Rare diseases overview for a clinical trial perspective



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1. Introduction

Rare diseases are those diseases which affect a very few number of people. They are also termed as orphan diseases and are associated with improper management, long term deterioration, adverse effects and fatalities as well. As per the Committee for Orphan Medicinal Products (COMP), European Medicines Agency (EMA), a disease can be categorized as a 'rare disease'(RD) when the number of affected individuals is less than 5 members across 10,000 individuals in the European Union EU (1). The United States Food and Drug Administration (USFDA) designates a disease as 'rare' if the number of people in the USA suffering from it are less than 2,00,000 i.e. less than 6.4 persons in 10,000 (2). The WHO specifies it as a condition occurring in 1 or lesser persons per 1000 individuals. India has not given any specification for disease categorization based on prevalence but segregated based on treatment/management options (3). In case where fewer than 2 patients among 100,000 suffer from a disease, then it is termed as an 'ultra-rare' disease (4).

2. Rare disease burden

In the EU 6000 - 7000 RDs have been identified, most of them being of genetic origin. Although a RD affects very less individuals, together RDs affect approximately 30 million in the EU and 9, 20,000 people in Spain as per 2022 data (5). In the USA too, 7,000 RDs affect more than 30 million people (2). India has around 100 million patients suffering from RDs. In addition to the global count of 7000-8000 known RDs India reports 450 more (6). Africa too is no exemption to these numbers related to RDs. 80% of RDs have been identified to have genetic origin, and 50–75% being paediatric onset (7,8).

Quantification of the prevalence of RDs itself has been a challenge due to lack of awareness, the disease being undiagnosed and unreported /under reported. Currently healthcare systems make wide use of electronic medical record (EMR) systems to perform studies effectively across large sections of population in order to identify and characterize individuals with RDs. The team from Clinical Sequencing Exploratory Research (CSER) and Electronic Medical Records & Genomics (eMERGE) employed genomic information from the EMR data and identified the subjects with RDs (9). However, it has been noticed that genetic information still had missing ends.

Tsevdos, D. *et al*. (2024) developed an innovative digital phenotyping algorithm to find out from the EMR, paediatric subjects who had a high probability of being susceptible to genetic disorders, thus aiding to provide appropriate treatment and avoid errors. They also addressed about PheIndex algorithm, which is a boon to detect rare genetic disorders in children, thereby solving the problems such as under diagnosis and delayed diagnosis issues (10).

3. Classification of Rare Diseases

RDs may be categorized in various ways. Table 1 below presents some RDs based on the organ system affected.

Table 1. Brief list of organ system wise categorization of RD

S. No.	Category	Disease name	Remarks	Ref.
1.	Allergic and Immunologic disorder	Agammaglobenemia or hypogammaglobulinemia	Characterized by low or absent mature B cells, occurs in infants around 6 months age	(11)
2.	Cardiac and vascular disorders	Eisenmenger syndrome	Untreated congenital cardiac defects leading to pulmonary hypertension and cyanosis	(12)
3.	Endocrine and metabolic disorders	Gaucher's disease	Genetic disorder - deficiency of the enzyme glucocerebrosidase	(13)
4.	Gastroenterologic conditions	Dubin-Johnson syndrome	Genetic disease -mutations in the bilirubin transporter MRP2 leading to jaundice and conjugated hyperbilirubinemia	(14)
5.	Hematologic disorders	Paroxysmal nocturnal hemoglobinuria	Acquired hematopoietic stem cell (SC) disorder which leads to the lysis of red blood cells, hemoglobinuria, thrombotic events, etc.	(15)
6.	Skin and soft tissues conditions	Epidermolysis bullosa	Genetic dermatoses characterized by mucocutaneous fragility and blister formation	(16)

The other categories include rare bacterial, fungal, viral, parasitic disorders; rare nutritional, congenital, environmental, psychological, newborn diseases; chromosomal aberrations, chromosomal disorders; glycogen storage & lysosomal storage disorders and many more (6).

The National Policy on Rare Disorders (NPRD) 2021 segregated and described elaborately RDs based on clinical considerations. A brief summary is given below (3).

Group 1: Diseases suitable for a one-time curative treatment like SC transplantation (e.g. Lysosomal storage disorder, etc.), organ transplantation (e.g. Fabry disease, maple syrup urine disease, etc.)

Group 2: Diseases that need long term / lifelong treatment which is relatively less expensive and benefit has been documented in literature; these diseases need an annual or more frequent monitoring: like those managed by special diet (e.g. Phenylketonuria, galactosemia), or other hormonal and medicinal therapies (e.g. Osteogenesis Imperfecta, Cystic fibrosis, etc.)

