CALL FOR A NATIONAL RARE DISEASE FRAMEWORK

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Presented by participants in the Rare Diseases Access Initiative (RDAI) and supporters of the objectives:

Board of Healthcare Funders (BHF)
Discovery Health
Government Employees Medical Scheme (GEMS)
Health Funders Association (HFA)
Innovative Pharmaceutical Association South Africa (IPASA)
Medihelp
Medscheme
Momentum
Rare Diseases South Africa (RDSA)

INTRODUCTION

The Rare Diseases Access Initiative (RDAI) is focused on improving the quality of life for those impacted by rare diseases.

The steering committee of the Rare Diseases Access Initiative (RDAI) in South Africa (SA) was formed as a coalition of interested groups, with the aim to promote an environment which is favourable for those with rare diseases. In particular, the participants seek to improve equitable access for those who need, but who do not currently have, access to the appropriate diagnosis, treatment and healthcare services regardless of healthcare sector utilised to access treatment.

South African's living with rare diseases will have extended and improved lives, if they are able to freely access appropriate healthcare services without barriers. People with rare disease often have very complex needs and face unique challenges:

- A rare disease affects less than 1 in 2000 people affected (see Appendix 1).
- There are approximately 7000 different rare diseases described to date.
- Although individually rare, rare diseases are collectively common.
- Many patients with their respective rare diseases face similar challenges regardless of healthcare sector; the diagnostic odyssey, lack of access to information, feeling isolated, funding and access to high priced treatments, lack of treatment options.

Rare diseases are often:

- Life threatening, life limiting or chronically debilitating.
- Complex, often affecting multiple body systems and requiring specialised and coordinated care that comes at considerable cost to families and the health system.
- 80% of rare diseases are genetic, and therefore not readily preventable.
- Incurable, many with no effective treatment and symptoms often worsen over time.

People, often children, living with a rare disease fight against their disease each day. Unfortunately, in many cases the SA health system is not equipped to respond to the needs of those living with rare diseases, being overwhelmingly geared towards supporting diseases that affect large numbers of people. This presents an opportunity for collaboration to improve the SA health system and health outcomes for people with rare diseases.

The burden of rare disease remains unacceptably high for patients, families, communities and the health system. Collectively, it is estimated that rare diseases affect an over 3 million South Africans. Prioritisation of rare diseases by the health system will not only make a difference to the lives of families affected by rare disease but will help reduce the economic impact. There is an opportunity to address the current imbalance in SA's healthcare system and make it fair and equitable for all as provide for in the Constitution.

"No country can claim to have achieved universal healthcare if it has not adequately and equitably met the needs of those with rare diseases."

- Helen Clark, United Nations Development Programme
RareX/ICORD 2016, Cape Town, South Africa

To ensure the most equitable, effective, efficient and coordinated approach to rare diseases and to place SA on par with the EU, UK, and other parts of the world including BRICS (Brazil, Russia, India, China and SA), a **National Rare Disease Framework for South Africa is needed** that provides for:

- A system that is equitable, accessible, consistent, transparent, timely and patient-centred.
- Collaborative action that includes input from patients, healthcare, government, research, and industry.
- An opportunity for the South African government to provide bi-partisan support, leadership and work in partnership towards a national coordinated and collaborative approach.
- Most importantly, effective rare disease policy to transform patients' lives.

Without a Rare Disease Framework – South Africa is falling behind other countries and our chance of achieving Universal healthcare is diminished.

CALL TO ACTION

The RDAI calls for all Government Departments and organs of state to work together to develop a National Rare Disease Framework and Strategy for South Africa, including the following six key strategic priorities.

1. DIAGNOSIS
2. ACCESS TO TREATMENTS
3. DATA COLLECTION & MANAGEMENT
4. COORDINATED CARE
5. ACCESS TO SERVICES
6. COLLABORATIVE RESEARCH

While long-term, a comprehensive rare disease framework is required, a phased implementation approach to reach this goal will ensure greater sustainability and enable much needed immediate policy reform in critical areas.

