NATIONAL POLICY

FOR

RARE DISEASES, 2021

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1. Background

Ministry of Health and family Welfare, Government of India formulated a National Policy for Treatment of Rare Diseases (NPTRD) in July, 2017. Implementation of the policy, however, faced certain challenges. A limiting factor in its implementation was bringing States on board and lack of clarity on how much Government could support in terms of tertiary care. Public Health and Hospitals is primarily a State subject. Stakeholder consultation with the State Governments at the draft stage of formulation of the policy could not be done in an elaborate manner. When the policy was shared with State Governments, issues such as cost effectiveness of interventions for rare disease vis-à-vis other health priorities, the sharing of expenditure between Central and State Governments, flexibility to State Governments to accept the policy or change it according to their situation, were raised by some of the State Governments.

In the circumstances, though framed with best intent, the policy had implementation challenges and gaps, including the issue of cost effectiveness of supporting such health interventions for limited resource situation, which made it not feasible to implement. Given the challenges in implementing the policy, the need for wider consultation and recommendations, a decision was taken to reframe the National Policy for Treatment of Rare Diseases. An Expert Committee was constituted by Ministry of Health and Family Welfare in November, 2018 to review the NPTRD, 2017. The Terms and References of the Expert Committee are given below:

a. To review the national Policy for Treatment of rare Diseases, 2017 and to suggest amendments/changes as may be required.
b. To define Rare diseases for India.
c. To draft National Policy for Rare Diseases.
d. To suggest vision and strategy in country's context.

Pending reframing the policy, the earlier policy has been kept in abeyance vide a non-statutory Gazette Notification dated 18-12-2018, till the revised policy is issued or till further orders, whichever is earlier.

Based on the report of the Expert Committee and with the approval of the competent authority, the draft National Policy for Rare Diseases, was finalized and placed in the public domain on 13.1.2020 inviting comments/views from all the stakeholders, general public, organisations and States/UTs.

Comments/suggestions received from general public/organisations/stake holders/States/UTs were referred to DGHS for examination and to submit recommendations. DGHS constituted an Expert Committee to examine the comments/suggestions received. Based on the examination of the comments/suggestions received and recommendations of the same Expert Committee and after further deliberation, the National Policy for Rare Diseases has been finalised.

2. Rare Diseases: Issues & Challenges

The field of rare diseases is complex and heterogeneous. The landscape of rare diseases is constantly changing, as there are new rare diseases and conditions being identified and reported regularly in medical literature. Apart from a few rare diseases, where significant progress has been made, the field is still at a nascent stage. For a long time, doctors, researchers and policy makers were unaware of rare diseases and until very recently there was no real research or public health policy concerning issues related to the field. This poses formidable challenges in development of a comprehensive policy on rare diseases. Nevertheless, it is important to take steps, in the short as well as long term, with the objective of tackling rare diseases in a holistic and comprehensive manner.

2.1 The varying definitions of rare diseases

WHO defines rare disease as often debilitating lifelong disease or disorder with a prevalence of 1 or less, per 1000 population. However, different countries have their own definitions to suit their specific requirements and in context of their own population, health care system and resources. In the US, rare diseases are defined as a disease or condition that affects fewer than 200,000 patients in the country (6.4 in 10,000 people). EU defines rare diseases as a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 people. Japan identifies rare diseases as diseases with fewer than 50,000 prevalent cases (0.04%) in the country. A summary of the prevalence based definitions of rare diseases used in various countries is tabulated below:

Table 1: Definitions of Rare Disease in different countries

S No.	Country	Prevalence less than per 10,000 population
1	USA	6.4
2	Europe	5.0
3	Canada	5.0
4	Japan	4.0
5	South Korea	4.0
6	Australia	1.0
7	Taiwan	1.0

Source: *The I.C. Verma Sub-Committee Report 'Guidelines for Therapy and Management'*

The use of varying definitions and diverse terminology can result in confusion and inconsistencies and has implications for access to treatment and for research and

development. According to a study[1,] that reviewed and analysed definitions across jurisdictions, most definitions, as discussed above, appear to consider disease prevalence, but other criteria also apply sometimes, such as - disease severity, whether the disease is life-threatening, whether there are alternative treatment options available, and whether it is heritable. The study found that relatively few definitions included qualifiers relating to disease severity and/or a lack of existing treatments, whereas most definitions included a prevalence threshold. The average prevalence thresholds used to define rare diseases ranges among different jurisdictions from 1 to 6 cases/10,000 people, with WHO recommending a prevalence less than 10/10,000 population for defining rare diseases. The study concluded that attempts at harmonising the differing definitions, should focus on standardizing objective criteria such as prevalence thresholds and avoid qualitative descriptors like severity of the disease.