Group 3: Diseases for which definitive treatment is existing but it is difficult to make optimal patient selection for benefit, is highly expensive and treatment has to be administered lifelong. Good long term outcomes of the treatment have been seen for some diseases in this group (e.g. Gaucher disease, Pompe Disease, etc.), and for some literature/ scientific data is less or the treatment costs are high (e.g. Duchenne Muscular Dystrophy, Wolman Disease, etc.)

4. Treatment

Despite promising diagnostic advancements, only 5% (about 500 out of 7,000) of the identified RDs, those with known molecular causes, have approved treatments (17,18). Gene therapies have received FDA approval, with numerous others undergoing clinical evaluation. Utilizing adenoviral vectors, a common tool in gene therapy, shows promise in treating various diseases, including hematological disorders, genetic conditions, rare diseases, and tumors (19,20). Some marketed therapies are (21):

- ALLOCORD (HPC, Cord Blood) from SSM Cardinal Glennon Children's Medical Center
- BREYANZI (Lisocabtagene Maraleucel) by Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
- LUXTURNA (Voretigene Neparvovec-Rzyl) developed by Spark Therapeutics, Inc.
- IMLYGIC (Talimogene Laherparepvec) from BioVex, Inc., a subsidiary of Amgen Inc

Stem cells: Hematopoietic stem cell transplantation (HSCT) and white umbilical cord blood stem cells (UCBT) (e.g. used for cytomegalovirus infection); Antibody therapy; Enzyme replacement therapy (e.g. FDA approval of Genzyme's recombinant glucocerebrosidase in 1994) have been the other treatment options (20).

5. Clinical trials for orphan drugs

From the overview of RDs. it is self-explanatory how diverse the diseases and their therapies are. Orphan drug is a drug intended for use in a RD. In the development pathway for a new drug/ therapy, one of the stages is the conduct of clinical trials. The usual pathway includes conduct of Phases 1, 2 and 3 and submitting a New Drug Application. In order to conduct a clinical trial, the study protocol has to be drafted and then approved by the Institutional Ethical committee. The investigators brochure and the informed consent form are integral parts of the protocol along with the details of compensation and other relevant information about the rights of the trial participants. Generating an informed consent form itself would be a challenge when it comes to orphan drugs. Leaving aside financial concern, developing therapies for rare disorders is fraught with challenges. The constraints of small populations magnify these necessities into formidable hurdles (22). For a RD, there is not much validated information available to be provided to the study volunteers and secondly getting participants enrolled is itself a challenge. With more than 50% RD being paediatric, ethical issues pose a concern too to conduct clinical trial. Some more factors are:

- **Trial designs**
  In research settings, the randomized controlled trial is frequently regarded as the benchmark for establishing efficacy but this design is challenging to execute in case of RDs.

- **Patient history and registries**
  Lack of understanding the disease progression hinders identification of key milestones, assessment of crucial disease aspects, inclusion/exclusion criteria, and defining clinically significant differences

- **Subject recruitment and retention**
  Recruiting eligible participants in a timely manner poses a challenge with patients being at different disease stages, different geographic locations and also may have physical impairment to participate in a trial.

- **Drug development and funding**
  Drug development is costly and time-consuming, particularly for rare, fatal paediatric disorders lacking industry funding. Funding agencies prioritize projects with broad public health impact amid economic competition.

- **Training the researchers**
  A shortage of clinical researchers proficient in designing and conducting trials exists when it comes to RDs (22).

- **Choosing study endpoint**
  Endpoint selection is a challenge due to the lack of proper understanding of the RD. Small study sizes call for endpoints with large effect sizes. For diseases impacting multiple organ systems, endpoints evaluating mean change within individuals across multiple parameters may be preferable (23).

6. Regulatory considerations for orphan drug clinical trials

As per USFDA, for an Orphan drug, upon approval, the sponsor benefits by obtaining tax credits for qualified clinical trials, getting exemption from user fees and securing potential 7 years of market exclusivity. 21CFR Part 316 on orphan drug allows a sponsor to provide and investigational drug under a treatment protocol, to those who need it (24). USFDA also supports approvals of orphan drugs based on early phase, nonrandomized, unblinded trial designs with less subjects unlike studies on nonorphan drugs (25). Central Drugs Standard Control Organization (CDSCO) has considered giving a waiver of conducting clinical trials on Indian population for drugs approved outside India if the drug is an orphan drug. CDSCO also provides scope for expedited review for orphan drugs (26). The New Drugs and Clinical Trial Rules 2019 gives a provision that sponsor need not pay any fee for conduct of a clinical trial in the case of orphan drugs.

7. Conclusion

Approved treatment options are desperately needed to treat patients with RDs. The regulatory bodies and policies of various nations across the globe are aligned to facilitate, fund and support clinical development and the approval of drugs to address RDs. Technological advancements too using organ on chip for clinical trials/ AI tools aid in diagnosis and approval of therapy for RDs (27–29). There is tremendous scope for collaborative work in the health care sector to tackle RDs.