Proposal:
Establish and lead a Rare Diseases Advisory Committee to:

1. Map the gaps/opportunities/challenges in rare disease policy.
2. Identify the system issues required to adequately address these.
3. Develop a road map of actions that can be taken [by both National and Provincial Governments]; and
4. Identify an implementation timeline.

DEFINITION OF RARE DISEASES IN SOUTH AFRICA (See Appendix 1)

In SA, there is no formally agreed definition of RD implemented at a national level and uncertainty continues to surround the use of this term. Based on the available research and with its application to the South African population, the following definition is proposed:

"a condition affecting less than 1 in 2000 people (50 per 100,000 of population)".

Based on the current population in SA, this equates to an individual rare condition affecting 30,000 or less people. When considered as a collective of the 7000+ RD characterised to date, it is estimated that 6-8% of the population are affected, which equates to 3.5 million to 4.7 million South Africans (4.1 million) living with a RD.

1) DIAGNOSIS

The early and accurate diagnosis of rare diseases will lead to better outcomes for patients, and long-term economic benefits to the South African healthcare system. Early diagnosis enables the best clinical care, treatment options, access to services, support, increased reproductive confidence and participation in clinical trials (research). For the patient, diagnosis provides a medical explanation, prognosis and management plan that benefits them and their families physically, psychologically, emotionally and financially.

The value of a diagnosis is undeniable and cannot be underestimated, even in the absence of an effective treatment.

A timely, accurate rare disease diagnosis means:

- Early intervention and treatment, often preventing unnecessary deterioration in progressive diseases, mitigating disability, and ensuring best possible patient outcomes.
- Easier access to health and disability services.
- Enables families to make informed decisions about reproduction and family planning.
- Provide easier access to peer support and connections with others affected by the same/similar disease(s).
- Collaboration around rare diseases where clinical knowledge is limited, and sharing anecdotal wisdom is crucial; for example, including the use of Centres of Excellence to facilitate the collaboration.
- Reducing the number of medical specialist visits and unnecessary expensive and invasive investigations during the lengthy diagnostic odyssey of a rare disease patient and providing efficient and cost-effective healthcare delivery.

Rare disease diagnosis challenges:

- Delayed or incorrect diagnosis contributes to the diagnostic odyssey. This has physical, psychological, emotional and financial costs for the patient, family and the health system due to multiple hospital admissions, tests and procedures.
- Without a correct diagnosis the true burden of rare disease continues to be underreported, preventing an appropriate health care response to be implemented.
- Clinicians cannot be expected to recognise all rare diseases described to date, since many have not been fully identified and/or characterised.

- Where a diagnosis is not found, the undiagnosed rare disease patient group needs to be recognised as a distinct group with different needs from those with a diagnosis.

RDAI calls for a National Rare Disease Framework that supports:

- Investigation into the viability of the New-born Screening [NBS) options available. This is vital to ensure an effective mechanism to add to screening panels and early diagnosis of a greater number of rare diseases. It is important that screening and diagnostic programs and services are up to date and accessible.
- Clinical diagnosis of rare diseases in combination with genetic and genomic technology has enormous potential to reduce the diagnostic odyssey commonly experienced by those with rare diseases. This requires comprehensive investment, development and implementation, supported by relevant health care professionals including clinical medical geneticists, genetic counsellors and medical scientists.
- Clinical interfaces that capture phenotypic information and that are aligned to clinical flow. Phenotypic information (i.e., describing manifestations of disease) is the cornerstone of medicine, including genomic medicine. Use of such approaches can significantly increase the diagnostic accuracy of genomic tests and link to genotyping specifically in Africa. Historically, this information is lacking in Africa, although efforts are underway through the Human Heredity and Health in Africa (H3Africa) project, which aims to facilitate a contemporary approach to the study of genomics and environmental determinants of disease.
- A focus on diagnosis, ensuring patients with suspected but undiagnosed rare disease are systemically identified and monitored.
- The development of a South African Undiagnosed Rare Disease Guideline, to support clinicians in the management of the suspected undiagnosed RD patient to aid diagnosis and effective pre- and post-diagnosis management.
- Undiagnosed rare disease patients to have priority access to a specialised and expert diagnostic response, e.g., specialist testing technology (genomics, Specialist diagnostic experts, Interdisciplinary Undiagnosed Diseases Programs and Centres of Excellence), genetic counsellors and peer support.