However, it has been contested that disease prevalence alone may also not be an accurate basis for defining rare diseases, as it does not take into account changes in population over time. Hence, some have suggested that a more reliable approach to arriving at a definition could be based on the factors of – a) location - a disease which is uncommon in one country may be quite common in other parts of the world; b) levels of rarity - some diseases may be much more rare than other diseases which are also uncommon; and c) study-ability - whether the prevalence of a disease lends itself to clinical trials and studies.

This underscores the need for further research to better understand the extent of the existing diversity of definitions for rare diseases and to examine the scope of arriving at a definition, which is best suited to the conditions in India. It shall be done on a priority basis as soon as sufficient data is available. Steps have already been taken for creation of a hospital based National Registry for rare diseases in India by ICMR.

1. [1] *Richter, T., Nestler-Parr, S., Babela, R., Khan, Z. M., Tesoro, T., Molsen, E., & Hughes, D. A. (2015). Rare Disease Terminology and Definitions – A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group [Electronic version]. Value in Health, 18, 906-914. Available at: https://www.ispor.org/rarediseases-terms-definitions.pdf*

2.2 Diagnosis of rare diseases

Early diagnosis of rare diseases is a challenge owing to multiple factors that include lack of awareness among primary care physicians, lack of adequate screening and diagnostic facilities.

Traditional genetic testing includes tests that can only address a few diseases. As a result, physicians most often provide their best guess on which tests are to be done. If the test is negative, further testing will be required using next generation sequencing based tests, or chromosomal microarray which are applicable, but expensive and time-consuming processes with interpretation and counselling issues at times.

There is a lack of awareness about rare diseases in general public as well as in the medical fraternity. Many doctors lack appropriate training and awareness to be able to correctly and timely diagnose and treat these conditions. According to a recent report[2], it takes patients in United States (US) an average of 7.6 years and patients in United Kingdom (UK) an average of 5.6 years to receive an accurate diagnosis, typically involving as many as eight physicians (four primary care and four specialists). In addition, two to three misdiagnoses are typical before arriving at a final diagnosis. Delay in diagnosis or a wrong diagnosis increases the suffering of the patients exponentially. There is an immediate need to create awareness amongst general public, patients & their families and doctors, training of doctors for early and accurate diagnosis, standardization of diagnostic modalities and development of newer diagnostic and therapeutic tools.

2.3 Challenges in research and development

A fundamental challenge in research and development for the majority of rare diseases is that there is relatively little known about the pathophysiology or the natural history of these diseases. Rare diseases are difficult to research upon as the patient pool

[2] Rare Disease Impact Report: Insights from patients and the medical community available at: https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf

is very small and it often results in inadequate clinical experience. Therefore, the clinical explanation of rare diseases may be skewed or partial. 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 characterised.

This makes it necessary to explore international and regional collaborations for research, collaborations with the physicians who work on any rare disease and with patient groups and families dealing with the consequences of these disorders. This will help gain a better understanding of the pathophysiology of these diseases, and the therapeutic effects that would have a meaningful impact on the lives of patients. There is also a need to review and where possible modify, clinical trial norms keeping in mind the particular challenges in rare diseases, without compromising on the safety and quality of the drugs or diagnostic tools.

2.4 Challenges in treatment

2.4.1 Unavailability of treatment

Availability and access to medicines are important to reduce morbidity and mortality associated with rare diseases. Despite progress in recent years, effective or safe treatment is not available for most of the rare diseases. Hence, even when a correct diagnosis is made, there may not be an available therapy to treat the rare disease. There are between 7000 - 8000 rare diseases, but less than 5% have therapies available to treat them. About 95% rare diseases have no approved treatment[3] and less than 1 in 10 patients receive disease specific treatment. Where drugs are available, they are prohibitively expensive, placing immense strain on resources.

[3] https://www.thelancet.com/journals/landia/article/PIIS2213-8587(19)30006-3/fulltext

2.4.2 Prohibitive cost of treatment

As the number of persons suffering from individual rare diseases is small, they do not constitute a significant market for drug manufacturers to develop and bring to market drugs for them. For this reason, rare diseases are also called 'orphan diseases' and drugs to treat them are called "orphan drugs". Where, they do make drugs to treat rare diseases, the prices are extremely high apparently to recoup the cost of research and development. At present very few pharmaceutical companies are manufacturing drugs for rare diseases globally and there are no domestic manufacturers in India except for Food for Special Medical Purposes(FSMP) for small molecule inborn errors of metabolism. Due to the high cost of most therapies, the government has not been able to provide these for free. It is estimated that for a child weighing 10 kg, the annual cost of treatment for some rare diseases, may vary from Rupees 10 Lakhs to more than 1 crore per year with treatment being lifelong and drug dose and cost increasing with age and weight.

Countries have dealt with this unique problem of high cost through various means that were suited to their local needs. Instruments like the Orphan Drug Act (ODA) in US & Canada, provide incentives to drug manufacturers to encourage them to manufacture drugs for rare diseases. The economic incentives & safeguards offered under the Act ensure benefits to the local patients. However, the exorbitant prices of drugs for rare diseases has led to concerns even in the developed countries about maintaining sustainability of the rare diseases funding/reimbursement programmes. The exorbitant prices have led to calls for transparency in setting prices of drugs and for price control and have even prompted scrutiny and congressional inquiries.

