



BANGALORE

Draft Framework Rare Diseases and Orphan Drugs Policy for Karnataka

Submitted by Vision Group for Biotechnology to
Secretariat of Health and family Welfare

**VGBT, Karnataka
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The Karnataka Vision Group for Biotechnology along with the state's health-related agencies recognizes the need to take a leadership position in the country for the welfare and improved health outcomes of all citizens affected by rare diseases. The group recognizes that the state has strengths in research capabilities and innovation through the application of genomic science and other biotechnologies for effecting substantive health access for rare disease affected communities. This policy has been drafted to be a forward looking and progressive plan for the state to implement through its institutions and partnerships with India's leading biotechnology cluster.



DRAFT FRAMEWORK , February 2016

Vision Document on Rare Diseases Policy in Karnataka State¹

1. Background

1.1 The aim of formulating a vision policy is to create a comprehensive document in the coordinated multi-disciplinary care for children, adults and their families who are affected with rare diseases. It also aims to ensure that people with rare diseases have the best quality evidence-based care and treatment, which is accessible and affordable. The diagnosis, management and treatment of rare diseases require the highest level of partnership between various stakeholders and this can be achieved by establishing robust links. There is also a need to strengthen the best research, diagnosis and service provisions that already exist in Karnataka and elsewhere. To sustain the highest quality of care, collaboration at all levels needs to be established. Thus, a comprehensive state public policy on rare/genetic diseases is vital for delivering quality healthcare for people with rare diseases.

1.2 At least 80% of rare diseases have an identified genetic origin and 50% of all new cases manifest in childhood. Other causes of rare disease are infections, allergic disorders and teratogens in pregnancy. These rare disorders affect multiple organs and systems and are often complicated with other associated morbidities that further complicate management.

1.3 The aim of this vision document is to identify and adopt a systemic approach to rare disorders towards:

- Early identification and prevention of rare diseases where possible
- Early diagnosis and timely intervention

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- Optimal co-ordination of care
- Facilitation of audit and research within the system
- Empowering those affected by rare diseases

2. Vision

2.1 The Karnataka Vision Group for Biotechnology along with the state's health-related agencies recognizes the need to take a leadership position in the country for the welfare and improved health outcomes of all citizens affected by rare diseases. The group recognizes that the state has strengths in research capabilities and innovation through the application of genomic science and other biotechnologies for effecting substantive health access for rare disease affected communities. This policy has been drafted to be a forward looking and progressive plan for the state to implement through its institutions and partnerships with India's leading biotechnology cluster.

2.2 The Centre for Human Genetics (CHG), Institute for Bioinformatics and Applied Biotechnology IBAB, Ganit Labs, Bangalore Bioinnovation Centre BBC and Helix Park are outstanding state-funded initiatives playing a significant role within this plan. CHG in particular has been a thought leader in connecting patients, clinicians and researchers in human genetics to collectively bear on the issues related to rare diseases. The state also hosts outstanding national institutions (IISc, NCBS, CFTRI) with substantial research capabilities to push the frontiers of research in rare disease. Finally, the biotech clusters of the state are the leaders in their respective areas of expertise, which can be leveraged positively for rare disease treatment and drug development. Therefore, Karnataka is the ideal state to launch a public policy and carry out research in rare diseases because of strength in policy, governance, health institutes, biotechnology parks and industry and research organizations.

2.3 This document has been formulated following the European Union's Recommendation on action in rare diseases. The Recommendation which outlined strategies for rare diseases by 2013 was unanimously adopted by each of the EU's Member States in June 2009 (Rare Disease UK). Accordingly, a strategy for rare diseases should include the following:



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- Research
- Prevention, diagnosis and screening
- Commissioning and planning
- Access to treatment
- Multidisciplinary Care
- Access to information and support