Some rare diseases patients may attain an extended lifespan and improved quality of life if diagnosed early and properly managed, enabling patients to maintain an active life, employment and make informed reproductive choices.

2) ACCESS TO TREATMENTS

SA requires a health system that provides equitable access to treatments for rare disease. There are limited treatment options for many rare diseases and existing treatments, while often available in other countries are not accessible to South Africans.

- Treatments need to be assessed under criteria that are appropriate for rare disease, characterised by small patient populations, progressive disease, and limited data.
- The reimbursement pathway needs to be equitable, consistent, transparent and timely.
- Patients and their families are increasingly required to advocate for access to treatments, in addition to dealing with the daily management of the disease.
- Recognition of rare disease patients as some of the most vulnerable in South African society.

Rare Disease patients should have equitable and timely access to the best available, current treatment options regardless of their demographic or financial status.

RDAI calls for a National Rare Disease Framework that provides:

- Inclusion in the National Health insurance (NHI) benefit package.
- In the interim towards NHI, a formal response to the Prescribed Minimum Benefits (PMB) Review that commenced in 2016. The rare disease community engaged with the PMB Review process in 2016 and are greatly concerned by the lack of progress in this regard.
- Improved access to treatments. The PMB Review is welcomed and the opportunity for participation. As part of this Review, RDAI calls for the following reforms: -
    - A new and separate fit-for-purpose model to be developed for the reimbursement and management of therapies for rare and very rare disease on the PMB List (PBS]
    - A 'fit-for-purpose · assessment to be developed in the adoption of these therapies that recognises the key principles and issues for rare diseases. The assessment approach should include a range of workable criteria, including: the rarity of the condition, its nature and severity, the existing options for treatment, and the impact of the condition on patients in terms of life expectancy but also quality of life.
    - A new Rare Disease Subcommittee of the Pharmaceutical Therapies Committee to be formed with the specific responsibility of assessing submissions for rare conditions in the public

healthcare setting, including clinical experts with rare disease expertise, and consumer representation from the rare disease community.

- Increased and earlier consumer involvement in the reimbursement process.

3) DATA COLLECTION AND MANAGEMENT

The healthcare system should enable approaches to data collection, management and use that better meet the needs of South Africans living with a rare disease. The greatest challenge in responding to rare disease is lack of data, which is required to define the scale of this health burden. Currently the healthcare system does not systematically code (and therefore identify) rare diseases and only congenital anomalies (obvious, structural abnormalities) are reported within the South African burden of disease based on chapter XVII (Congenital Malformations, deformations and chromosomal abnormalities) of the international Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10. By definition, this chapter excludes functional conditions such as those due to single gene and environmental aetiologies, which account for an estimated 40% of total congenital disorders, which are listed elsewhere in the ICD-10 due to diverse aetiologies.

"If you can't measure it, you can't improve it."

- Peter O'Rucker

Lack of data on rare diseases has a direct negative impact on:

- Diagnosis
- Patient care
- Support
- Development of treatments
- Reimbursement of these treatments (access)
- Quality improvement
- Improving outcomes

RDAI calls for a National Rare Disease Framework that supports:

- A healthcare coding system to identify and measure rare disease in SA.
- Rare disease data collection for clinical care and translational research that improves quality of life, quality of care and survival for patients.
- Development of evidence-based rare disease policy based on data that quantifies the collective impact of rare diseases on healthcare, service planning, clinical guidelines and research.