3. The Indian Scenario

Data on how many people suffer from different diseases that are considered rare globally, is lacking in India. The cases identified so far have been diagnosed at tertiary hospitals. The lack of epidemiological data on incidence and prevalence of rare diseases impedes understanding of the extent of the burden of rare diseases and development of a

definition. It also hampers efforts to arrive at correct estimation of the number of persons suffering from these diseases and describe their associated morbidity and mortality. In such a scenario, the economic burden of most rare diseases is unknown and cannot be adequately estimated from the existing data sets.

Although extremely challenging, considering the complexity of various diseases and the difficulty in diagnosis, there is a clear need to undertake systematic epidemiological studies to ascertain the number of people suffering from rare diseases in India.

So far only limited number of diseases has been recorded in India from tertiary care hospitals that are globally considered as rare diseases though ambit may encompass from 7000 to 8000 disorders. The commonly reported diseases include Primary immunodeficiency disorders, Lysosomal storage disorders (Gaucher's disease, Mucopolysaccharidoses, Pompe disease, fabry disease etc.) small molecule inborn errors of metabolism (Maple Syrup urine disease, organic acidemias, etc.), Cystic Fibrosis, osteogenesis imperfecta, certain forms of muscular dystrophies and spinal muscular atrophy, etc.

4. Experiences from other countries:

While preparing the policy for rare diseases in India, policies of other countries have been reviewed. In United States of America, development of drugs for rare disease is sought to be encouraged through the Orphan Drugs Act, which incentivises industry by way of market exclusivity, grants to researchers and tax incentives on expenditure incurred during evaluation of drugs for their therapeutic potential. However, critics have pointed out that pharmaceutical companies have taken advantage of this arrangement and 'gamed the system' to maximise profits. The European Joint Programme on Rare Disease mostly focuses on research. National Health Service (NHS) England, for example, provides that the treatment for Spinal Muscular Atrophy (SMA) will be made available to the youngest and most severely-affected (SMA Type 1) patients immediately by Biogen (The pharmaceutical company that manufactures treatment for SMA), with NHS England offering funding on

National Institute for Health and Care Excellence (NICE) publication of final guidance. In Singapore, a fund - Rare Disease Fund – has been created to fund five medicines to treat three rare disease conditions. In Malaysia and Australia subsidised access for eligible patients is provided for expensive and lifesaving drugs.

5. Need to balance competing priorities of public health in resource constrained settings

Rare diseases place a major economic burden on any Country and especially in resource-constrained settings. The financial capacity to support exorbitant cost of treatment, is an important consideration in public health policy development with reference to treatment for rare diseases. In resource-constrained settings, it is pertinent to balance competing interests of public health for achieving optimal outcome for the resources allocated. As resources are limited and have multiple uses, the policy makers have to make choice of prioritizing certain set of interventions over others- the appropriate choice is then to support those interventions that would provide more number of healthy life years for given sum of money while simultaneously looking at the equity i.e., interventions that benefit poor who cannot afford healthcare are prioritized. Thus, interventions that address health problems of a much larger number of persons by allocating a relatively smaller amount are prioritized over others such as funding treatment of rare diseases where much greater resources will be required for addressing health problems of a far smaller number of persons.

Hence, any policy on rare diseases needs to be considered in the context of the available scarce resources and the need for their utmost judicious utilization for maximizing the overall health outcomes for the whole of society measured in terms of increase of healthy life years.

6. Definition of Rare Diseases:

6.1 There is no universal or standard definition of rare disease. A disease that occurs infrequently is generally considered a rare disease, and it has been defined by different countries in terms of prevalence – either in absolute terms or in terms of prevalence per 10,000 population. A country defines a rare disease most appropriate in the context of its own population, health care system and resources.

6.2 As mentioned above, India faces the limitation of lack of epidemiological data to be able to define rare diseases in terms of prevalence or prevalence rate, which has been used by other countries. To overcome this, a hospital based National Registry for Rare Diseases has been initiated by ICMR by involving centers across the Country that are involved in diagnosis and management of Rare Diseases. This will yield much needed epidemiological data for rare diseases. In the absence of epidemiological data on diseases considered as rare in other countries, it is not possible to prescribe threshold prevalence rates to define a disease condition as rare.