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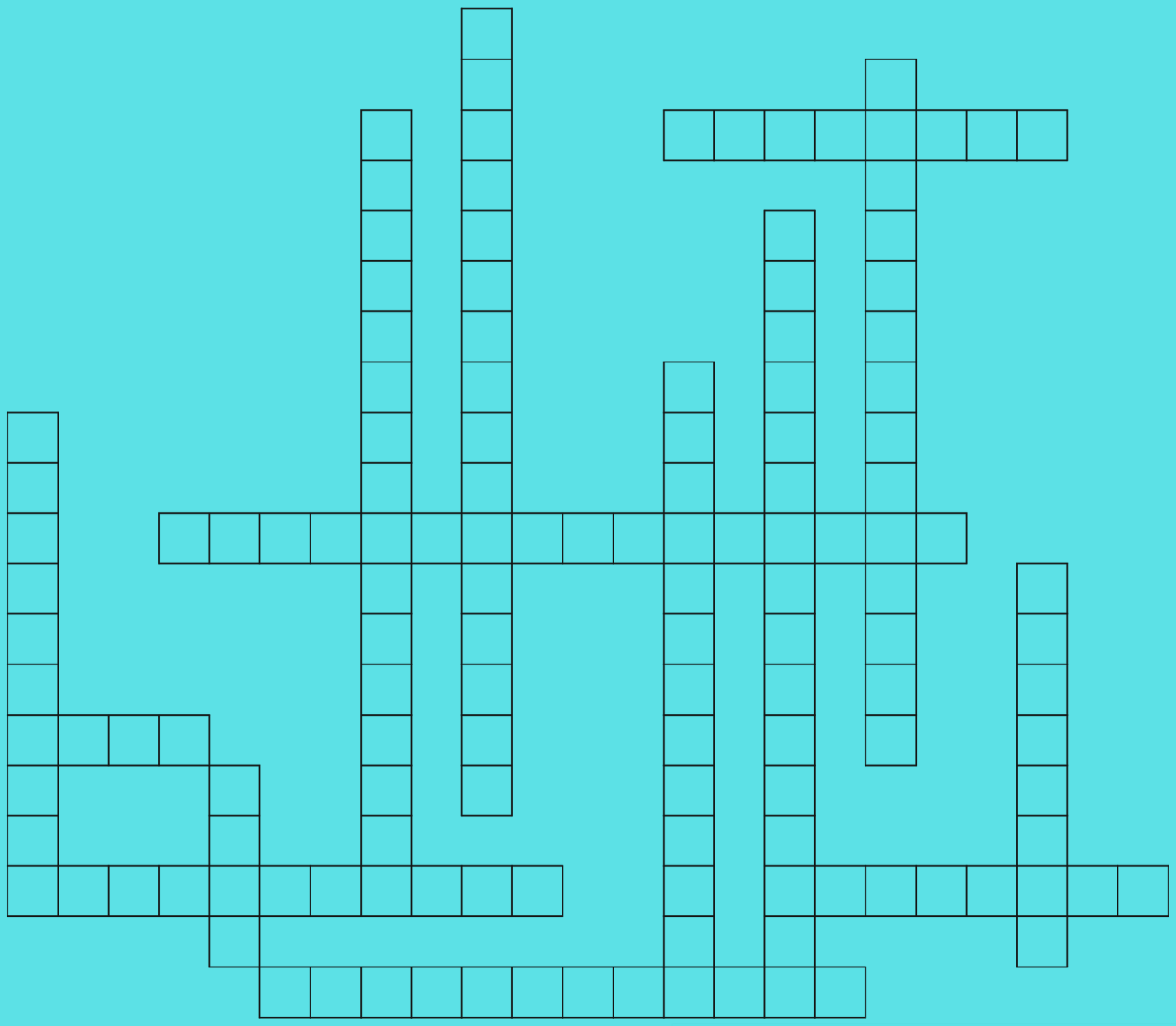
Complete the crossword puzzle below



Across

4. Database of information on rare diseases and orphan drugs for all publics
8. Rare disease associated with adrenal glands
10. Indian Organization for Rare Diseases
12. Rare autoimmune disorder causing abnormal skin thickening
13. Rare skin condition
14. Rare Lysosomal Storage Disease

Down

1. Rare hereditary disorder that causes mental retardation
2. Rare Disease associated with deficiency of glucocerebrosidase enzyme
3. Rare autoimmune disorder involving lymphocyte
5. Rare autoimmune disorder affecting muscles
6. Rare gluten disorder
7. Rare disease involving inflammation of blood vessels
9. Rare aging related disease
11. Group of leading companies committed to helping people with rare diseases

Answers are on page 185