2.4 The rare disease policy in Karnataka state should accordingly include the following guidelines:

- **Promote equity of access** – allowing families with affected members with a rare disease to follow clear, well defined care pathway, through a systematic ‘pyramid of care’ approach which is accessible and uniform over all centers
- **Prioritize care optimization** – prioritizing rare diseases has public health importance for our population towards optimal utilization of the available resources
- **Family centered approach to care** – to establish linkages to converge all components of treatment services, specialist healthcare and social support around the needs of patients, their families and other care-givers
- **Deliver evidence-based cost-effective diagnosis and therapy of rare diseases** which should evolve through the best use of available regional and national resources
- **Capacity building** – to develop a structure for easy accessibility to the best evidence-based care and treatment. Support for education and training programs that train health and social care professionals to better identify rare diseases, optimize diagnosis and access to treatment for affected
- **Specialized clinical centers to provide expert, high-quality clinical care and expertise to patients, families and caregivers** - financial and technical support to develop infrastructure such as laboratories and treatment units for the delivery of accessible care, treatment and research
- **Surveillance** – to develop future strategies to expand and scale up the program within a resource constrained setting



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- **Promote excellence in research** which will enable a better understanding of the magnitude, profile and therapy of rare disorders
- **To develop an orphan drug policy** to scale up and fast track development of therapies for these disorders
- **Deliver rapid and effective translation of advances in management of rare diseases** into clinical care by creating appropriate infrastructure, care pathways and clinical competences

3. Definition and Classification of Rare Diseases

3.1 The definition and classification of rare diseases is arbitrary in different countries. There is no universally accepted definition of rare diseases though it is generally accepted that a “rare disease occurs infrequently in a population”. A rare disease is defined through three key elements:

- a) the total afflicted population
- b) prevalence
- c) frequency of occurrence and

Rare diseases often pose challenges of availability and accessibility to treatment as do several other neglected or orphan diseases.

3.2 It is important to first have a definition in place so that a country may develop a public health policy and encourage the development of relevant treatment options and protocols. In USA, a rare disease is defined by its prevalence as “a disease that affects less than 200,000 persons”². Currently, India does not have a standard definition for rare diseases. Considering India’s total population, Rajasimha, et al., (2014) suggest that a rare disease be defined as 1 in 5000.

3.3 Nearly 7 crore of the India population is afflicted with some form of rare/genetic disorders. Of the total, 30-40 lakh people are affected by one of the globally known approximately 7000 rare/genetic diseases in Karnataka. However, an accurate estimate is lacking because we do not have a quantitative database with classifications on the number afflicted by these 7000 rare diseases. It is believed that approximately 80% of the total is due to genetic causes given the high

² Ibid.



rates of consanguineous marriages within various Indian communities³. Estimation of prevalence, population count and genetic surveillance is important towards formulating a robust state/national policy.

4. Identification, Prevention and Diagnostics

4.1 Many rare diseases are present at birth and are either caused by:

- A genetic problem (for example sickle cell disease and Thalassemia Major) or
- Deficiencies or exposures to substances around the time of conception or during pregnancy (for instance, spina bifida is associated with a folic acid deficiency around conception and early pregnancy or intrauterine infections)

4.2 Some of these diseases may manifest later in the childhood or even in adulthood (Thalassemia Minor, Duchenne muscular dystrophy, Huntington chorea, Disorders of Sexual Development).

4.3 Newborn Screening

The Govt. of Karnataka has announced a new born screening program on pilot basis which is now expected to be scale up to cover the entire state. Testing will be made available to all new born children for a range of rare disorders including phenylketonuria, congenital hypothyroidism, Glucose-6-phosphatase deficiency, congenital adrenal hyperplasia and galactossemia. With all of these diseases, early intervention results in better long-term outcome for the affected individual.

Screening programs raise complex ethical, legal and social issues for the people who are offered screening – either as an adult for their own information or as parents on behalf of their child. There is a need to establish a state screening committee, which should advise the Govt. on all aspects of screening in newborn as well as beyond newborn period. Using research evidence, pilot programs and economic evaluation, the committee should assess the evidence for screening programs against a set of internationally recognized criteria covering:

- The epidemiology of the disorder

³ [Ibid](#)



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- The test methodology
- The treatment options
- The effectiveness and acceptability of the screening program

Early, effective screening means that parents/patients can be immediately referred to specialist centres for diagnosis and onward management. The committee should regularly assess current screening programs against new evidence for screening of other conditions and to ensure that these programs are both useful and cost effective.