Till the time such data is available and the Country arrives at a definition of a rare disease based on prevalence data, the term rare diseases, for the purpose of this policy, shall construe the following groups of disorders identified and categorized by experts based on their clinical experience:

Group 1: Disorders amenable to one-time curative treatment:

a) Disorders amenable to treatment with Hematopoietic Stem Cell Transplantation (HSCT) –

i. Such Lysosomal Storage Disorders (LSDs) for which Enzyme Replacement Therapy (ERT) is presently not available and severe form of Mucopolysaccharoidosis (MPS) type I within first 2 years of age.

ii. Adrenoleukodystrophy (early stages), before the onset of hard neurological signs.

iii. *Immune deficiency disorders like Severe Combined Immunodeficiency (SCID), Chronic Granulomatous disease, Wiskot Aldrich Syndrome, etc.*

iv. *Osteopetrosis*

v. *Fanconi Anemia*

b) Disorders amenable to organ transplantation

i. *Liver Transplantation -Metabolic Liver diseases:*

a. *Tyrosinemia,*
b. *Glycogen storage disorders (GSD) I, III and IV due to poor metabolic control, multiple liver adenomas, or high risk for Hepatocellualr carcinoma or evidence of substantial cirrhosis or liver dysfunction or progressive liver failure,*
c. *MSUD (Maple Syrup Urine Disease),*
d. *Urea cycle disorders,*
e. *Organic acidemias.*

ii. *Renal Transplantation-*

a. *Fabry disease*
b. *Autosomal recessive Polycystic Kidney Disease (ARPKD),*
c. *Autosomal dominant Polycystic Kidney Disease (ADPKD) etc.*

iii. *Patients requiring combined liver and kidney transplants can also be considered if the same ceiling of funds is maintained. (Rarely Methyl Malonic aciduria may require combined liver & Kidney transplant) etc.*

Group 2: Diseases requiring long term / lifelong treatment having relatively lower cost of treatment and benefit has been documented in literature and annual or more frequent surveillance is required:

a) ***Disorders managed with special dietary formulae or Food for special medical purposes (FSMP)***

- ***i)*** *Phenylketonuria (PKU)*
- ***ii)*** *Non-PKU hyperphenylalaninemia conditions*
- ***iii)*** *Maple Syrup Urine Disease (MSUD)*
- ***iv)*** *Tyrosinemia type 1 and 2*
- ***v)*** *Homocystinuria*
- ***vi)*** *Urea Cycle Enzyme defects*
- ***vii)*** *Glutaric Aciduria type 1 and 2*
- ***viii)*** *Methyl Malonic Acidemia*
- ***ix)*** *Propionic Acidemia*
- ***x)*** *Isovaleric Acidemia*
- ***xi)*** *Leucine sensitive hypoglycemia*
- ***xii)*** *Galactosemia*
- ***xiii)*** *Glucose galactose malabsorbtion*
- ***xiv)*** *Severe Food protein allergy*

b) ***Disorders that are amenable to other forms of therapy (hormone/ specific drugs)***

- ***i)*** *NTBC for Tyrosinemia Type 1*
- ***ii)*** *Osteogenesis Imperfecta – Bisphosphonates therapy*
- ***iii)*** *Growth Hormone therapy for proven GH deficiency, Prader Willi Syndrome and Turner syndrome, Noonan syndrome.*
- ***iv)*** *Cystic Fibrosis- Pancreatic enzyme supplement*
- ***v)*** *Primary Immune deficiency disorders -Intravenous immunoglobulin and sub cutaneous therapy (IVIG) replacement eg. X-linked agammablobulinemia etc.*

vi) *Sodium Benzoate, arginine, citrulline ,phenylacetate (Urea Cycle disorders), carbaglu, Megavitamin therapy (Organic acidemias, mitochondrial disorders)*

vii) *Others - Hemin (Panhematin) for Acute Intermittent Porphyria, High dose Hydroxocobalamin injections (30mg/ml formulation – not available in India and hence expensive if imported)*

viii) *Large neutral aminoacids, mitochondrial cocktail therapy, Sapropterin and other such molecules of proven clinical management in a subset of disorders*

Group 3: Diseases for which definitive treatment is available but challenges are to make optimal patient selection for benefit, very high cost and lifelong therapy.

3a) Based on the literature sufficient evidence for good long-term outcomes exists for the following disorders

1. *Gaucher Disease (Type I & III {without significant neurological impairment})*
2. *Hurler Syndrome [Mucopolysaccharisosis (MPS) Type I] (attenuated forms)*
3. *Hunter syndrome (MPS II) (attenuated form)*
4. *Pompe Disease (Both infantile & late onset diagnosed early before development of complications)*
5. *Fabry Disease diagnosed before significant end organ damage.*
6. *MPS IVA before development of disease complications.*
7. *MPS VI before development of disease complications.*
8. *DNAase for Cystic Fibrosis.*

3b) For the following disorders for which the cost of treatment is very high and either long term follow up literature is awaited or has been done on small number of patients

1. *Cystic Fibrosis (Potentiators)*

2. *Duchenne Muscular Dystrophy (Antesensce oligoneucletides, PTC)*
3. *Spinal Muscular Atrophy (Antisense oligonucleotides both intravenous & oral & gene therapy)*
4. *Wolman Disease*
5. *Hypophosphatasia*
6. *Neuronal ceroid lipofuschinosis*

6.3. The list of diseases under Group 1, Group 2 and Group 3 are not exhaustive and will be reviewed periodically based on updated scientific data by the Technical Committee.

