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RESEARCH ARTICLE

RARE DISEASE REGISTRIES- PURPOSE, CHALLENGES & SOLUTIONS

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Abstract

Rare diseases are defined, as any condition or disease having a low prevalence in the United States and the European Union. There is a scarcity of relevant knowledge and experience with rare diseases due to an incomplete understanding of the underlying disease mechanisms, relevant clinical endpoints, lack of correct diagnosis in the population. These challenges create a unique need for cooperation and infrastructure. Data registry is a critical tool in building a comprehensive knowledge base for these rare diseases. Our paper will provide the overview of patient registries for rare diseases, current use, limitations, challenges and proposed plan for improvement.

Introduction:-

Rare diseases are defined, as any condition or disease having a low prevalence in the United States and the European Union(Barr et al., 2015).Rare diseases could be life threatening or chronic debilitating conditions. Rare diseases are rare in occurrence so the patient data to understand these diseases is insufficient. There is a scarcity of relevant knowledge and experience with rare diseases due to an incomplete understanding of the underlying disease mechanisms, relevant clinical endpoints, lack of correct diagnosis in the population. Patients suffering from these diseases require multidisciplinary management approaches to reduce hospitalization rates, morbidity, and mortality in these patients. The biggest challenge in the current patient care of rare diseases is knowledge gaps in understanding of etiopathogenesis of disease, risk factors, diagnostic markers, prognostic factors, risk calculators, quality of life parameters and evidence-based multidisciplinary care(Barr et al., 2015). These challenges create a unique need for cooperation and infrastructure. Research initiatives and funding is needed to understand the distribution and etiopathogenesis of these diseases better and develop new biologic agents as treatment modalities.

Data registries help in the systematic collection of clinical, genetic, and biologic data for further research in relevance to the better understanding of the risk factors, pathogenesis, clinical symptomatology, diagnostic and treatment modalities, and prognostic factors(Barr et al., 2015).Rare disease registries have patient data to support research activities and contribute to evidence-based approaches to improve patient care.Thedata registries serve as observational database and prospective long-term patient registries. Data registry is a critical tool in building a comprehensive knowledge base for these rare diseases. Vital data elements in this database comprise of prevalence, distribution of disease patient symptomatology, and natural history of the disease. Registry planning, design, and implementation are essential to meet the healthcare goals and objectives of the targeted disease(Barr et al., 2015).

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For a better understanding of the disease mechanisms, it is essential to identify more patients. Increase in sample size increases the power of the study. Rare diseases have broader scope and objectives as compared to typical disease registry due to significant knowledge gaps. The absence of treatment guidelines in rare diseases, more use of adjuvant therapies, lack of understanding of these conditions, lack of available biomarkers provide opportunities for more research. Novel approaches are required to both define rare diseases and their treatment guidelines. Rare disease registries in contrast to traditional disease registries are less well-known diseases, and hence for, the advocacy and support groups are smaller, and their roles are also different(Barr et al., 2015).

Our paper will provide the overview of patient registries for rare diseases, current use, limitations, challenges and proposed plan for improvement.

Rare Disease Registry Objectives and Scope:-

In rare diseases we have limited patient population due to the low prevalence of these diseases; therefore clear research agenda does not exist, standard treatment guidelines are missing. Patient registries for rare diseases are an intuitive first step to understand the geographical distribution, basic demographics and clinical characteristics of the disease. The scope of these registries may evolve from a means for a better understanding of the disease characteristics to a mechanism for research funding and initiatives to attract more stakeholders. Ideally, a well-designed registry provides a database that supports the needs of the stakeholders efficiently and eliminates barriers to scientific progress(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).

Rare diseases include both inherently rare diseases and demographically rare diseases. Current objectives of rare disease registries are patient identification, recruitment, disease classification disease-specific outcomes. Design of the registry is based on the research plan, funding, and prevalence of the disease(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).