- Development of an integrated rare disease registry for SA. Registries are critical clinical tools and powerful cost-effective instruments to support clinical trials and translational research that improves quality of care, quality of life and survival. Registries are critical for rare diseases with low prevalence and propensity for variation in treatment and outcomes. RDAI supports the concept of a National Rare Disease Registry - to increase evidence-based knowledge and encourage research.

4) COORDINATED CARE

Providing a coordinated approach to care will contribute to an equitable South African healthcare system and better health outcomes for people living with rare diseases. These services should provide continuity of care across service providers and deliver comprehensive services specific to the individual patient. This type of approach is already a feature of the National Health Insurance Initiative which uses a package of care approach across the life course. Effectively coordinated care provides personalised patient care and contributes to a better quality of life; allows service providers to provide effective services; assists in avoiding unnecessary tests, referrals and hospital admissions; improves the quality and consistency of healthcare provision; results in financial savings; and a more efficient health system.

- It is important that care for each rare disease patient is coordinated across a multi-disciplinary and range of health settings, such as a Centre of Excellence (COE) where appropriate and practical, due to the often complex and long-term care needs, requiring care and input from a range of specialities.
- Coordination of care will support earlier diagnosis, provide access to appropriate interdisciplinary care and enhance the potential for research in these rare and neglected disorders.
- Coordinated care is essential to ensure holistic service delivery across the lifespan of people living with rare diseases.
- Centres of Excellence are important in care provision as well as increasing rare disease knowledge and expertise.

Current areas for improvement:

- Patients and families have multiple appointments, with a range of specialties and services that are not provided in a coordinated manner.
- Many services do not provide adequate transition support for patients and families going from paediatric to adult health services.
- Fragmented health systems and the lack of a unified electronic health record system leads to patients being unable to access adequate ongoing care regimes, disease management and other centralised

information, which is crucial for people with rare diseases even where no treatment is available.

RDAI calls for a national rare disease framework that enables:

- Development of rare disease guidelines that establish standards for coordinated care and clear referral pathways.
- Centres of clinical and research expertise (including undiagnosed rare disease clinics] to:
    - Deliver interdisciplinary services (including mental health] from pre-diagnosis, diagnosis, ongoing care and management.
    - Collaborate with and support the patient's community service and primary care providers.
    - Connect patients with relevant patient support organisations.
    - deliver medical training (pre-and post-graduate] on rare diseases in respective fields of expertise.
    - Be involved in translational research, data collection, rare disease coding and rare disease registries.
    - Provide virtual clinics (telehealth/telemedicine) for rural and regional patients.
    - Collaborate with respective counterparts internationally.
- Improved transitional services, such as child to adult services, change in patient location, and change in service requirements, such as end of life care.
- Promotion and increased uptake of the Patient Care Continuous Health Record.

Delivery of coordinated care for patients with rare diseases has significant cost saving potential and the ability to improve patient outcomes.

5) ACCESS TO SERVICES

The South African health system should provide equitable access to high quality services for all people living with a rare disease, irrespective of the rarity of their condition, a lack of diagnosis, or location. Services also should be economically accessible to all.

- People living with rare diseases are likely to require complex case management and access to a range of government and non-government services and programmes. This includes allied and mental health professionals, clinical specialists, general practitioners, disability and social support services, rehabilitative services and psychosocial support.

- Equitable access to services reduces health inequities and positively impacts on quality of life and health outcomes for people with rare disease and their families.

The South African Government recognises the need for equitable access to services. The National Policy Guidelines for the Care and Prevention of Genetic Disorders, Birth Defects and Disabilities published in 2001 provided recommendations for the development of medical genetic services countrywide. A revision process of this policy into more practically implementable guidelines is underway.

Improved access to services for people with rare and undiagnosed rare diseases also aligns with the Department of Health aim to achieve Universal Health and with Sustainable Development Goal 3 and ensuring that no child is left behind.