7. Policy Direction

The policy aims at lowering the incidence and prevalence of rare diseases based on an integrated and comprehensive preventive strategy encompassing awareness generation, premarital, post-marital, pre-conception and post-conception screening and counselling programmes to prevent births of children with rare diseases, and, within the constraints on resources and competing health care priorities, enable access to affordable health care to patients of rare diseases which are amenable to one-time treatment or relatively low cost therapy.

Considering the limited data available on rare diseases, and in the light of competing health priorities, the focus would be on prevention of rare diseases as a priority for all the three groups of rare diseases identified by Experts. Public Health and hospitals being a State subject, the Central Government would encourage & support the States in their endeavour towards screening and prevention of rare diseases through Centres of Excellence under Rare Disease Policy and Nidan Kendras under Department of Biotechnology.

8. Prevention & Control of Rare Diseases:

8.1 Capacity building of health professionals

The Central Government will work with the State governments to build capacity of health professionals at various levels. The content of such capacity building would be based on the roles of various health professionals. The Centres of Excellence would develop Standard Operating Protocols to be used at various levels of care for patients with rare diseases to improve early diagnosis, better care coordination and quality of life.

8.2 Prevention at different levels

Though in the last two decades, due to advancement in technologies, understanding of the pathophysiological mechanisms of rare genetic disorders has somewhat improved, yet the treatment modalities are few and the available therapies may not lead to "cure'. More importantly these are exorbitantly costly and not universally available &accessible. Accordingly, prevention needs to be the focus for all genetic disorders. The prevention of genetic disorders can be done at multiple levels. For application of these strategies, the first step is to build the capacity of health professionals and increase awareness in the population at large about the prevalence of such diseases and prevention measures. Frontline workers will be adequately capacitated for screening of rare diseases. Adequate IEC material will be designed and made available across multiple levels of the health care pyramid as this forms a basic pillar of tackling the issue of limited awareness.

8.2.1: Primary Prevention: This aims at preventing the occurrence of the disease, i.e., preventing birth of an affected child. Though not always feasible, this strategy yields the highest returns in terms of decreasing the incidence & prevalence of rare disorders in the population in the long run. Some of the strategies can be as follows:

Examples include avoidance of pregnancy in advanced age, or any other rare monogenic disorder by not marrying a carrier, carrier couples not reproducing etc., but these are not feasible options in the real world scenario. So in most situations the feasible preventive

strategy is secondary prevention. However, a simple checklist will be made available to primary health care providers in the health and wellness clinics to identify a couple at risk based on disease in a previous sib or family history of that disorder.

8.2.2: Secondary prevention: This strategy focuses on avoiding the birth of affected fetus (prenatal screening and prenatal diagnosis), early detection of the disorders, appropriate medical intervention to ameliorate or minimize the manifestations (newborn screening).

a) ***Prenatal screening:*** The common screening methods presently recommended for all pregnancies include biochemical screening and ultrasonography for chromosomal disorders like Down syndrome etc. and ultrasonography for other structural defects. In the context of rare diseases objective of the prenatal screening and diagnosis is to identify the high risk mothers for having an affected fetus with a rare disease. These mothers can be identified based on the family history (previous affected child or affected relative with a known or suspected genetic disorder). Based on the suspected disease a targeted screening of the affected child or couple for a specific disorder or a carrier testing for monogenic disorders using next generation sequencing technique can be offered, the later being presently expensive.

b) ***Prenatal diagnosis by invasive testing (e.g., by Chorionic villus sampling and amniocentesis):*** is possible for any single-gene disorder if the disease causing variant in the gene / enzyme defect is known and for any chromosomal abnormality. Most common indications are known single gene disorders or chromosomal abnormality in a previous affected child in the family. These tests can also be offered if the married couple is found to be carrier for any single gene disorder and mutations have been identified in the couple. Now a day, prenatal diagnosis for above mentioned disorders are widely available in India at many institutions. The invasive procedures are performed by obstetricians and fetal

medicine experts. These procedures however carry a small risk of fetal loss which is very low if done by experienced specialists. This has to be explained to the family before the procedure. Cost would primarily depend on the type of the test to be performed on the sample. If the fetus is found to be affected, the couple has the option for termination of pregnancy, the legal age of which in India has been increased to 24 weeks of pregnancy.

c) ***Newborn screening (NBS):*** is the best example of secondary prevention in which the babies are screened with in few days of birth before symptoms of the disease manifest and treatment is initiated which prevents morbidity and mortality. In the developed world NBS is being offered for many rare disorders particularly the treatable ones (e.g., LSDs, SCID) apart from the common disorders.

d) ***Early postnatal diagnosis and treatment:*** before development of severe manifestations /complications which are irreversible is also included in secondary prevention for disorders amenable to therapy which would require increasing awareness and better availability of diagnostics. Timely referral of the suspected patients & their families to appropriate facilities that are equipped to make a correct diagnosis and where indicated, initiate treatment is the key. Genetic testing will also be augmented by laboratories under the National Genomics Core funded by the Department of Biotechnology and Institute of Genomics and Integrative Biology (IGIB) & Centre for Cellular and Molecular Biology (CCMB) under CSIR.