4.4 Preventive Testing

Preventive steps towards reducing the risk of rare/genetic disease births are a significant component of a public policy. Pre-family counselling with education and information on the risk of genetic transmission of diseases is desirable. While adhering to ethical considerations, it is also necessary to take such preventive steps. Government-sponsored genetic counselling centres could be setup to advice and counsel couples who are about to start families. Voluntary testing for disease traits among couples can reduce the incidence of genetic disease births. Preconception and prenatal screening should be voluntary and confidential.

4.4.1 Carrier testing

Carrier testing involves testing people who are at increased risk of being carriers of a specific inherited disorder. This may be because a relative is known to be a carrier or has the condition or because certain genetic conditions might be more prevalent in their community.

Cascade testing can also be used to identify 'at risk' relatives of an affected person in pre-symptomatic stage. Used effectively, it can reduce morbidity and mortality. For example, when a child with Wilson's disease is diagnosed in hepatic failure, cascade testing can identify other younger siblings who may benefit from early treatments, preventing cirrhosis and death.



Carrier testing for autosomal recessive disorders assumes importance in the context of high rate of consanguineous marriages in our state, for example in Thalassemia, carrier testing of at-risk relatives is not usually offered until the diagnosis of index case in the family. However, with the availability of surveillance data, high-risk populations can be mapped and carrier testing can be offered to such groups. This will allow more informed choices about having a family, pre-conception or fetal screening or testing a child in early life. All this will need to be addressed taking into consideration socio-ethical issues, patient information confidentiality and organized management of the return of results of such testing.

4.4.2 Preconception and antenatal care

The community-based strategies developed to reduce the number of babies born with congenital disorders (disorders that are there from birth) are most effective and give parents reproductive choice through continuing programs that:

- Raise awareness on adequate nutrition and periconceptual folic acid supplement for all women likely to become pregnant
- Awareness about avoidance of exposure to harmful substances or organisms before and during pregnancy (for example by having the rubella immunization, creating awareness about common teratogens and medications especially over the counter (OTC) drugs)
- Serum screening and ultrasound scans in 1st and 2nd trimester to screen women during pregnancy for genetic structural birth defects in the fetus
- Safe and institutional delivery facilities for all pregnant women

4.4.3 Diagnosis and early intervention

The initial presentation of most of these rare diseases mimics common childhood illnesses as a result of which diagnosis is delayed and often missed. This delay in diagnosis leads to missed opportunities for timely interventions. Often the diagnosis of rare diseases requires specialized expertise and laboratory tests.

Although rare diseases are covered in the curriculum of undergraduate and postgraduate medical training, it is unrealistic to expect primary care staff such as general pediatricians and other non-



pediatric health care staff (who are very often the first point of contact) to recognize all rare diseases. Many diseases are so rare that it is unlikely for a primary health care staff member to see a single case in their whole career.

Timely and accurate referral to specialized centres can therefore be achieved by teaching primary health care staff to recognize a handful of key warning signs, highlighted through care pathways. In 2008, a large study identified five aspects of diagnosis that are particularly difficult for general physicians (Kostopoulou, Delaney & Munro, 2008). These include:

- Atypical presentations
- Non-specific presentations
- Very rare conditions
- Co-morbidity (more than one disease present)
- Perceptual features that could be missed

Therefore, there is a need to evolve simplified algorithms to help health care professionals with limited resources for early identification these disorders and appropriate referral.

5. Treatment and Care

5.1 Clearly defined care pathways

It is essential to have clearly defined; easily accessible and effective care pathways. To achieve this, a pyramid model of care is proposed which includes primary care at the base, regional centres and specialist clinical centres at the apex. There should be common protocols for identifying patients at risk of rare diseases at every level of care. Affected individuals should be referred to a coordinated diagnostic service so that they can get a rapid and accurate diagnosis of the suspected disorder. This is an important component of the overall policy, which should define the health care deliverables and delivery system for these rare diseases. Operational guidelines need to be developed to help in implementation of the policy.