Yet challenges persist:

• Rare disease patients may be unaware of the services available.
• Rare disease specialists and services are also rare and, as patients predominantly have complex health care needs, finding appropriate specialists and services is a challenge.
• Not having a diagnosis is a barrier to accessing services.
• Services that could benefit rare disease patients are only available (or more easily available) for specific conditions, regardless of level of unmet need. Linking service eligibility to a finite list of diseases is problematic for those with a rare disease.
• There is disparity in access to services. There is greater access to services for those who can afford to pay for their care or those able to travel to receive expert advice and relevant care.

RDAI calls for a national rare disease framework that:

- Includes a Health Needs Assessment for rare diseases to identify the needs of patients countrywide, and available services, capacity and infrastructure to enable relevant health care services to be planned and implemented.
- Ensures an improved response to rare disease patients in all currently funded services and programs, including:
    - Chronic Health
    - Early Intervention
    - Disability
    - Mental Health
- Increases consultation with the rare disease community to identify service gaps and how to better provide equitable service access.

- Enables service providers to understand the specific challenges faced by rare disease patients.
- Provides appropriate services to rare disease patients, including genetic testing services and genetic counselling.

6) COLLABORATIVE RESEARCH

SA should establish a nationally coordinated program of research on rare diseases that includes active participation by patients, carers and patient advocacy groups. Ideally research should be embedded into clinic care. For many rare diseases, there are no active research programs, and no policy incentives to support research into rare conditions. Obtaining grant funding for rare diseases is extremely challenging and requires national and international collaboration.

Often it falls to patients and their families to join together and fundraise to progress rare disease research. Rare disease research can increase awareness, improve accuracy and speed of diagnosis, advance treatments and improve the quality of life for individuals with rare diseases. In many cases, research on rare diseases can also help better understand the mechanisms of related common conditions.

Patients, families and patient advocacy groups can contribute to research with their disease knowledge and experience in the form of lay expertise.

Challenges of rare disease research:

- Due to low patient numbers of rare conditions compared with common diseases, and the high number of children with rare diseases (ethical implications) it can be challenging to coordinate statistically robust studies i.e., double blind randomised controlled trials are generally not achievable for rare diseases
- Research activities are less common limiting the development of treatments.
- Patients and scientific experts may be widely dispersed, and lay expertise overlooked.
- Lack of data from natural history studies, which follow a group of people with a specific medical condition over time impacts on their ability to inform trial design.
- Rare diseases are not the focus of an intramural unit of the Medical Research Council (MRC) of South Africa and are not included as a priority condition in the NDOH Strategy 2020/2021-2024/25.

- Researchers choose to study more common diseases due to funding opportunities and availability.

RDAI calls for improved research efforts and coordination in the field of rare diseases.

This would include:

- Greater access and support for patients to participate in both local and international clinical trials.
- Prioritised rare disease research through the MRC and other relevant Research Centres, e.g., National Research Foundation (NRF).
- Active participation by patients, carers and patient advocacy to provide advice on the needs of the rare disease patient community.
- Research to contribute to and develop international patient registries and biospecimen repositories; enrolment in studies and trials, monitoring, evaluation and sharing of data.
- Policy and action that recognises the importance of rare disease research including consideration of economic incentives for researchers and pharmaceutical development.

For many rare disease patients, participating in a clinical trial may be their only way to access (any) treatment.

Conclusion

South Africans, including many children, living with a rare disease fight against their disease each day. Unfortunately, in many cases the health system is not equipped to respond to the needs of those living with rare diseases and is overwhelmingly geared towards supporting diseases that affect large numbers of people. This presents an opportunity for collaboration to improve the health system and health outcomes for people with rare diseases. The burden of rare disease remains unacceptably high for patients, families, communities and the health system. Collectively, it is estimated that rare diseases affect more than 3 million South Africans. Prioritisation of rare diseases by the health system will not only make a difference to the lives of families by extending lifespans and improving quality of life of those affected by rare disease but will help reduce the economic cost and impact. This strategy offers an opportunity to address the current imbalance in SA's healthcare system and make it fair and equitable for all South Africans.