The Practical Utility and Implications

1. To connect stakeholders (patients, families, physicians, care providers.): Many rare diseases are genetic diseases. Genetic linkage creates curiosity among the family members of affected individuals to know more about the disease, clinical symptomatology, risk ratio, patterns of disease. Family members are driven by their desires to understand more about the disease, its natural course, alternative treatment modalities clinical courses and outcomes. The anxiety of the patient and their family members is enhanced when they are unable to find an expert and genetic counselor to seek proper advice regarding the condition. Inadequate knowledge about the disease amongst healthcare providers further complicates the situation(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).
2. Registry meetings provide an opportunity for patients, families, and clinicians to interact with each other and share their personal and professional experiences (International Rare Diseases Research Consortium, 2013). These meetings include lectures, discussions, workshops, webinars as an educational resource. The advent of social media has increased the participation of patients in their caregiving process. The patient can connect to advocate support groups for assistance. They can relate to new upcoming researches and get enrolled in recruiting clinical trials to advance therapeutic options further. Similarly, clinicians can connect to researchers, other clinicians to learn more about available innovative treatment options. Registries offer essential information in the disease area to healthcare providers for advising and counseling the patients(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).
3. To learn the disease etiopathogenesis, mechanisms and disease progression: Stakeholders often initiate registries to learn about the typical presentation of the disease and natural course. With more advancement in diagnostic techniques, genetic, physiological and biochemical testing the disease descriptions are broadened regarding presentation and specific outcomes(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015)

With the advent of better therapeutic options, adjuvant modalities, classical description, and classification of the disease no longer apply. New complications can be recognized. New treatment change life expectancy and so the trajectory of disease changes drastically. A versatile disease registry gathers data from broader areas of safety, efficacy, diagnostic and prognostic information(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).

Disease registries help in understanding the natural history of the disease including, the burden of disease, disease progression, genotypic alleles, phenotypic traits, clinical endpoints that may be used for drug development. These registries help to understand the quality of life and economic burden of these diseases(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).

To support research:
The registries also support basic and clinical research. Clinical research helps in understanding complications and specific disease outcomes of the disease. These complications include autoimmune complications, unusual infections, and malignancies. The comprehensive database helps to address critical clinical questions for the benefit of the patients. Registries maintain a centralized biorepository that can serve as a research source for understanding diseases at genetic, molecular and cellular level. The existing parallel clinical data in the registry allows for the assessment of genetic and environmental disease modifiers(Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Breitner et al., 2017; Barr et al., 2015).

Support drug development process:
Rare disease registries support the drug development process. The use in the drug development process attracts stakeholders interested in developing drugs for rare diseases. Developing a treatment option for a rare disease provides information about the pathophysiology of the disease. Rare disease registries also provide information to regulators about available treatment options and help them to relax drug registration requirements if no treatment options are available (Food and Drug Administration, 2016).Ahmed et al. (2019) discussed the role of patient registries in regulatory decision-making on medicines. The authors recommended proposals to consolidate registry value in patient and public health. Registries have a significant role in drug in supporting drug development process (Ahmed et al., 2019).

To contribute in Global Policy making:
The CONCORD programme collected data from 320 population-based cancer registries in 71 countries and used this data to derive an international comparison among health care systems providing cancer care and contribute to the evidence base development of global policy on cancer control (Allemani et al., 2018).

Challenges and Proposed plan of Improvement:
Rare disease registries present governance challenges due to international collaboration with stakeholders(Adams et al., 2013). Governance challenges include funding, privacy, outreach, information, ownership, agenda, partnerships, publications.Breitner et al. (2017) conducted a systematic literature review on dementia registries, identified gaps in the existing registries and recommended that registries are long-term data repositories and to maintain quality of the repositories it's important to maintain adequate funding of the repositories. Federal government should fund the rare disease registries to maintain their integrity (Breitner et al., 2017).

Rare disease registries pose unique research challenges. Rare diseases affect a small number of patients hence for the clinical experience is limited(Adams et al., 2013).The clinical description of rare diseases is inadequate. Systemic literature has limited number of case reports, case series; therefore the understanding of the natural history of rare diseases is limited. Furthermore, the small sample size makes clinical trials extremely difficult to assess treatment outcomes. In rare diseases long-term follow is difficult, this further adds barrier in the conduct of clinical trials (Adams et al., 2013). As a result, rare diseases are incompletely characterized due to the lack of published data on disease course and treatment outcomes(Adams et al., 2013).