5.2 Prioritization

As these rare diseases are a very heterogeneous group, it is difficult to evolve common guidelines for the identification and intervention in all situations. Many of these disorders are so varied and so rare that it may not be possible to formulate a single policy for each of them. As resources available are scarce, allocation of resources for optimal value for the money is important, as is the prioritization of these rare diseases for the inclusion in the rare diseases management program. Prioritization should depend on disease burden in the state, availability of cost effective diagnostic methods and therapy that can modify the course of the disease substantially. The specialist committee should decide on the prioritized list of rare diseases to be included in the program and regular re-evaluation of such a programme.

5.3 Genetic testing

As more than 80% of the rare disorders have a clearly defined genetic basis, it is important to have access to laboratory services, which can ensure high quality genetic testing for inherited disorders. The care pathway for the rare disorder should include the guidance to clinicians as to when they should request a test. There is a need to formulate policy to order a test, transport the samples, conduct a high quality tests at an affordable cost and to disseminate the test result and future options to the family including link to care, treatment and prevention. There is also need to main the highest degree of quality while performing these tests.

5.4 Coordination of Care

Interdisciplinary and intra-disciplinary coordinated care is essential when several specialists and hospital departments are involved in a patient's care for optimal utilization of resources, time and cost. It is essential to coordinate care across the 'boundaries' between different services, so that care is effective, accessible and convenient to patients (for example, it should not disrupt their work or education).

Telemedicine especially means geographical distance does not have to be a barrier to coordinated care. It can improve access to specialist medical services that might not be available in some areas.



Some of the scope of telemedicine includes tele consultation with specialists, tele review, tele tracking the progress of the children and tele learning to improve the capacity of the health care professional involved in the care. This improves the accessibility to the highest quality of care at an affordable cost.

Primary care services often manage a patient's day-to-day care including immunization, nutritional support and monitoring of overall child's health. It is therefore important that general practitioners involved in the routine care of these children feel supported and that they can manage care efficiently. Following diagnosis, a patient should have an evidence based care plan that identifies the anticipated course of the condition and sets out the responsibilities of specialist, general and primary care services in care management. Good communication between patients, their families and professionals is essential to ensure that the primary care plan is agreed and the care team has information and appropriate specialist support. The ultimate aim will be to ensure that the agreed care plan is delivered effectively.

As therapies for many of these rare diseases are long term if not lifelong, maintaining optimal adherence to the therapy is a challenge as well as paramount to the success of such therapy. One of the strategies to improve adherence is easily accessible well-coordinated multidisciplinary care with family as the centre of care and pretreatment counseling to prepare them for the long term therapy. For successful coordination of care and optimal adherence to the life-long therapy, it is extremely important to identify the primary care givers who are willing to take the responsibility. The primary care giver should be adequately prepared for the long-term care and therapy needs and should be made aware of the expected outcome of such therapy before initiation of therapy. It is also important to assess the social and economic support available to the family, which plays a vital role in the success of such therapy. Support groups can offer such social support system and can help in bringing back the non-compliant back to loop of care pathway.

Responsibility for coordination will depend on the case and the circumstances. For those receiving complex treatment where only one discipline is involved, a highly specialized professional might have responsibility for coordinating their care. Where there are many disciplines, the clinical



geneticist may have that responsibility. In any case, the aim should be to ensure that care is always coordinated in a hub and spoke fashion.

5.5 Specialist clinical centres

Specialist clinical centres or centres of excellence can provide an opportunity to acquire and maintain knowledge through research and interaction with patients. They bring together multidisciplinary teams of health and social care professionals to manage patient care and local resources effectively and efficiently. The centres need not necessarily be in specific locations but may be 'virtual', using appropriate technologies to bring experts together. Timely referrals to appropriate centres can be important in reducing the time it takes to receive a diagnosis. The use of new technologies such as telemedicine will increasingly mean that patients can access expert services remotely. This reduces the need for patients to travel and allows the creation of networks of experts who work together across hospitals. These centres should also be uniquely placed to provide a focal point for undertaking research and for implementing evidence based practices across all aspects of the patient pathway.