8.2.3: Tertiary prevention refers to provision of better care and medical rehabilitation to those rare disease patients who present at an advanced stage of the disease. It encompasses providing best supportive care to the affected patients with various rare disorders including the ones for which no specific treatment is available. This would improve quality of life of affected individuals and families. Supportive care includes developmental assessment and intervention including early stimulation and behavioural

intervention, physical therapy and rehabilitation, provision of visual and hearing aids and above all emotional and psychological support to affected individuals and families.

8.2.4: **Optimal screening and diagnosis strategy:** Considering the competing priorities within available resources, universal screening of all pregnancies and/or all newborns in the country for all rare disorders is not feasible. The policy recommends a screening and diagnostic strategy wherein those pregnant women in whom there is a history of a child born with a rare disease and that rare disease diagnosis has been confirmed, would be offered prenatal screening test(s) through amniocentesis and / or chorionic villi sampling. This strategy is in sync with the policy direction of reducing the incidence of rare diseases in the population. In cases where, the diagnosis could not be established during the prenatal period, it would be imperative to offer to the newborn or the infant as the case may be and would include newborn screening for (a) small molecule Inborn Errors of Metabolism by liquid chromatography – tandem mass spectrometry (LC-MS/MS), (b) diagnosis of SCID by T cell receptor excision circles (TREC) and (c) diagnosis of lysosomal storage disorders (LSDs) by microfluids / LC-MS/ MS. (d) diagnosis of disorders by newer but economical molecular diagnostic platforms.

9. Centres of Excellence (COE) and Nidan Kendras

9.1 The Government will notify selected Centres of Excellence, which will be premier Government tertiary hospitals with facilities for diagnosis, prevention and treatment of rare diseases. To begin with the following institutes would be notified as Centers of Excellence for Rare Diseases:

a) All India Institute of Medical Sciences, New Delhi
b) Maulana Azad Medical College, New Delhi
c) Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow
d) Post Graduate Institute of Medical Education and Research, Chandigarh
e) Centre for DNA Fingerprinting & Diagnostics, Hyderabad
f) King Edward Medical Hospital, Mumbai

g) Institute of Post-Graduate Medical Education and Research, Kolkata

h) Center for Human Genetics (CHG) with Indira Gandhi Hospital, Bengaluru

However, more Centres of Excellence can be added for regional outreach if they are found to be suitable in terms of infrastructure and human resources based on recommendations of technical committee.

9.2 The responsibilities and activities of the COEs would be as follows:

- Education & Training at all levels
- Screening – Antenatal, neonatal (specified disorders), High risk screening (both antenatal & in newborns and children)
- Diagnostics- Cytogenetic, molecular, Metabolic
- Prevention by prenatal screening & diagnosis
- Research in the area of low cost diagnostics & therapeutics.
- Treatment of rare diseases.

9.3 The proposed COEs shall be given one-time financial support upto a ceiling of Rs 5 crore for procurement of equipment as per individual centers need for strengthening patient care services for screening, diagnosis and prevention (prenatal diagnosis) of rare diseases based on a gap analysis. The list of equipments which are likely to be useful for these activities is annexed.

9.4 These Centre of Excellence will take the required decision for treatment and fund allocation on rare diseases cases within 02 weeks of receiving the fresh application.

9.5 Nidan Kendras: Nidan Kendras have been set up by Department of Biotechnology (DBT) under Unique Methods of Management and treatment of Inherited Disorders (UMMID) project for genetic testing and counseling services. These Nidan Kendras will be performing screening, genetic testing and counseling for rare diseases. Nidan Kendras possessing the facility for treatment may do so under the guidance and supervision of a CoE.

List of Nidan Kendras is given below:

- Lady Hardinge Medical College (LHMC), Delhi
- Nizam's Institute of Medical Sciences (NIMS), Hyderabad, Telangana
- All India Institute of Medical Sciences (AIIMS), Jodhpur
- Army Hospital Research & Referral, Delhi
- Nil Ratan Sircar (NRS) Medical College and Hospital, Kolkata

Currently Nidan Kendras / Mentor Institutes are supporting aspirational districts for screening of rare diseases. List of aspirational districts covered under the programme is given below:

Name of the Mentor Institute	Aspirational District	State
LHMC, New Delhi	Mewat	Haryana
CDFD, Hyderabad	Yadgir	Karanataka
AIIMS, New Delhi	Haridwar	Uttarakhand
CMC, Vellore	Washim	Maharashtra
MAMC, New Delhi	Ranchi / Bokaro	Jharkhand
SGPGIMS, Lucknow	Shrawasti	Uttar Pradesh
NIIH (KEM hospital campus), Mumbai	Nandurbar	Maharashtra

More aspirational districts will be covered in future either by setting up of more Nidan Kendras or by adopting more than one aspirational districts by existing Nidan Kendras.