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Appendix 1: Definition of Rare Diseases in South Africa

There is currently no global consensus on the universal definition of rare diseases (RD). Different countries and regions worldwide have implemented a variety of definitions and prevalence thresholds, often linked to local RD policy and legislation and other contextual issues. Within many countries or populations, including those with an agreed national definition of RD, there is often disparity on definition usage by different stakeholders operating in different contexts of the RD community.

In South Africa (SA), there is no formally agreed definition of RD implemented at a national level and uncertainty continues to surround the use of this term. The lack of defined boundaries and clarity around this neglected health priority has implications for all stakeholders, and particularly for RD advocacy. This vacuum has largely been filled by the informal uptake of the European definition of RD in SA which describes a RD as a condition affecting less than 1 in 2000 people in the population (equivalent to less than 5 in 10,000). This prevalence threshold was initially chosen by Rare Diseases SA NPO (RDSA), when the organisation was formally launched in 2013 and required a definition to implement. This choice was informed by the strength of agreement demonstrated by the European region and by similar rates of consanguinity observed with SA.

Research now offers an evidence-base to inform decision-making around the definition of RD, and prevalence thresholds. Work by Richter et al in 2015[1] provides an overview of the RD definitions used globally and findings of this study offer useful insights for consideration. Results of this study, which identified 296 RD definitions from 109 organisations in 32 international jurisdictions, included a range of prevalence thresholds from 5-79 cases per 100,000 people. The average prevalence threshold of most jurisdictions (66%) was between 40-50 cases per 100,000 people, with a global average of 40 cases per 100 000. Across the 32 jurisdictions, umbrella patient organisations tended to use more liberal and inclusive prevalence thresholds (47 per 100 000) whereas private payers used lower thresholds (18 per 100 000). The study recommended that qualitative descriptors be avoided and efforts to harmonize RD definitions should focus on standardizing objective criteria, such as prevalence thresholds[1].

These findings, together with prevalence thresholds from other studies, were used to compile and evaluate a number of options for a RD prevalence threshold in SA, summarised in Table 1, below.

Table 1: Summary of prevalence threshold for a rare disease and related descriptive statistics applied to the South African population 20201

% population	1 in n People Affected	Prevalence threshold (per 100 000)	Number affected in SA population	Citation Source
0.01	20,000	5.00	2,981	Richter et al 2015 (Korea)[1]
0.04	2,500	40.00	23,849	Richter et al 2015[1]
0.05	2,000	50.00	29,811	EU 1999[3], Richter et al 2015[1]
0.06	1,630	61.35	36,578	US Orphan Drug Act 1983[4] & Amendments
0.08	1,316	76.00	45,313	Richter et al 2015 (China)[1]

Recommendation

Based on this study and taking into consideration the abundance of research on this issue in Europe, it is recommended that an individual RD in SA be defined as:

"*a condition affecting less than 1 in 2000 people (50 per 100,000 of population)*"

Based on the current population in SA[2], this equates to an individual rare condition affecting 30,000 or less people. When considered as a collective of the 7000+ RD characterised to date[5], it is estimated that 6-8% of the population are affected, which equates to 3.5 million to 4.7 million South Africans (4.1 million) living with a RD.

Considerations

It is recommended that the following considerations be taken into account:

While further terms and inclusive nomenclature may be considered for use in the future (e.g., 'ultra-rare' etc), the first step should be to adopt the recommended definition countrywide with buy-in and consensus by all stakeholders.

[1] Based on South African Population of 59,622,350[2]

Once adopted, implementation of the recommended definition should not be used as a tool to exclude patients or other stakeholders. A holistic, case by case should be applied, taking into account availability of clinical and therapeutic treatments, cost of treatment, severity of case, natural history of the condition and other factors relevant to the context, as well as the prevalence of the condition itself.

As agreement and consensus is developed globally on a universal definition and prevalence threshold for a RD, this recommendation may be subject to revision.

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