In providing specialist health and care services, specialist medical professionals assist with the coordination of professional care and provide information & advice to patients and professionals, identifying where the care pathway can be improved. Of vital importance in scientific communication is genetic counselling, the art of communication of a scientifically complex topic in nonprofessional terms as applicable to the family. Expert training and experience is required in this form of communication. Successful counselling is the mainstay in families understanding of complex diseases and when and where to seek appropriate care.

Although specialist clinical centres may provide all the essential expertise, in almost all cases most of the care is provided locally – by local hospitals, primary care teams, social care and education teams, and in the patient's home. Therefore, centres must have protocols in place to share their expertise with local services. This will require the development of shared protocols for effective communication and information sharing between the centre, local teams and the patient.



6. Paramedical and Palliative Care Support

Often people with rare/genetic diseases require simple procedures like injections, tracheostomy draining etc. Paramedical care centres can be setup to provide basic nursing and care services to patients and families. Such a centre also provides employment opportunities as people from lower-income groups with limited education access can be provided training and placement.

7. Orphan Drugs and Devices

7.1 Orphan drugs policy

Support and funding for affordable therapeutics in orphan disease application is a significant component of a public policy. Companies developing therapeutics for orphan diseases need to be given government support and adequate funding. Karnataka needs to put into place an “orphan drug act” (ODA) which would be the first-of-its-kind in India. A good starting point in putting together such an act is the US ODA which was passed in 1983 which facilitates the development and commercialization of drugs and biologics to treat rare diseases. Under the current US ODA, orphan drug developers have three incentives:

- federal funding of grants and contracts for clinical trials of orphan disease products
- tax credit of 50% of clinical testing costs
- exclusive right to market the orphan product for 7 years from the date of marketing approval

There is also a need to facilitate clinical research in rare diseases by waving off clinical trial application fees, priority review & approval of study protocols and accelerated development programs.

7.2 Orphan Diseases Devices, Dietary Supplements

Along with incentives for developing therapeutics for this sector, there are several additional products like medical devices (infusion pumps), aids and diet foods (often used for



phenylketonurics, PKU) which are often required in the care and treatment of rare/genetic diseases. These are mostly imported at exorbitant prices and place a heavy burden on patient families. An Orphan Drugs Policy should be extended to incentivize companies to develop domestic alternatives for imported substitutions.

7.3 Compassionate use policies

As delay in treatment is an important criterion in rare disease intervention, many countries have put in place a Compassionate Use Program. This permits the doctors treating a rare disease patient to request a manufacturer for access to a drug that is in the process of getting approval for public use. Compassionate use policies specify conditions under which this access can be granted and are usually subject to a drug having cleared clinical phase II studies and the patient having a favorable benefit/risk ratio.

8. Disease Surveillance Programs

As the burden of these rare diseases is largely unknown, it is important to assess the prevalence of these diseases individually to formulate, prioritize and scale up the program. The evidence generated through this surveillance program should guide the future course of the program. This can be an integral to the existing screening program or can be through a formulation of registry.

8.1 Monitoring

Monitoring is an integral part of any program for its ongoing success. Monitoring and evaluation should guide future changes in the policy. There is a need to develop monitoring indicators both technical as well operational, which help in assessing the impact of the program.

8.2 Documentation

High quality healthcare, diagnosis and intervention rely upon accurate methods of recording health information to detail the incidence and prevalence of disease, and to enable service planning and international collaboration. To enable updated documentation requires development of infrastructure and training of appropriate human resources.



8.3 Assessing treatments

It is important to have appropriate procedures for evaluating the benefits and costs of diagnosis and treatment so that patients with rare diseases get the most effective care. These procedures should be transparent and robust enough to be able to take account of the particular challenges that occur when evaluating treatments for rare diseases.