10. Government of India support in treatment

The following initiatives shall be taken for patients of Rare Diseases:

i. Financial support upto Rs. 20 lakh under the Umbrella Scheme of Rashtriya Arogaya Nidhi shall be provided by the Central Government for treatment, of those rare diseases that require a one-time treatment (diseases listed under Group 1). Beneficiaries for such financial assistance would not be limited to BPL families, but extended to about 40% of the population, who are eligible as per

norms of Pradhan Mantri Jan Arogya Yojana, for their treatment in Government tertiary hospitals only.

ii. State Governments can consider supporting patients of such rare diseases that can be managed with special diets or hormonal supplements or other relatively low cost interventions (Diseases listed under Group 2).

iii. Keeping in view the resource constraints, and a compelling need to prioritize the available resources to get maximum health gains for the community/population, the Government will endeavour to create alternate funding mechanism through setting up a digital platform for voluntary individual and corporate donors to contribute to the treatment cost of patients of rare diseases.

iv. **Voluntary crowd-funding for treatment**

Keeping in view the resource constraint and competing health priorities, it will be difficult for the Government to fully finance treatment of high cost rare diseases. The gap can however be filled by creating a digital platform for bringing together notified hospitals where such patients are receiving treatment or come for treatment, on the one hand, and prospective individual or corporate donors willing to support treatment of such patients. The notified hospitals will share information relating to the patients, diseases from which they are suffering, estimated cost of treatment and details of bank accounts for donation/ contribution through online system. Donors will be able to view the details of patients and donate funds to a particular hospital. This will enable donors from various sections of the society to donate funds, which will be utilized for treatment of patients suffering from rare diseases, especially those under Group 3. Conferences will be organised with corporate sector companies to motivate them to donate generously through digital platform. Ministry of Corporate Affairs will be requested to encourage PSUs and corporate houses to contribute as per the Companies Act as well as the provisions of the Companies (Corporate Social Responsibility Policy) Rules, 2014 (CSR Rules). Promoting health

care including preventive health care is included in the list in the Schedule for CSR activities.

Treatment cost of the patient will be first charge on this fund. Any leftover fund after meeting treatment cost can be utilized for research purpose also.

11. Development of manpower

Following initiatives will be taken for strengthening of manpower:

- State Governments will be requested to create Department of Medical Genetics at least in one medical colleges in the State for imparting education and increasing awareness amongst health care professionals.
- Services of Nidan Kendras set up under Department of Biotechnology will also be utilised for training of medical practitioners and staff for screening for rare diseases.

12. Constitution of Consortium

(a) **Consortium of Centres of Excellence** so created will synchronize prevention and treatment efforts. AIIMS, Delhi will be the nodal hospital to coordinate with other Centres of Excellence for various activities relating to prevention and treatment of rare disease.

(b) **National Consortium for Research and Development on therapeutics for Rare Diseases**: National Consortium can be provided with an expanded mandate to include research & development, technology transfer and indigenization of therapeutics for rare diseases. It will be convened by Department of Health Research (DHR) with ICMR as a member.

13. Increasing affordability of drug related to rare diseases

(a) Research & Development activities on rare diseases

Indian Council of Medical Research (ICMR), Department of Biotechnology, Department of Pharmaceuticals, Department of science and Technology and Council for Scientific Education & Research will be requested to promote research and development in the field of rare diseases for diagnosis and treatment of rare diseases.

Creation of an integrated research pipeline to start the development of new drugs, for which pharmaceutical companies would be encouraged and research organizations as well as funding agencies would be involved in this important endeavour. Research for repurposing the drugs and use of biosimilar would be encouraged. Approval for new drugs and decision related to trials will continue to be provided by Drugs Controller General of India under the New Drugs and Clinical Trial Rules, 2019.

(b) Ministry of Finance will be requested for reduction in custom duties on import of medicines related to rare diseases.

(c) Ministry of Chemicals and Fertilizers, Department of Pharmaceutical (DoP), National Pharmaceutical Pricing Authority (NPPA) shall take measures to document and make publicly available the prices of drugs for rare diseases and work towards affordability of drugs for rare diseases, in consultation with the Ministry of Health and Family Welfare.