We suggest a plan that will undoubtedly address this challenge. Ongoing, international, longitudinal disease registry, open to voluntary participation by patients, physicians and researchers should be established. Every piece of data including patient demographics, clinical manifestation, treatment regimens, laboratory panels, radiological findings, quality of life outcome measures should be entered and analyzed to address the current challenges of the rare disease. Reliable, comprehensive registry will serve as an educational resource not only for care providers but also for patients. Integrity and objectivity of the data will help physician-investigators worldwide in designing the medical and scientific agendas of the registry. With the growth of the registry and the availability of data on rare diseases interest in unique patient population and specific aspects of the disease will continually emerge; as a result research initiatives can be launched continuously. The collective clinical experience of the registry at international level will lead to the development of recommendations for evaluation and monitoring of the disease (Bartek et al.,

2011). These registries will also help in creating disease awareness amongst patients, families, and communities at the global level(Bartek et al., 2011).

Further, we suggest changing the technology platform to simplify data entry to maintain data completeness and accuracy and ease data access for patients and physicians. Registries should allow data download to support research at every level. We also propose the application of research tools in the registry database for analysis of existing data to plan management regimens further. These technological tools will help in addressing clinical and scientific questions and will assist in designing useful disease management tools. Our plan will assist in establishing a larger, better- connected worldwide community of physicians and patients who can share information globally and improve best practices and build awareness of rare diseases to optimize patient outcomes. A global registry with the comprehensive patient database will serve as a resource of study subjects for focused investigation on rare diseases(Ayme et al., 2012). Our proposed plan will help the sponsors to identify academic and professional interest in the registry findings and will support in engaging investigators in the study. These sponsor initiatives will assist in building an active approach to disease management practices. Our plan also proposes site engagement in rare disease registries, because of the limited number of patients. These recommended steps will build networking at a global level that can bolster investigator's motivation.Ahmed et al. (2017) performed a quality check assessment on the I-DSD and I-CAH Registries, to identify their strengths and weaknesses and to assess whether these registries are in agreement with the legal and ethical standards set by expert organizations. The authors found that I-DSD and I-CAH Registries are in compliance with the standards of expert organizations(Ahmed et al., 2017). Registries should be assessed for data validity and accuracy as part of continuous quality improvement. Our plan proposes continuous assessment of registries for quality check and improvement.

Conclusion:-

Existing literature suggests that rare diseases have a low prevalence, scarce information, inaccurate diagnosis and appropriate identification of patients with the rare disease is a global issue(Adam et al., 2013; Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Ahmed et al., 2017; Breitner et al., 2017; Barr et al., 2015). Inconsistencies in diagnostic criteria's and inadequacies in data gathering procedures reflect lack of information. Global awareness about rare diseases, improved access to information fostered by electronic communication and social media, knowledge about rare diseases should increase(Adam et al., 2013; Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Ahmed et al., 2017; Breitner et al., 2017; Barr et al., 2015).

Stakeholders have both convergent and divergent agendas with disease registries. Registry data serve as a source of information to stakeholders. The vision of disease registries has engaged a variety of commercial application providers in the field. Disease registries help in developing treatment algorithms that allow more choices for physicians and patients. Disease registries fill in the blanks about outcomes that are not addressed. The productive partnership of stakeholders at the global level can be a powerful agent in the success of a product in development or evaluation(Adam et al., 2013; Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Ahmed et al., 2017; Breitner et al., 2017; Barr et al., 2015).

Global multidisciplinary cooperation for rare disease registries in a more efficient way will serve the needs of stakeholders. Technological advances, means of integrating data sources, will generate a more streamlined process for data providers and analysts. The growth of web-based communities and social media will increasingly help in registry data collection as community building across geographical boundaries continues to become more straightforward(Adam et al., 2013; Bartek et al., 2011; Ayme et al., 2012; Alonso Olmo et al., 2019; Ahmed et al., 2017; Breitner et al., 2017; Barr et al., 2015).

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