9. Research

Research is an integral part of a programme that is developed at the cutting edge of scientific and medical knowledge. Research can be at three main levels:

- *9.1 Epidemiological research* - into prevalence, causation, prevention and socio-cultural aspects of rare disorders. Information gleaned from this type of research will be important to feedback into the programme for improving prioritization and programme efficiency
- *9.2 Translational research* - is of vital importance when laboratory and scientific discoveries can be translated into improvement of patient care services. Gene manipulation techniques and gene editing research are being carried out extensively in the West and if we are to reap the benefits of gene therapy research, we need to establish research labs, which can do the same. This is critical if therapeutic interventions have to reach the Indian population. The Vison Group for Biotechnology (VGBT) in Karnataka has submitted a proposal for an institute of integrated and synthetic biology. Entrepreneurial efforts for example, (Aten Biotherapeutics) in this domain have also started in the Bengaluru.
- *9.3 Operational research* - Ongoing audit of all systems and processes are important in assessing positive and negative trends in achieving health care goals. This will also help identify lacunae, strengthen systems that are robustly functioning and create avenues for better operational models at all levels of the programme.



10. Health Education

Integrating rare disease curriculum in medical education is important to create awareness and competence in the medical community. Rare disease intervention has been prevalent in the United States for more than three decades, and its value has been widely acknowledged. We need to integrate a rare disease curriculum into medical education. This can provide a significant boost to the critical problem of public awareness, as well as promoting research into rare diseases. CHG has a well-developed CME programme for physician exposure to recent developments in human genetics. Such curricula need to be disseminated on a wide scale through the use of digital media. Massive Online Open Courses (MOOCs) developed in English and Kannada can be created to prepare medical personnel from physicians to health workers in remote locations of the state in recognizing genetic diseases in their community health interventions.

11. Facilities and Support for Rare Disease Patients & Families

11.1 Health Insurance

Insurance exclusions are a major issue for people with rare diseases who are forced to pay out of their pockets for every procedure/hospitalization. Private insurance companies exclude people with pre-existing conditions. Genetic pre-dispositions are identified by the IRDA (Insurance Regulatory and Development Authority) Act to be pre-existing and hence insurance companies are permitted to exclude coverage. There are no government health schemes covering people with rare diseases. This discrimination in insurance exclusions increases the financial burden on families. At this stage, IRDA intervention is necessary to ensure that private insurance companies at least provide hospitalization coverage at reasonable premiums. Health insurance under government schemes also need to include people with rare/genetic diseases. If people with rare diseases have to access quality healthcare, insurance exclusions must be dealt with to ensure maximum coverage during health crises.



11.2 Access to Education

Access to education is another serious issue faced by children/adults with rare diseases. Families often spend huge amounts of out-of-pocket money for medical treatment and may not be able to support educational facilities for children. Scholarships/financial aid for children/adults with rare diseases must be instituted to support access to education. The state must also be able to identify a network of institutions that can support students with rare diseases by making their spaces accessible and inclusive.

11.3 Caretaker aid

In countries like Australia, state health services appoint trained caretakers/nurses to provide care to people affected with rare/genetic/chronic conditions. These caretakers could be paid student interns from medical colleges. This provides relief to the family who is burdened with chronic care for a child or adult 24/7 and a way of motivating medical college students to understand more about rare/genetic conditions.

12.Resource Mobilization

Funding for a programme of this magnitude will have to be sustained and defined. Some of these could be provided by the government as a corpus grant.

- Existing pediatric programmes such as *Bala Sanjeevani*, *Yeshaswini* and other insurance schemes for the economically backward groups can support some of the patients requiring investigations and therapy for rare disorders
- *Rashtriya Bal Seva Karyakram* and *National Rural Health Mission* can contribute to specific programmes in detection and health education
- Identifying and tapping CSR funding can contribute towards additional funding and developing a larger corpus resource
- Support organizations such as ORDI and disease specific parent support groups can help raise funding for research and education



- Philanthropic organizations can be approached by regional health services for programme support

13. Review

For the successful operation of a programme of this magnitude, it is vital to have systematic review and objective assessment of all processes. It is proposed that the policy is reviewed at 2-3 yearly intervals to evaluate short term achievements and revise focus of emerging health priorities. With the development and enforcement of this policy document Karnataka state can hope to develop as a leader in the country on rare diseases and their management.

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