population was 72,611,605 as per published data of national population census of 2011 or later^[1].

Research and development: Rare diseases are difficult to research upon and carry distinct challenges. Since the patient pool is very small, it often results in inadequate clinical experience within different centers. Therefore, the clinical explanation of rare diseases may be skewed or partial. Individual case reports or small case series limit the understanding of the natural history of the disease. In rare diseases, it is either extremely difficult or not feasible to achieve adequate sample size and follow up to assess treatment outcomes vide Randomized Controlled Trials (RCT). The challenge becomes even greater as rare diseases are chronic in nature, where long term follow up is particularly important. As a result, rare diseases lack published data on long-term treatment outcomes and are often incompletely characterized^[4].

Even though bodies like US Food and Drug Administration (FDA)^[5] and National Institutes of Health (NIH)^[6] have been granting funds for research on rare diseases, approximately 50% of rare diseases do not have a disease specific foundation for research and support^[2].

DISCUSSION

Definition of patient registry: A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes^[4].

Patient registry and RCT: From a clinical standpoint there are considerable differences between efficacy and effectiveness of a therapy. Clinical trials assess the clinical efficacy of new treatments and are based on “ideal protocol”, which differs from routine clinical practice when the treatment is implemented in an actual healthcare setting^[7]. Registries can provide data on effectiveness of interventions in a real-world setting. A patient registry can be a powerful tool to assess the effectiveness and monitor the safety of a treatment. It also can describe the natural history of a disease, cost-effectiveness of healthcare products and services, real-world view of clinical practice, patient outcomes, factors that influence prognosis, quality of care and quality of life^[4].

Patient registry in rare disease: In the domain of rare diseases, patient registries and databases are the key instruments for the development of clinical research, leading to improvement of patient care and healthcare planning as well as outcomes on economic, social and quality of life^[7]. A rare disease registry can also supplement the formation of an international community of expert physicians who can collaborate and develop recommendations on the clinical management of patients^[4]. The consistent longitudinal collection of patient data enables the foundation of standards of care and radically improves patient outcomes and life expectancy even in the absence of new treatments. Rare disease patient registries are considered as crucial infrastructure tools for interpreting basic and clinical research into therapeutic solutions making them building blocks of any sound policies on rare diseases. This has elevated their status to one of a major precedence for all stakeholders^[8]. Patient registries also provide an inventory of patients for a particular disease/rare disease and aid in re-contact for clinical research^[7]. It collects data on the natural history of the disease and evaluates patient reported outcomes. In the long run, it facilitates access to care and establishes evidence-based treatment. A rare disease registry also aids in bringing different stakeholders onto a single platform where epidemiologists, physicians, pharmaceutical companies, patient representatives, patient advocacy groups, voluntary organizations, registry management organizations and other relevant stakeholders collaborate for a cause.

Patient registry in rare diseases in India: India is the second highest populated country in the world, and it has a substantial share of rare disease population. Patient registries are instrumental in monitoring prevalence and incidence of rare diseases. Since patient registries are basically non-interventional, longitudinal and observational by design, they are well-suited tool to study the etiology and natural history of such diseases and assess clinical effectiveness and safety of a therapy. Furthermore, in case of rare diseases, a patient registry may provide an inventory for re-contacting patients. From an Indian standpoint for rare diseases, all these factors are pertinent.

Challenges in conduct of patient registries: Patient registries require extensive time, manpower and financial investment. There are no uniform, accepted standards currently available to govern the collection, organization, or availability of data for rare disease patient registries. Considering the interest of patients, it is of utmost importance that collaborative efforts of stakeholders at all levels are maintained to establish and manage such registries and derive relevant outcomes in the most effective manner. The existence of data-sharing barriers calls for the development of globally accepted definitions, classifications, data standards, favorable and congruent policies and resources facilitating data sharing and pooling^[8]. Enhancing the completeness and quality of the data, which needs systems and resources for data validation and management is a major challenge^[9]. To improve data collection and data quality, additional efforts may be necessary as rare disease registries face unique challenges. These may comprise site visits, ongoing training programs and regular audits of the data for completeness^[4].

Patient registries have been in place for long, but rare disease patient registries have some additional features which make them specific^[7]:

- The paucity of cases and the complexity of these diseases demand coverage of larger geography for data collection which usually involves multiple transnational collaborations and exchange of data
- It is necessary that family related cases are traceable as most of the rare disease are genetic in origin and may have one family member affected
- The financial implications to establish and maintain a patient registry are nearly equal for a common disease and a rare disease. But, it is more difficult to obtain budgets for a rare disease patient registry

Recommended minimum standards for registries used for Patient-Centered Outcomes Research (PCOR)^[10]:

Though the conduct of a patient registry is extensive in process and diligence, the recommended minimum standards for design, conduct and analysis of disease or treatment registries for PCOR are listed below:

- The basic block of starting a patient registry begins with the development of a formal study protocol. This protocol needs to be specific about the patient population, subgroups, exposure of interest, measures of effect, study design, objectives, clinically relevant endpoints, data sources, linkage plans, measures of effect, sample size, statistical power, use of standardized dictionaries and sources of bias, as per applicability
- Plans for data analysis that correlates to major aims to be specified
- Outcomes that are clinically meaningful, patient-centered and relevant to decision-makers are to be considered
- For studies which involves linkage of registry data to another data source, data linkage plans to be adequately described
- Follow-up to be planned based on registry objectives
- Validated tests and scales to be used
- When using previously collected data, potential for re-identification to be addressed as per applicable regulations
- If previously collected data is being used then assessment of the legal and patient privacy conditions under which the data was initially collected to be made and its impact to be addressed
- Adequate steps to be taken to ensure data quality
- Any modification to the protocol to be explained and documented
- Data to be collected consistently
- Patients to be enrolled and followed-up systematically
- Loss to follow-up to be monitored and minimized
- Confounding to be addressed using appropriate statistical techniques
- Sensitivity analysis to be used to determine the impact of major decisions
- The extent of missing data to be assessed and reported
- Sufficient data needs to be provided in the reports of the registry findings allowing assessments of the study's internal and external validity

CONCLUSION

Since rare diseases are relatively difficult to understand and treat, collaboration on a global scale will aid in tangible results. India being the second highest populated country in the world, with roughly 70 million people suffering from rare diseases, the necessity of it contributing to rare disease outcomes becomes crucial. Patient registries may serve as appropriate tool to aid in understanding the natural history and clinical characteristics of rare diseases and assess the long-term outcomes of treatment.

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