(d) Measures for creating conducive environment for indigenous manufacturing of drugs for rare diseases would be taken**.** Department of Pharmaceuticals, , Department for Promotion of Industry and Internal Trade (DPIIT) will be requested to promote local development and manufacture of drugs for rare diseases at affordable prices and take legal/legislative measures for creating conducive environment for indigenous manufacturing of drugs for rare diseases at affordable prices. PSUs would be encouraged for local manufacturing of drugs for rare diseases.

14. Implementation strategy

Keeping in view lack of availability of epidemiological data on rare diseases, constraints on resources and competing health priorities, the focus of the Government will be on the following:

i. The Government will have a hospital based National Registry for Rare Diseases at ICMR with the objective of creating a database of various rare diseases. Steps have already been taken in this direction by ICMR. Over a period of time, the registry is expected to yield information on hospital based data and disease burden.

ii. The Government shall take steps to create awareness amongst all the levels of health care personnel as well as general public towards the rare diseases. This will encourage people to seek pre-marital genetic counselling, identification of high-risk couples & families and also result in prevention of births as well as early detection of cases of rare diseases. Simple standard protocols/algorithms would be developed for screening and diagnosis in order to avoid missing cases and provide best possible management

iii. Public Health and hospitals being a State subject, the Central Government shall encourage and support the State Governments in implementation of a targeted preventive strategy.

iv. The Government shall provide financial assistance upto Rs. 20.00 lakh (under the Umbrella Scheme of Rashtriya Arogya Nidhi) to the entitled population, as per PMJAY norms, for their treatment in Government tertiary hospital, for rare diseases amenable to one-time treatment (identified under Group 1).

v. The State Governments may undertake treatment of disorders managed with special dietary formulae or food for special medical purposes (FSMP) and Disorders that are amenable to other forms of therapy (hormone/ specific drugs)-diseases covered under Group 2.

vi. The Government shall notify selected Centres of Excellence at premier government hospitals for comprehensive management of rare diseases. The Centres of Excellence will be provided one time grant subject to maximum of Rs. 5 crore

each for infrastructure development for screening, tests, treatment, if such infrastructure is not available.

vii. The Government shall create a digital platform for bringing together notified Centres of Excellence where patients of rare diseases can receive treatment or come for treatment, on the one hand and prospective voluntary individual or corporate donors willing to support treatment of such patients. Funds received through this mechanism will be utilized for treatment of patients suffering from rare diseases.

viii. In order to maintain transparency of transactions in provision of funding under RAN/ crowd funding etc., the Centres of Excellence receiving the funds should have linkages with the ICMR registry.

ix. The Government shall facilitate the creation of an enabling environment that promotes research & development of diagnostic and therapeutic modalities within the Country**.** Consortium of Centres of Excellence shall be created so that research efforts are synchronized. AIIMS, Delhi will be nodal hospital to coordinate with other Centres of Excellence for various activities.

x. State Governments will be requested to create Department of Medical Genetics at least in one medical college in the State for imparting education and increasing awareness amongst health care professionals. This will strengthen manpower base in the country for managing Rare Diseases.

xi. Department of Pharmaceuticals, Department for Promotion of Industry and Internal Trade (DPIIT) will be requested to promote local development and manufacture of drugs for rare diseases by public and private sector pharmaceutical companies at affordable prices and take legal/legislative measures for creating conducive environment for indigenous manufacturing of drugs for rare diseases at affordable prices. PSUs could also be encouraged for local manufacturing of drugs for rare diseases.

xii. Ministry of Finance will be requested for reduction in custom duties on import of medicines related to rare diseases.

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Annexure

Suggestive List of Equipment, which may be required for strengthening of patient services at Centres of Excellence for screening, diagnosis and preventive (prenatal diagnosis) of rare disease.

- *Cytogenetic workstation with software with Fluorescent in situ hybridization*
- *Multimode readers for both ELISA and fluorescent enzyme assays*
- *DNA Sequencer with 8 capillary sequencer*
- *Mi Seq next generation sequencer*
- *Next Seq next generation sequencer*
- *Liquid chromatography Mass Spectroscopy (Tandem Mass Spectrometry)*
- *HPLC (quarternery pump high Performance Liquid Chromatography)*
- *GCMS (gas chromatography Mass Spectrometry)*
- *Microfluidics platform*
- *Real Time PCR (96 well format) for real time polymerase chain reaction*
- *High throughput rNA and DNA extraction systems*
- *Quality Check stations and microtips station*
- *Chromosomal Micro array platform*
- *Newborn Screening platfrom for fluroimmunoassay*
- *Antenatal screening equipment (one stop screening for pre-ecclampsia and chromosomal aneuploidies)*
- *Bio-informatics set up for Nest generation data analysis using High End desktop*
- *Eonis tm system for DNA based newborn screening for rare disorders*
- *Capillary Electrophoresis system for newborn screening of hemoglobinopathies*
- *Upgradation of existing equipment's may also be considered to save costs benefiting a larger section*
- *Any other with permission of the MOHFW with proper justification and as decided by a technical committee of experts set up by MoHFW.*